

Official Protocol Title:	A Phase III, Multicenter, Open-label Long-term Treatment Trial to Assess the Safety and Efficacy of Addition of Ipragliflozin in Japanese Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Sitagliptin Monotherapy in Addition to Diet and Exercise Therapy
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One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

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TITLE:

A Phase III, Multicenter, Open-label Long-term Treatment Trial to Assess the Safety and Efficacy of Addition of Ipragliflozin in Japanese Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Sitagliptin Monotherapy in Addition to Diet and Exercise Therapy

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-0431J Phase III Ipragliflozin Add-on LTSS in T2DM Patients on Sitagliptin
Sponsor Product Identifiers	MK-0431J sitagliptin phosphate hydrate and ipragliflozin L-proline
Trial Phase	III
Clinical Indication	Type 2 Diabetes Mellitus
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Ipragliflozin 50 mg once-daily (q.d.)
Number of trial subjects	Approximately 75 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 18 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit. Study Duration: From September 2015 to April 2017 (Subject enrollment will be discontinued once the target number of subjects has been achieved).
Duration of Participation	Each subject will participate in the trial for up to 64 weeks from the time the subject signs the Informed Consent Form (ICF) through the final visit. After a screening period of up to 2 weeks followed by a pre-treatment period of 0 or 10 weeks, each subject will receive the assigned treatment for approximately 52 weeks. After the end of treatment each subject will be followed for 14 days.

A list of abbreviations used in this document can be found in Section 12.2.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-controlled, multicenter, open-label trial of addition of ipragliflozin in Japanese patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control on sitagliptin monotherapy in addition to diet and exercise therapy, to be conducted in conformance with Good Clinical Practices.

This study consists of a screening period of up to 2 weeks, a pre-treatment period of 0 weeks or 10 weeks, and a treatment period of 52 weeks. For the duration of the pre-treatment period, subjects will be assigned to Group A (10 weeks) or Group B (0 weeks) based on their pre-treatment for T2DM (use or no use of other AHAs within 10 weeks of Visit 1).

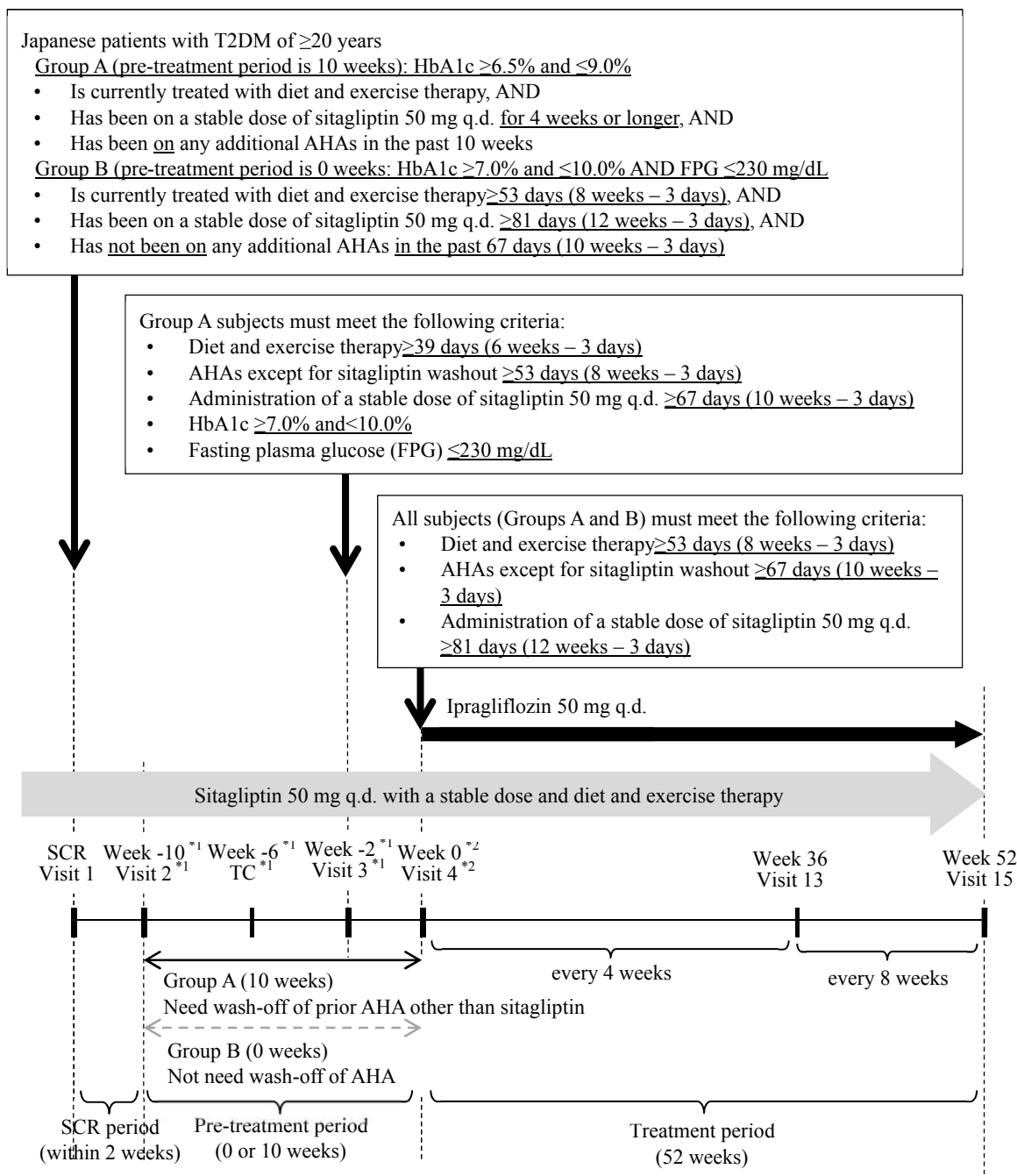
Subjects will take one ipragliflozin 50 mg tablet daily (q.d.) orally for 52 weeks in an open-label manner. Treatment with a stable dose of sitagliptin will be maintained throughout the clinical study. Rescue therapy (administration of glimepiride) will be initiated if the subject meets the hyperglycemia rescue criteria after Visit 4/Week 0.

Approximately 75 subjects will be enrolled. The target population includes Japanese patients ≥ 20 years of age with T2DM who have inadequate glycemic control on sitagliptin 50 mg q.d. monotherapy in addition to diet and exercise therapy, with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$ for all subjects regardless of Groups A or B.

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.



SCR = Screening, TC = Telephone contact

*¹ A subject in Group B proceeds to Visit 4 after Visit 1, skipping Visit 2 and Visit 3.

*² Visit 4/Week 0 is baseline.

Figure 1 Trial design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In Japanese patients with T2DM who have inadequate glycemic control on sitagliptin 50 mg monotherapy in addition to diet and exercise therapy:

Objective: To assess safety and tolerability of the addition of treatment with ipragliflozin 50 mg q.d. over 52 weeks.

3.2 Secondary Objective(s) & Hypothesis(es)

In Japanese patients with T2DM who have inadequate glycemic control on sitagliptin 50 mg monotherapy in addition to diet and exercise therapy:

Objective: To describe the effect of the addition of ipragliflozin 50 mg q.d. on the change from baseline (Week 0) in HbA1c over 52 weeks.

3.3 Tertiary Objectives

In Japanese patients with T2DM who have inadequate glycemic control on sitagliptin 50 mg monotherapy in addition to diet and exercise therapy:

Objectives: To describe the effect of the addition of treatment with ipragliflozin 50 mg q.d. on the following parameters over 52 weeks.

- Change from baseline (Week 0) in fasting plasma glucose (FPG)
- Change from baseline (Week 0) in body weight
- Percentage of subjects with HbA1c <7.0%

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling of sitagliptin and ipragliflozin for detailed background information on MK-0431J.

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). T2DM, which accounts for more than 95% of DM [2], is associated 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].

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 antihyperglycemic agent (AHA) such as sulfonylureas, glinides, biguanides, thiazolidinediones, α -glucosidase inhibitors, 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].

It is estimated that 382 million people worldwide (8.3% of adults) have DM in 2013, and the number of people with the disease is predicted to rise to 592 million by 2035 (55% increase compared to 2013) [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, Labour 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]; however, there are many patients with T2DM who have inadequate glycemic control. The survey in the fiscal of 2013 of Japan Diabetes Clinical Data Management Study Group indicates that 40% or more of patients with T2DM do not achieve the HbA1c goal $< 7.0\%$ for prevention of complication. Non-adherence to AHAs is a significant barrier to achieving glycemic treatment goals of patients with T2DM [5]. In the treatment of T2DM, common patient-reported reasons for poor medication adherence are side effects associated with oral AHA therapies that include hypoglycemia, weight gain, and gastrointestinal intolerance [6] [7] [8]. Poor medication adherence to oral AHAs is also directly related to dosing burden (polytherapy) and dosing frequency [9] [10] [11] [12] [13]. Studies of ex-Japan patients have demonstrated that medication adherence is markedly decreased (ranging from 15% to 54%) when patients were prescribed multiple drugs to treat DM [14]. Among the patient with T2DM using combination therapy, it is reported that adherence tends to be greater with fixed-dose combinations (FDCs) than with separate pills and greater after switching from monotherapy to an FDC rather than to separate-pill combinations [14] [15] [16] [17].

Based on the above, it is considered that a FDC product with low number of tablets and containing the products which have low risk of hypoglycemia, weight gain, and gastrointestinal intolerance, for which some other oral AHAs are known, is an important option for the patients who have inadequate glycemic control on AHA monotherapy and have benefit of improvement of the status of medication adherence.

MK-0431J is a FDC drug containing two active ingredients; a DPP-4 selective inhibitor, sitagliptin phosphate, and a SGLT2 selective inhibitor, ipragliflozin L-proline.

Sitagliptin slows the degradation of the incretin peptides, such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), by inhibiting DPP-4. The resulting increase in the active forms of these incretin hormones leads to glucose-dependent increases in insulin levels and reductions in glucagon levels, which together improve glycemic control in patients with T2DM. Previous clinical studies show that sitagliptin has significant lowering effect on HbA1c and FPG, as well as on postmeal hyperglycemia. In the safety side, sitagliptin has a low risk of gastrointestinal side effects for which some other oral AHAs are known, as well as weight gain. Hypoglycemia did not increase with sitagliptin monotherapy, or co-administration therapy with an additional AHA which has a low risk for hypoglycemia.

Ipragliflozin provides glucose-lowering effect without depending on insulin action by inhibiting SGLT2 in the renal proximal tubule and suppressing the reabsorption of glucose, resulting in elimination of excessive blood glucose from the body. In the conducted clinical studies, ipragliflozin improved overall glycemic control (lowering HbA1c) and also lowered fasting and postmeal hyperglycemia. Ipragliflozin reduced body weight significantly compared to placebo in the placebo-controlled studies, an effect which is in contrast to some other AHAs that can lead to weight gain. In the safety side, there was a low risk for hypoglycemia in ipragliflozin monotherapy or in the combination with ipragliflozin and another AHA.

As indicated above, ipragliflozin and sitagliptin are AHAs with different mechanisms of actions. From this point, since it is considered that the combination of ipragliflozin and sitagliptin can provide additive glucose-lowering effect with low risk of hypoglycemia, weight gain, and so on, for which some other oral AHAs are known, the Sponsor believes that combination therapy with ipragliflozin and sitagliptin will come to be one of the useful treatments for patients with T2DM. In addition, reducing the number of tablets will be helpful for the patients to improve and maintain their drug compliance. Because of these rationales, the Sponsor plans to develop of FDC containing ipragliflozin and sitagliptin, MK-0431J.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The one strength of MK-0431J sitagliptin 50 mg/ipragliflozin 50 mg will be developed and the target population of MK-0431J will be patients with T2DM who have inadequate glycemic control on ipragliflozin monotherapy, patients with T2DM who have inadequate glycemic control on sitagliptin monotherapy, or patients with T2DM co-administered of sitagliptin and ipragliflozin. Therefore, the target population of this trial, i.e., target treatment population, is patients with T2DM who have inadequate glycemic control on sitagliptin 50 mg monotherapy to study the efficacy and the safety of addition of ipragliflozin

50 mg in patients with T2DM who have inadequate glycemic control on sitagliptin 50 mg monotherapy.

4.2.2 Rationale for Dose Selection/Regimen

The regimen of MK-0431J will be once-daily to conform to the regimens of ipragliflozin and sitagliptin. In addition, considering the standard daily dose of both products and the drug utilization situations in the clinical practice (50 mg/day is most common for each product), the combination ratio of MK-0431J was sitagliptin 50 mg/ipragliflozin 50 mg.

Note that in this study, sitagliptin 50 mg and ipragliflozin 50 mg will be co-administered as separate tablets, not as a fixed-dose combination tablet.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The following endpoints will be collected to assess the safety when co-administered with sitagliptin and ipragliflozin.

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

4.2.3.2 Efficacy Endpoints

HbA1c is recommended as a parameter of glycemic control in “Guideline on Clinical Evaluation Methods for Oral Hypoglycaemic Agents”, PFSB/ELD Notification No. 0709-1, 9th July 2010.

Based on the above, the key efficacy endpoint is change from baseline in HbA1c.

4.2.4 Rationale for duration of the treatment period

By reference to ‘Considering the number of subjects required for evaluating safety according to ICH E1 Guideline, it is set to be one year or longer.’ for a long-term study with safety assessment as a primary endpoint in “Guideline on Clinical Evaluation Methods for Oral Hypoglycaemic Agents”, PFSB/ELD Notification No. 0709-1, 9th July 2010, the duration of the treatment period of this trial is 52 weeks.

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 Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with T2DM at least 20 years of age who have inadequate glycemic control on sitagliptin 50 mg monotherapy 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
- 3) meet any one of following criteria at Visit 1:

Group A (pre-treatment period is 10 weeks): HbA1c $\geq 6.5\%$ and $\leq 9.0\%$

- is currently treated with diet and exercise therapy, AND
- has been on a stable dose of sitagliptin 50 mg q.d. for 4 weeks or longer, AND
- has been on any additional antihyperglycemic agent (AHA) monotherapy (single active ingredient) or low-dose dual combination therapy (i.e., $\leq 50\%$ maximum labeled dose of each active ingredient) in the past 10 weeks

Group B (pre-treatment period is 0 weeks): the following laboratory criteria

- is currently treated with diet and exercise therapy ≥ 53 days (8 weeks – 3 days), AND

- has been on a stable dose of sitagliptin 50 mg q.d. ≥81 days (12 weeks – 3 days), AND
- has not been on any additional AHAs in the past 67 days (10 weeks – 3 days)

Table 1 Laboratory Inclusion Criteria (Visit 1) (Group B Only)

Parameter	Study Limit for Inclusion
HbA1c	≥7.0% and ≤10.0%
FPG ¹	≤230 mg/dL
¹ FPG may be re-tested once (within approximately 3 days after receiving the report) upon the investigators discretion if he/she believes that the value does not reflect the subject's recent glycemic control.	

- 4) meet one of the following criteria:
- (1) is a male
 - (2) 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.
 - (3) 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 14 days after the last dose of study medication. Acceptable methods of contraception include:
 - Hormonal contraception
 - IUD
 - Diaphragm with spermicide
 - Condom for male partner
 - Vasectomy for male partner
- 5) understand the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent.

At Visit 3/Week -2 (Group A Only)

- 6) be treated with diet and exercise therapy ≥ 39 days (6 weeks - 3 days)
- _____

- 7) not be on AHAs except for sitagliptin ≥ 53 days (8 weeks - 3 days)

- 8) be on a stable dose of sitagliptin 50 mg q.d. ≥ 67 days (10 weeks - 3 days)

- 9) meet all following glycemic criteria at Visit 3

Table 2 Laboratory Inclusion Criteria (Visit 3) (Group A Only)

Parameter	Study Limit for Inclusion
HbA1c	$\geq 7.0\%$ and $\leq 10.0\%$
FPG ¹	≤ 230 mg/dL
¹ FPG may be re-tested once (within approximately 3 days after receiving the report) upon the investigators discretion if he/she believes that the value does not reflect the subject's recent glycemic control.	

At Visit 4/Week 0

- 10) be treated with diet and exercise therapy ≥ 53 days (8 weeks - 3 days)
- _____

- 11) not be on AHAs except for sitagliptin ≥ 67 days (10 weeks - 3 days)

- 12) be on a stable dose of sitagliptin 50 mg q.d. ≥ 81 days (12 weeks - 3 days)

5.1.3 Subject Exclusion Criteria

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

At Visit 1/Screening

Criteria related to Diabetes

- 1) has type 1 diabetes mellitus or has a history of diabetic ketoacidosis.
- 2) has a history of being administered any of the following AHAs including FDC containing the following ingredients:
 - Insulin: within 12 weeks prior to Visit 1
 - Thiazolidinediones (TZD): within 12 weeks prior to Visit 1
 - SGLT2 inhibitors: any time

Diabetic complications

- 3) has unstable diabetic retinopathy

*

Concomitant Disease of Organs and Systems

- 4) Group A only: has poorly controlled hypertension defined as systolic blood pressure of ≥ 160 mm Hg or diastolic blood pressure of ≥ 100 mm Hg and blood pressure is unlikely to be within these limits by Visit 3/Week -2 with an adjustment in antihypertensive medication.

Group B Only: has poorly controlled hypertension defined as systolic blood pressure of ≥ 160 mm Hg or diastolic blood pressure of ≥ 100 mm Hg.

- 5) has any of the following disorders within the past 3 months prior to Visit 1:
 - Acute coronary syndrome (e.g., MI or unstable angina)
 - Coronary artery intervention (e.g., CABG, PTCA, or similar procedure)
 - Stroke or transient ischemic neurological disorder

Hepatobiliary disorders

- 6) has hepatic cirrhosis, chronic active hepatitis, or symptomatic gallbladder disorder.

Renal or urological disorders

- 7) has a history of medically important renal disorders (such as renovascular occlusion disease, nephrectomy, or renal transplant).
- 8) currently has a symptom of dysuria, anuria, oliguria, or urinary retention.
- 9) currently has a urinary tract infection or genital infection with subjective symptom.
- 10) has a history of recurrent urinary tract infection such as occurred 3 times or more within 6 months of Visit 1.

Laboratory Abnormalities

- 11) has any exclusionary laboratory values as listed in [Table 3](#) below at Visit 1.

Table 3 Laboratory Exclusion Criteria (Visit 1)

Parameter	Population	Study Limit for Exclusion
Alanine aminotransferase (ALT)		>2 times ULN
Aspartate aminotransferase (AST)		>2 times ULN
C-peptide		<0.6 ng/mL
Estimated glomerular filtration rate (eGFR) ¹		<60 mL/min/1.73 m ²
Hemoglobin	Male Female	<11 g/dL <10 g/dL
Thyroid-stimulating hormone (TSH)		Outside central laboratory normal range
¹ eGFR (mL/min/1.73 m ²) = 194 x serum Cr ^{-1.094} x age (years) ^{-0.287} (x 0.739 for female).		

Medications

- 12) requires treatment with a prohibited medication (See Section [5.5.1](#)).
- 13) has received another investigational compound or device in the past 3 months at Visit 1 or is currently receiving treatment with another investigational compound or device.

Other Conditions

- 14) meets one or more following criteria related to malignancy.
- has a history of malignancy ≤5 years prior to Visit 1. (Subject who has a history adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer may be enrolled.)

- has evidence of residual or recurrent disease.
 - has any history of melanoma, leukemia, lymphoma, or renal cell carcinoma.
- 15) has a clinically important hematological disorder (such as aplastic anemia, myeloproliferative syndrome, myelodysplastic syndrome, or thrombocytopenia).
- 16) has a history of severe drug allergy (e.g., anaphylactoid reaction).

Other Criteria

- 17) is currently hospitalized or has planned hospitalization during the study period.
- 18) meets any contraindication or warning listed on package inserts of sitagliptin and ipragliflozin and which are not contained in the exclusion criteria of this study protocol.
- 19) has a body mass index (BMI) $<20.0 \text{ kg/m}^2$ and $>45.0 \text{ kg/m}^2$.
- 20) has a history of alcohol abuse in the past 2 years at Visit 1, or consumes $>50 \text{ g/day}$ of alcohol on average (e.g., at least three 350 mL cans of beer per day).
- 21) has undergone surgery in the past 8 weeks at Visit 1, or has major surgery planned during the study.
- _____
- 22) is pregnant or breast-feeding, or is expecting to conceive during the study, including 14 days following the last dose of study medication.
- 23) For women of childbearing potential: has a positive urine pregnancy test.
- 24) 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.
- 25) is disqualified from the study by the primary investigator or sub-investigator for any reasons other than those given above.

At Visit 2/Week -10 (Group A only)

Other Criteria

- 26) is disqualified from the study by the primary investigator or sub-investigator for any reasons other than those given above.

At Visit 3/Week -2 (Group A only)

Concomitant Disease of Organs and Systems

27) has poorly controlled hypertension defined as systolic blood pressure of ≥ 160 mm Hg or diastolic blood pressure of ≥ 100 mm Hg.

Renal or urological disorders

28) has or had urinary tract infection or genital infection with subjective symptom from Visit 1/Screening.

Laboratory Abnormalities

29) has any exclusionary laboratory values as listed in Table 4 below at Visit 3.

Table 4 Laboratory Exclusion Criteria (Visit 3)

Parameter	Population	Study Limit for Exclusion
Alanine aminotransferase (ALT)		>2 times ULN
Aspartate aminotransferase (AST)		>2 times ULN
Estimated glomerular filtration rate (eGFR) ¹		<60 mL/min/1.73 m ²
Hemoglobin	Male Female	<11 g/dL <10 g/dL
¹ eGFR (mL/min/1.73 m ²) = $194 \times \text{serum Cr}^{-1.094} \times \text{age (years)}^{-0.287}$ (x 0.739 for female).		

Other Criteria

30) For women of childbearing potential: has a positive urine pregnancy test.

31) is disqualified from the study by the primary investigator or sub-investigator for any reasons other than those given above.

At Visit 4/Week 0

Renal or urological disorders

32) has or had urinary tract infection or genital infection with subjective symptom from Visit 1/Screening.

Other Criteria

33) For women of childbearing potential: has a positive urine pregnancy test.

34) is disqualified from the study by the primary investigator or sub-investigator for any reasons other than those given above.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in [Table 5](#).

Table 5 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Screening and pre-treatment periods					
sitagliptin	50 mg tablet	QD	Oral	Up to 12 weeks	Base therapy
Treatment period					
sitagliptin	50 mg tablet	QD	Oral	52 weeks	Base therapy
ipragliflozin	50 mg tablet	QD	Oral	52 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 From screening period to pre-treatment period (From the day after Visit 1/Screening to the day of Visit 4/Week 0)

From the day after Visit 1, each subject will take one tablet of sitagliptin 50 mg for this study once daily orally in the morning (it may be taken with or without regard to meals) for up to 12 weeks in an open-label manner.

5.2.2.2 Treatment period (From the day after Visit 4/Week 0 to the day before Visit 15/Week 52 or discontinuation visit)

From the day after Visit 4, each subject will take one tablet of ipragliflozin 50 mg for the treatment period once daily orally in the morning (it may be taken with or without regard to meals) for 52 weeks in an open-label manner at the same time as taking one tablet of sitagliptin 50 mg for this study.

5.2.2.3 Handling of Missed Doses

If the subject missed a dose(s) in the morning, the missed dose(s) of study medication may be taken on that day as soon as he/she remembers. Two or more tablets of the same medication must not be taken on the same day, even if the subject failed to take drug(s) the day (or more days) before.

5.2.2.4 Timing of Dosing of Study Drug on Days of Study Visits

After Visit 1/Screening, on the day of study visit, the subject should visit the study site before taking study medication(s) and the study medications (sitagliptin for the study and ipragliflozin for the study) prescribed at the previous visit should be taken as a witnessed dose after completion of all study visit procedures.

The study medications will not be administered at Visit 15/Week52 or discontinuation visit.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatments administered.

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

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

From the day after Visit 1

- For Group A: The following antihyperglycemic agents except sitagliptin for the study
 - Insulin

- Thiazolidinediones (TZD) (pioglitazone)
- SGLT2 inhibitors
- DPP-4 inhibitors
- Fix dose combination products containing the above active ingredient(s)

For Group B: All antihyperglycemic agents except sitagliptin for the study

- Systemic corticosteroids ≥ 14 consecutive days or repeated courses
- Other investigational medications

After Visit 2

- All antihyperglycemic agents except sitagliptin for the study, ipragliflozin for the study and rescue medication.

-
- Sulfonylureas (SUs) (sulfonylureas, sulfonamides)
 - Glinides (nateglinide, mitiglinide, repaglinide, etc)
 - α -glucosidase inhibitors (α -GIs)
 - Biguanides (BGs)
 - GLP-1 receptor agonists
 - Fix dose combination products containing the above active ingredient(s)

Within 10 hours of the visit

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

5.5.2 Limited Concomitant Medications

Medications for complication, which are used prior to Visit 1 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 primary investigator or sub-investigator judges that it is necessary to change the regimen considering the individual subject's condition and safety.

5.6 Rescue Medications & Supportive Care

5.6.1 Timing of Dose Administration

The subject who meets the following rescue criteria in Table 6 should initiate rescue therapy with open-label glimepiride. The investigator is responsible for determining the starting dose of rescue medication based on the condition of each individual subject.

Table 6 Rescue Criteria

Timing	Criteria	Administration Timing
After Visit 4/Week 0	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, rescue medication can be adjusted by judgment of the investigator even if the FPG does not show "repeatedly" the above criteria.		

Once the rescue therapy is initiated, the investigator is responsible for the management of adjustment (up-titration, down-titration or discontinuation) of rescue medication(s) based on the condition of each individual subject. Reassessment of FPG and adjustment of rescue medication should continue at the scheduled visit (or at unscheduled visit as needed) until the subject no longer meets rescue criteria. The maximum dosage of rescue medication should be the maximal tolerated dose for individual subject judged by the investigator or the maximal approved dose based on its package insert.

Subjects will continue on study medication after initiation of rescue therapy until completion unless they meet discontinuation criteria (Section 5.8).

5.6.2 Handling of Missed Doses

The missed dose should be taken in accordance with the package insert and/or available subject's leaflet for glimepiride.

5.6.3 Timing of Dosing of Rescue Medication on Days of Study Visits

On the day of study visit, subjects should not take their rescue medication before visits. Subjects should take their rescue medication after completion of all study procedures and in accordance with the package insert.

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. Diet therapy is mandatory and should remain stable throughout the study.

5.7.2 Exercise therapy

The subject will be asked to continue the exercise therapy which was undergone at Visit 1. 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 experience (e.g., arthritis in a lower limb).

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 are provided in Section 7.1.4 – Other Procedures.

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

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

- The subject withdraws consent.
- Lack of efficacy

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

- After Visit 4/Week 0 to Visit 10/Week 24, FPG >240 mg/dL (as reported by the central lab) and is confirmed again (by the central lab) ≥ 4 weeks after administration of rescue therapy at the maximal tolerated dose for the individual subject or the maximal approved dose based on its package insert.
- After Visit 10/Week 24, FPG >200 mg/dL (as reported by the central lab) and is confirmed again (by the central lab) ≥ 4 weeks after administration of rescue therapy at the maximal tolerated dose for the individual subject or the maximal approved dose based on its package insert.

- Adverse event

In the case that the primary investigator or sub-investigator assesses that administration of the study medication should be discontinued due to the occurrence of adverse experiences. When subjects meet the following criteria, they should discontinue the study, regardless of the investigator's assessment.

- Hypoglycemia

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

- Repeated (2 or more episodes since the prior study visit) FPG (as reported by the central lab) or fingerstick glucose <50 mg/dL with or without symptoms of hypoglycemia

OR

- Repeated (2 or more episodes since the prior study visit) FPG (as reported by the central lab) or fingerstick glucose ≤ 70 mg/dL with symptoms of hypoglycemia

- Increased ALT or AST

- a) ALT or AST ≥ 3 -fold above the ULN continuously.

-
- b) Elevations in ALT or AST ≥ 3 -times the upper limit of normal with concurrent total bilirubin ≥ 2 -times the upper limit of normal and alkaline phosphatase < 2 -times the upper limit of normal.
-

- Decreased renal function

If the repeat measurement performed as early as possible meets the criteria in [Table 7](#), the subject must discontinue the study.

Table 7 Discontinuation Criteria of eGFR

Parameter	Study Limit for Discontinuation
eGFR ¹	<50 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).	

- 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.

- Non-compliance with study drug

There is an indication that a subject has not agreed with or followed the instructions related to the study medication.

- 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

A positive urine pregnancy test after initiating study medication for the treatment period requires immediate interruption of study medication until serum β -hCG can be performed and found to be negative. Subject will be able to restart the study medication intake if serum β -hCG test has found to be negative. Subject must be permanently discontinued from study treatment if pregnancy is confirmed by a positive serum pregnancy test. In addition, the investigator or study coordinator must notify the Sponsor.

- Physician Decision

In addition, the primary investigator or sub-investigator judges that subject should discontinue for any other reason.

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 (0 weeks or 10 weeks) 1			Treatment Period (52 weeks)													Discontinuation Visit	Telephone contact
Week		-10 ²	-6 ²	-2 ²	0	4	8	12	16	20	24	28	32	36	44	52	Rescue				
Visit		1	2 ²	TC ²	3 ²	4	5	6	7	8	9	10	11	12	13	14	15	Visit			
Scheduling Window (days)	Pre-treatment Period		0	±7	±3	±3															
	Treatment Period					0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		≤3 after last dose of study drug	≥14 after last dose of study drug		
Administrative Procedures																					
Informed Consent		X ³																			
Inclusion/Exclusion Criteria		X	A		A	X															
Medical History		X																			
Concomitant Medication Review		X	A		A	X	X	X	X	X	X	X	X	X	X	X	X	X			
Patient Registration		X	A		A	X															
Subject Identification Card		X																			
Diet and Exercise Therapy Counseling		X	A		A	X	X	X	X	X	X	X	X	X	X	X					
Patient's Log Dispensing		X ⁴	A		A	X	X	X	X	X	X	X	X	X	X	X					
Collection and Review of Patient's Log			A		A	A	X	X	X	X	X	X	X	X	X	X	X	X			
Self-monitoring blood glucose (SMBG) instruction			A			B															
Instructions on Hypoglycemic Symptoms, Management, and Recording of Hypoglycemic Assessment Log (HAL)						X															
Assignment of Treatment Number						X															
Sitagliptin for the study Dispensing		X	A		A	X	X	X	X	X	X	X	X	X	X	X					
Ipragliflozin for the study Dispensing						X	X	X	X	X	X	X	X	X	X	X					
Study Medications (sitagliptin and/or ipragliflozin) Compliance Monitoring			A		A	X	X	X	X	X	X	X	X	X	X	X	X	X			
Clinical Procedures/Assessments																					
Collection and Review of HAL							X	X	X	X	X	X	X	X	X	X	X	X			
Diet and exercise therapy monitoring		X	A		A	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			
Vital Sign (height)		X																			
12-lead electrocardiogram (ECG) Locally						X						X					X	X			
Assessment of need for rescue therapy							X	X	X	X	X	X	X	X	X	X					
Adverse experience monitoring			A	A	A	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

		Screening Period (≤2 weeks)		Pre-treatment Period (0 weeks or 10 weeks) 1			Treatment Period (52 weeks)												Discontinuation Visit	Telephone contact
Week		-10 ²	-6 ²	-2 ²	0	4	8	12	16	20	24	28	32	36	44	52	Rescue			
Visit		1	2 ²	TC ²	3 ²	4	5	6	7	8	9	10	11	12	13	14	15	Visit		
Scheduling Window (days)	Pre-treatment Period		0	±7	±3	±3														
	Treatment Period					0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		≤3 after last dose of study drug	≥14 after last dose of study drug	
Laboratory Procedures/Assessments																				
HbA1c		X			A	X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁵	
Glucose		X			A	X	X	X	X	X	X	X	X	X	X	X	X	X		
Insulin						X						X					X	X		
Hematology		X			A	X	X		X			X			X		X	X		
Chemistry		X			A	X	X		X			X			X		X	X		
Endocrinological ⁶		X																		
Urinalysis		X			A	X	X		X			X			X		X	X		
Urine Pregnancy Test ⁷		X			A	X	X	X	X	X	X	X	X	X	X	X	X	X		
X: Essential items, A: Only Group A, B: Only Group B, TC: Telephone Contact																				
1 For a subject who <u>needs</u> wash-off of AHA, the duration of the pre-treatment period is 10 weeks (Group A). For a subject who does <u>not need</u> wash-off of AHA, the duration of the pre-treatment period is 0 weeks (Group B).																				
2 For subjects in Group A. A subject in Group B proceeds to Visit 4 after Visit 1, skipping Visit 2 and Visit 3.																				
3 Informed consent must be obtained before any study procedures of Visit 1.																				
4 Instructions on recording of patient’s log is provided.																				
5 HbA1c should not be drawn if Discontinuation Visit occurs within 4 weeks after Visit 4/Week 0.																				
6 C-peptide and thyroid-stimulating hormone (TSH)																				
7 Urinary hCG. Only for females of childbearing potential. Subjects with a positive urine pregnancy test at the site after taking study medication for the treatment priod will have a confirmatory serum β-hCG test at central laboratory as a pregnancy test.																				

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. 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.

7.1.1.2 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.

7.1.1.3 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.

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 washout requirement, and record any prior medication taken by the subject below;

- SGLT2 inhibitors: any time
- Antihyperglycemic agents other than SGLT2 inhibitors: within 12 weeks prior to Visit 1.
- Prior medications other than antihyperglycemic agents: within 4 weeks prior to Visit 1.

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.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, 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)

The investigator or qualified designee will ask the subject about compliance with study medications based upon the number of tablets returned, information recorded in the patient's log, and patient's interview. In the event that the number of tablets returned is inconsistent with the number of tablets reported by the subject, the subject's reporting will be adopted.

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

7.1.1.9 Diet And Exercise Therapy Counseling

From Visit 1, the subject will be asked to continue the diet and exercise therapy which was undergone at Visit 1 with reference to "Treatment Guidance for Diabetes" (edited by Japan Diabetes Society). 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, if the subject's physical activity changed or he/she became unable to adhere to the exercise therapy instructed at Visit 1 due to an adverse event and so on.

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7.1.1.10 Patient Registration

The investigator or clinical research coordinator will register the subjects via the system of the patient registration center.

7.1.1.11 Instruction and Dispensing Recording of Patient's Log

The subject will be instructed to record diet and exercise therapy compliance and study medication compliance in the patient's log from the day after Visit 1. From Visit 2 (Group A) or from Visit 4 (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 study medication compliance.

The patient's log will be dispensed at Visit 1. The subject will be told to bring the subject-completed patient's log to the study 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, 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 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 Self-Monitoring Blood Glucose Procedures

Glucose meters will be supplied to all subjects at Visit 2 (Group A) or Visit 4 (Group B) in order to perform SMBG. The subjects will be instructed on the procedure to perform fingerstick glucose measurements. The subjects will monitor their fingerstick glucose concentrations with a frequency determined appropriate by the investigator with a minimum of 2 fasting (without taking 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 study 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.

- Fingertstick glucose ≤ 70 mg/dL throughout the duration of the entire study
- Fasting fingertick glucose > 230 mg/dL before Visit 4/Week 0
- Fasting fingertick glucose > 240 mg/dL after Visit 4/ Week 0 through Visit 10/Week 24
- Fasting fingertick glucose > 200 mg/dL after Visit 10/Week 24

7.1.1.14 Instructions on Hypoglycemic Symptoms, Management, and Recording of Hypoglycemic Assessment Log

The subject will be informed that there is a possibility of developing hypoglycemic symptoms (e.g., sweating, anxiety, palpitations, headache, blurred vision, and clouding of consciousness) after administration of the study medications. If a symptom that may be considered hypoglycemia occurs and/or fingertick glucose ≤ 70 mg/dL with or without symptoms, the subject will be instructed to;

- Promptly take countermeasures, such as the ingestion of glucose (5 - 10 g) or glucose supplement
- If a symptom that may be considered hypoglycemia occurs: Immediately (before taking glucose or within 2-3 minutes after taking glucose) perform a fingertick glucose measurement
- Complete all symptoms which occurred in HAL
- 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.)
- Bring HAL completed by the subjects at the next visit.

7.1.1.15 Study Medication Dispensing

From Visit 1, the study medications with an arbitrary component ID will be dispensed to the subject at each scheduled visit excepting the final visit, after all study procedures are completed.

—

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 Collection and Review of HAL

Based on review of the subject-completed HAL at each clinic visit, the investigator must assess the fingerstick glucose measurements and/or symptoms that they believe are related to hypoglycemia. Regardless of whether an episode is considered an adverse event, the HA eCRF must be completed for the following: For the entry of hypoglycemia episode into eCRF, see Section 12.5.

- all episodes determined by the investigator to be hypoglycemia (symptomatic or asymptomatic)
- all glucose values ≤ 70 mg/dL (with or without symptom)

7.1.2.2 Adverse Experience Monitoring

7.1.2.2.1 Hyperglycemia

A subject should be considered to have an adverse event of hyperglycemia if the subject has 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 “blood glucose increased.”

7.1.2.2.2 Hypoglycemia

If the fingerstick glucose measurements reported by the subject and/or symptoms that they believe are related to hypoglycemia are considered by the investigator to be an adverse experience of hypoglycemia or asymptomatic hypoglycemia, the event should be reported on the adverse events eCRF as an adverse experience of “hypoglycaemia” or “asymptomatic hypoglycaemia”, respectively. For the entry of hypoglycemia episode into eCRF, see Section 12.5.

7.1.2.3 Vital Signs

Vital signs will be measured according to the procedures in Section 12.4.

7.1.2.4 12-lead ECG

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

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

Laboratory efficacy tests are specified in [Table 8](#). All items will be measured by the central laboratory.

Table 8 Laboratory Tests (Efficacy)

Chemistry	Other
Glucose	Insulin
HbA1c	

At fasting

Laboratory fasting tests will be performed after at least a 10-hour fast.

7.1.3.2 Laboratory Safety Evaluations

Laboratory safety tests are specified in [Table 9](#).

Table 9 Laboratory Tests (Safety)

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Ketones (qualitative)	Serum β -hCG
Hemoglobin	ALP	pH	TSH
Platelet	ALT	Protein (qualitative)	C-Peptide
RBC	AST	Blood (qualitative)	Insulin
WBC (total)	Urea Nitrogen	Sediment	
WBC (differential)	Calcium		
	Chloride		
	Creatinine/eGFR		
	CK		
	γ -GTP		
	Glucose		
	HbA1c		
	HDL cholesterol		
	LDH		
	LDL cholesterol		
	Magnesium		
	Phosphorus		
	Potassium		
	Sodium		
	Bilirubin, Total		
	Cholesterol, Total		
	Protein, Total		
	Triglycerides		
	Uric acid		

Laboratory safety tests other than hematology tests, HbA1c and serum β -hCG will be performed after at least a 10-hour fast.

Urine pregnancy test

Urine pregnancy test will be performed at each study 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.

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 discontinuation visit 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.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

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:

None.

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.

Considerations before Visit

The investigator or clinical research coordinator will instruct the subjects to observe the following standards throughout the entire duration of the study period. The subject who does not meet the following criteria at Screening should re-visit.

- Fasting

The subjects should visit the study site at which the fasting samples are collected after having fasted (except for water) for ≥ 10 hours.

- Concomitant medications

The subjects should not have been on intravenous fluids (excluding those having a volume < 50 mL without any sugar content) and/or glucagon within 10 hours of the visit to the study site.

- Study visit

Subjects should visit the study site in the morning.

- Study medication and rescue medication

At the study visit, the subjects should visit the study site before taking study medications and rescue medication. The subject should bring any unused study medications prescribed at the last visit, without disposal and intake.

7.1.5.1 Screening Period

7.1.5.1.1 Visit 1/Screening

Inclusion/exclusion criteria will be evaluated after obtaining the consent from the subject. For the duration of a pre-treatment period, the subjects will be assigned to Group A (10 weeks) or Group B (0 weeks) based on their pre-treatment for T2DM (i.e., use or no use of other AHAs within 10 weeks of Visit 1).

For the subject who meets all the eligibility criteria of Visit 1, all study procedures of Visit 1 including the following instructions AND excepting patient registration and study medication (sitagliptin for the study) dispensing will be conducted.

- Diet and exercise therapy
- Recoding of patient's log

After the above procedures are completed, the patient registration and study medication dispensing will be conducted. The subject will be instructed to take the dispensed study medication from the day after tomorrow.

Visit 2 (for the subject in Group A) or Visit 4 (for the subject in Group B; Visit 2 and Visit 3 will be skipped) is arranged within 2 weeks after Visit 1. The subject who meets laboratory criteria of Visit 1 can proceed to Visit 2.

7.1.5.2 Pre-treatment Period

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

For the subject who meets the enrollment criteria of Visit 2 and can continue the study based on the review of concomitant medications, the monitoring of adverse experiences, implementation status of diet and exercise therapy, and study medication (sitagliptin for the study) compliance, all study procedures of Visit 2 including the following instructions AND excepting study medication administration, patient registration and study medication dispensing will be conducted.

- SMBG

After the above procedures are completed, the study medication dispensed at the last visit should be taken as a witnessed dose. After that, the patient registration and new study medication dispensing will be conducted.

Visit 3 is arranged approximately 8 weeks after Visit 2.

7.1.5.2.2 Telephone contact/Week -6 (Only for Group A)

The investigator or the clinical research coordinator will confirm the following subject's status with a telephone;

- Adverse events (including confirmation of SMBG value)
- Implementation status of diet and exercise therapy
- Maintenance of diet and exercise therapy instructed at Visit 1
- Study medication (sitagliptin for the study) compliance

7.1.5.2.3 Visit 3/Week -2 (Only for Group A)

For the subject who meets the enrollment criteria of Visit 3 and can continue the study based on the review of concomitant medications, the monitoring of adverse experiences, implementation status of diet and exercise therapy, and study medication (sitagliptin for the study) compliance, all study procedures of Visit 3 excepting study medication administration, patient registration and study medication dispensing will be conducted.

After the above procedures are completed, the study medication dispensed at the last visit should be taken as a witnessed dose. After that, the patient registration and new study medications (sitagliptin for the study) dispensing will be conducted.

Visit 4 is arranged approximately 2 weeks after Visit 3.

7.1.5.3 Treatment Period

As of Visit 4, the subject will visit at every 4 weeks visit until Week 36, at every 8 weeks visit after Week 36 to assess the efficacy and safety.

7.1.5.3.1 Visit 4/Week 0

For the subject who meets the enrollment criteria of Visit 4 and can continue the study based on the review of concomitant medications, the monitoring of adverse experiences, implementation status of diet and exercise therapy, and study medications (sitagliptin for the study) compliance, all study procedures of Visit 4 including the following instructions AND excepting study medication administration, patient registration and study medication dispensing will be conducted.

- SMBG (only for Group B)
- Hypoglycemic symptoms, management and recording of HAL

For subjects who meet the enrollment criteria of Visit 4 and are judged as eligibility, assignment of treatment number occurs only at Visit 4. After registering the subject, new

study medications (sitagliptin for the study and ipragliflozin for the study) will be dispensed to the subject. The subject will be instructed to take 2 tablets of the newly-dispensed study medications (one tablet of each study medication) once daily in the morning at the same timing from the day after tomorrow.

Visit 5 is arranged approximately 4 weeks after Visit 4.

7.1.5.3.2 From Visit 5/Week 4 to Visit 14/Week 44

For the subject who can continue the study based on the review of concomitant medications, the monitoring of adverse experiences, implementation status of diet and exercise therapy, and study medications compliance, all study procedures will be conducted.

Form this visit, the next visit is arranged approximately every 4 weeks or every 8 weeks.

7.1.5.3.3 Visit 15/Week 52 or discontinuation visit

All study procedures of Visit 15 or discontinuation visit will be conducted.

7.1.5.3.4 Rescue Visit

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 (at a scheduled or unscheduled visit), subjects meeting rescue criteria must undergo the rescue visit procedures.

7.1.5.4 After Last Dose of Study Medication

Fourteen days after the last dose of study medication, a follow up contact will be conducted by having subject visit or contacting the subject via telephone to collect the serious adverse experience information that might have occurred within the 14 days.

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 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 through 14 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 defined as below;

- Dosing with higher than a total of 100 mg/day of sitagliptin.

Or,

- Dosing with higher than a total of 100 mg/day of ipragliflozin.

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 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 through 14 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 10](#) for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until taking study medication, 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 through 14 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, 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 through 14 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 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in [Table 10](#). The investigator's assessment of causality is required for each adverse event. Refer to [Table 10](#) for instructions in evaluating adverse events.

Table 10 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.)

7.2.5 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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to the analyses made after the protocol has been finalized 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 8.2-8.12.

Study Design Overview	PhIII ipragliflozin add-on study in T2DM patients on sitagliptin
Treatment Assignment	All subjects enrolled in the study will receive open-label ipragliflozin 50 mg.
Analysis Populations	<u>Safety</u> All Subject as Treated (ASaT) population, defined as all subjects who received at least one dose of treatment period study medication. <u>Efficacy</u> Full Analysis Set (FAS) population, defined as all subjects who: <ul style="list-style-type: none">received at least one dose of treatment period study medicationhave at least one measurement of the outcome variable (baseline or post-baseline)have baseline data for those analyses that require baseline data
Primary Endpoint	AEs, pre-defined limits of change (PDLcs) in laboratory tests and vital signs, as well as change from baseline in laboratory tests, vital signs and ECG.
Secondary Endpoint	Change from baseline in HbA1c at respective timepoints
Statistical Methods for Key Safety Analyses	AEs and PDLcs will be summarized by the number and percentage of the subjects who experienced respective events. Change from baseline in laboratory tests, vital signs and ECG at respective timepoints will be summarized by descriptive statistics.
Statistical Methods for Key Efficacy Analyses	Change from baseline in HbA1c at respective timepoints will be summarized by descriptive statistics and 95% confidence intervals (CIs).
Interim Analyses	The results up to Week 24 will be summarized after all subjects remaining in the trial have completed Week 24.
Multiplicity	Not applicable.
Sample Size and Power	A total of 75 subjects will be enrolled. Assuming a discontinuation rate of approximately 14%, 64 subjects will complete 52 weeks of treatment.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR. This study will be conducted as a single-arm, open-label study.

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

8.4 Analysis Endpoints

Safety and efficacy endpoints that will be evaluated for within-treatment differences are listed below. For both safety and efficacy parameters, the baseline value is defined as the last available measurement prior to enrollment, which typically corresponds to the measurement obtained at Visit 4.

8.4.1 Safety Endpoints

Refer to Section 4.2.3.1 for a list of safety endpoints.

8.4.2 Efficacy Endpoints

Refer to Section 4.2.3.2 for a list of efficacy endpoints.

8.5 Analysis Populations

8.5.1 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least one dose of treatment period study medication.

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

8.5.2 Efficacy Analysis Populations

The FAS population will serve as the population for the analysis of efficacy data in this study. The FAS population consists of all subjects who:

- received at least one dose of treatment period study medication
- have at least one measurement of the outcome variable (baseline or post-baseline)
- have baseline data for those analyses that require baseline data

8.6 Statistical Methods

8.6.1 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs and ECG.

For analyses of AEs and PDLCs, the following two approaches will be used. The primary approach will include all safety-related data points that occurred prior to the initiation of rescue therapy or all safety-related data points if no rescue therapy was initiated. The secondary approach will include all safety-related data points for a subject, regardless of presence or absence of rescue therapy. Only the primary approach will be used to summarize hypoglycemia.

AEs and other safety events will be summarized by the number and percentage of the subjects who experienced respective events. Change from baseline in laboratory tests, vital signs and ECG at respective timepoints will be summarized by descriptive statistics. Missing values will not be imputed.

8.6.2 Statistical Methods for Efficacy Analyses

To avoid the confounding influence of rescue therapy on efficacy, the efficacy analyses will treat data as missing after the initiation of rescue therapy.

Change from baseline in HbA1c at respective timepoints will be summarized by descriptive statistics and 95% CIs. Missing values will not be imputed. Continuous tertiary endpoints will be summarized in a similar fashion.

The number and percentage of subjects achieving HbA1c <7.0%, along with the corresponding 95% CI based on the method of Clopper and Pearson [18], will be provided by timepoint. The denominator will be the number of subjects who are included in the FAS population and have HbA1c measurement at respective timepoints. Missing values will not be imputed.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

8.7 Interim Analyses

For the purpose of filing, all the safety and efficacy results up to Week 24 will be summarized after all subjects remaining in the trial have completed Week 24.

8.8 Multiplicity

No adjustment for multiplicity is planned for the study.

8.9 Sample Size and Power Calculations

A total of 75 subjects will be enrolled in the study. Assuming a discontinuation rate of approximately 14% based on those subjects treated with the active drug for 52 weeks in MK3102-020, 64 subjects will complete 52 weeks of treatment. In the study previously conducted for the filing of the single entity of ipragliflozin (CL-0110), there were 77 subjects treated with coadministration of sitagliptin and ipragliflozin for 52 weeks (45 of them were treated with coadministration of sitagliptin 50 mg and ipragliflozin 50 mg). Hence, with the planned sample size of this study, it is possible to obtain adequate amount of data from coadministration of sitagliptin and ipragliflozin for 52 weeks.

For an AE or a specific safety event of interest, if the underlying incidence is 2%, then there is 78% chance that it is observed in at least one subject among the 75 subjects enrolled. If none of the 75 subjects experiences the event, then the 95% upper confidence limit of the underlying incidence rate will be 4.8%.

With N=75, the half-width of the 95% CI for change from baseline in HbA1c will be 0.23% if the standard deviation estimate is 1%.

8.10 Subgroup Analyses and Effect of Baseline Factors

No subgroup analysis is planned in this study.

8.11 Compliance (Medication Adherence)

For each subject, percent compliance will be calculated using the following formula:

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

A subject will be considered compliant with study medication on a given day if the subject takes both one tablet of sitagliptin 50 mg and one tablet of ipragliflozin 50 mg. The "Number of Days in the Treatment Period" is defined for each subject as the total number of days from the date of the first administration of the study medication to the day before Visit 15 for those subjects who completed the study, and from the date of the first administration of the study medication to the date of the last administration of study medication for those subjects who discontinued from the study.

Descriptive statistics will be provided on percent compliance for the FAS population.

8.12 Extent of Exposure

The dose level and treatment duration will be summarized for the ASaT population.

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 11](#).

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
Sitagliptin phosphate 50 mg	Tablet
Ipragliflozin L-proline 50 mg	

9.2 Packaging and Labeling Information

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

In the screening period, subjects will receive one (1) open label bottle of Sitagliptin 50 mg.

In the pre-treatment period, subjects in Group A will receive two (2) and one (1) open label bottles of Sitagliptin 50 mg at Visit 2 and 3, respectively.

In the treatment period, subjects in Group A and B will receive one (1) open label kit of Ipragliflozin 50 mg and one (1) open label bottle of Sitagliptin 50 mg every 4 weeks until Visit 12, and receive two (2) open label kits of Ipragliflozin 50 mg and two (2) open label bottles of Sitagliptin 50 mg every 8 weeks at Visit 13 or later. Each kit of Ipragliflozin 50 mg will contain three (3) blister sheets.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

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 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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely

responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <http://www.clinicaltrials.gov>. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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 List of Abbreviations

Abbreviations	Definition
2-hr PMG	2-hour postmeal glucose
AE	adverse experience
AHA	antihyperglycemic agent
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASaT	All subject as treated
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BG	biguanide
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CI	confidence interval
CK	creatine phosphokinase
cLDA	constrained longitudinal data analysis
Cr	creatinine
CSR	clinical Study Report
DILI	drug-induced liver injury
DM	diabetes mellitus
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
ERC	ethics review committee
FAS	full analysis set
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FDC	fix dose combination
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GIP	gastric inhibitory peptide
GLP-1	glucagon-like peptide-1
HAL	hypoglycemia assessment log
HbA1c	hemoglobin A1c (glycosylated hemoglobin A1c)
hCG	human chorionic gonadotropin
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICF	informed consent form
ICH	international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IRB	institutional review board
IUD	intrauterine device
IVRS	interactive voice response system

Abbreviations	Definition
LDH	lactic acid dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
MHLW	Ministry of Health, Labour and Welfare
MI	myocardial infarction
MTT	meal tolerance test
OTC	over-the-counter
PDLC	pre-defined limit of change
PP	per-protocol
PTCA	percutaneous transluminal coronary angioplasty
q.d.	quaque die
QOL	quality of life
RBC	red blood cell
SAE	serious adverse experience
SAP	statistical analysis plan
SD	standard deviation
SGLT2	sodium glucose cotransporter 2
SMBG	self monitoring blood glucose
SOC	system organ classes
SOP	standard operating procedure
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WBC	white blood cell
α -GI	α -glucosidase inhibitor
γ -GTP	γ -glutamyltranspeptidase

12.3 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 ≥ 3 -times the upper limit of normal [ULN]). In addition, when ALT and/or AST levels are elevated beyond the clinical significant margin above, the investigators/coordinators must recall the subject, attempt to identify the cause of the elevation, and repeat the blood test(s). Detailed instructions are provided below.

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 alkaline phosphatase.
6. Perform serologic tests including: (a) Hepatitis A (IgM); (b) Hepatitis B (surface antigen and core IgM); (c) Hepatitis C (antibody).
7. Based upon initial abnormal ALT/AST level:
 - If ALT or AST levels are ≥ 3 -times ULN, but ≤ 5 -times ULN, consideration can be given to keeping subject on study medication until repeat determination.

- If ALT or AST levels are >5-times ULN, subjects should have their study medication interrupted immediately.
-

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 <3-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 \geq 3-times ULN, subjects will be discontinued from study medication.
-

All persistent elevations in ALT or AST \geq 3-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.

12.4 Anthropometric Measurement

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

A consistent arm should be used across the study for each measurement on a given subject.

[Instrument] Sphygmomanometer used in routine practice in each site [Mercury sphygmomanometer (least graduation of 2 mm Hg), automated sphygmomanometer, etc.]

[Procedure]

- 1) Measure in duplicate after the subject has been sitting quietly for at least 5 minutes.
- 2) Use Korotkoff Phase V for diastolic blood pressure determinations, and read the measurement to the nearest even mm Hg in case of using a mercury sphygmomanometer. (Reading of last 1 digit should be 0, 2, 4, 6, or 8 mm Hg. Do not round off the last 1 digit)
- 3) Continue to measure sitting blood pressure until becoming consecutive measurements within 5 mm Hg. Separate the 2 measurements by 1 ~ 2 minutes.
- 4) Record the 2nd measurement when consecutive measurements become within 5 mm Hg on the worksheet.

12.4.2 Body Weight

[Instrument] Scale at each study site

[Clothing] The subject should go the same condition (i.e., take off the jacket and/or socks, etc.) at each measurement, if possible.

[Procedure]

- 1) Read the measurements down to one place of decimal. (e.g., 79.4 kg)
- 2) Record the measurement (to one place of decimal) on the worksheet.

12.4.3 Height

Some people may have physical conditions that may limit the ability to measure height accurately (e.g., complication). In such cases, height should be measured in accordance with the following procedures as much as possible.

Measure the height **at Visit 1 only**.

[Instrument] Scale at each study site

[Clothing] The subject should remove his/her shoes and be measured bare foot.

[Procedure]

- 1) Make the subject stand against the vertical backboard.
- 2) Make the subject stand with the heels of their feet on the floor, look straight ahead, and put their chin down.
- 3) Read the measurements down to one place of decimal. (e.g., 167.5 cm)
- 4) Record the measurement (to one place of decimal) on the worksheet.

12.5 Entry of Hypoglycemic Episode into eCRF

Report from Subject		Investigator's Judgment		Enter into eCRF		
Subjective symptom	SMBG	Hypoglycemic episode	Adverse event	HA	FSG	AE
With (e.g., headache, feeling hungry)	>70 mg/dL or No data	Yes	Yes	X	X ¹	“hypoglycaemia”
		No	Yes			Relevant AE term (e.g., “headache”)
			No			
	≤70 mg/dL	-	Yes	X	X	“hypoglycaemia”
			No	X	X	
Without	≤70 mg/dL	-	Yes	X	X	“asymptomatic hypoglycaemia”
			No	X	X	
HA : Hypoglycemia Assessment eCRF FSG : Fingerstick Glucose eCRF AE : Adverse Events eCRF - : 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.						

12.6 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	