AstraZeneca

Clinical Study Protocol

Drug Substance	dapagliflozin (BMS-512148)
Study Code	D1695C00001
Version	3
Date	14 December 2016

A clinical pharmacology and long term study to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of dapagliflozin therapy in combination with insulin in Japanese subjects with type 1 diabetes who have inadequate glycemic control

Sponsor:

AstraZeneca KK, 3-1, Ofuka-cho, Kita-ku Osaka 530-0011, Japan

VERSION HISTORY

Version 3, 14th December 2016 **Changes to the protocol are summarised below.**		
Sections	**Revision Summary**	**Reason for Revision**
Synopsis/Objectives	From outcome measures for secondary objective (Part B), the parenthetic notes related excluding/insulin up-titration were deleted.	After reconsideration, it was concluded that efficacy analyses should primarily be based on all available data regardless of insulin up-titration.
Synopsis/Objectives	7-point SMBG for Part A was added to the Exploratory Objectives.	Additional data collection of 7-point SMBG in the eCRF for Part A has been decided as follows; As for Part A, last subject has completed the study in June 2016 and analysis of the result was performed. Sponsor judged the 7-point SMBG data which has already been collected in the subject diary was necessary to interpret the result of the PD variables more precisely and decided to collect the data exploratively.
2.2 Secondary objectives	From outcome measures for secondary objective (Part B), the parenthetic notes related to excluding/insulin up-titration were deleted.	After reconsideration, it was concluded that efficacy analyses should primarily be based on all available data regardless of insulin up-titration.
2.4 Exploratory objectives	7-point SMBG for Part A was added to the Exploratory Objectives.	Additional data collection of 7-point SMBG in the eCRF for Part A has been decided as follows; As for Part A, last subject has completed the study in June 2016 and analysis of the result was performed. Sponsor judged the 7-point SMBG data which has already been collected in the

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		subject diary was necessary to interpret the result of the PD variables more precisely and decided to collect the data exploratively.
5.3.1.1 Self Monitored Blood Glucose (SMBG)	The underlined parts (normal font) were added in the following paragraph; **In part A**, subjects should self-monitor their blood glucose whenever possible at least 7 times per day (before and after each meal and before going to bed) from Day -1 to Day 7 and in the occurrence of hypoglycemic symptoms, and contact the Investigators in the event of an unusually high or low blood glucose value. Study sites will review these diary entries and record these data on the eCRF. In addition, study subjects should comply with the site's instructions with regard to self-monitoring of blood glucose and insulin adjustments accordingly and should report to the investigator blood glucose values and/or signs and symptoms suggestive of a hypoglycemic episode. Subjects must report the values to the investigator on Day 3 to 5 by telephone (fax or email) at least once a day.	Additional data collection of 7-point SMBG in the eCRF for Part A has been decided as follows; As for Part A, last subject has completed the study in June 2016 and analysis of the result was performed. Sponsor judged the 7-point SMBG data which has already been collected in the subject diary was necessary to interpret the result of the PD variables more precisely and decided to collect the data exploratively.

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Sections	**Revision Summary**	**Reason for Revision**
5.3.2 Self-Monitored Blood Ketone Testing and Guidance on Management and Reporting of Diabetic Ketoacidosis (DKA) Episodes	The following paragraph was added; Dapagliflozin reduces blood glucose by urinary excretion of glucose, thus representing a daily removal of a substantial amount of carbohydrate from the body. We estimate (from insulin:carbohydrate ratios) that the amount of glucose excreted in the urine in subjects on dapagliflozin may correspond to the glycemic effect achieved from as much as 20% of a subject's total daily insulin dose and, therefore, insulin dose reductions will have opposite glycemic effects compared to those of dapagliflozin. Furthermore, since DKA is caused by gross insulin deficiency and is mechanistically unrelated to glucose levels per se (as can be seen in euglycemic DKA), reductions in insulin doses of more than 20% are not recommended regardless of glucose values. If subjects have repeatedly low blood glucose and could otherwise not avoid a 20% reduction in total daily insulin dose, their carbohydrate intake should be re-valuated and those who have insufficient amount of carbohydrate are recommended to increase their daily dietary carbohydrate intake. Similarly, subjects should be reminded that during/after elevated physical activity/exercise, dapagliflozin continues to remove glucose in addition to what is being consumed by the physical activity. Therefore, additional (re-) fueling with carbohydrates is important and should generally be preferred over higher than usual reductions in subjects' insulin doses.	How to manage the DKA was added and clarification was made

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	The underlined parts were added in the following paragraph; Study subjects must be properly instructed on the recognition and management of DKA. Subjects should contact the site for assistance with diabetes management in the event that the blood ketone reading is 0.6 mmol/L or above according to the glucose/ketone meter user guide. Investigator(s) is recommended to advise the subject to take extra insulin and extra carbohydrate if elevated ketones are registered and continue to measure blood ketones. If deemed necessary, dosing of study medication should be interrupted during sick days. The action, follow-up, and monitoring plan will be at the discretion of the investigator and will depend on his/her judgment of severity based on signs/symptoms of DKA, risk factors, relevant contributing factors, and blood glucose (with the caveat that the blood glucose may be lower than would be otherwise expected given elevated ketone levels). It is recommended that for subjects who report elevated ketones/ketosis, investigator(s) considers re-education concerning DKA at the next scheduled visit, at an un-scheduled visit or by telephone contact, as appropriate. Subjects must also be instructed that if attempts to contact the investigator are unsuccessful and if they are in urgent need of medical attention, e.g. sings/symptoms, that they should seek medical attention. They should provide information to the health care provider on their participation in a placebo controlled clinical study evaluating the effects of the SGLT2 inhibitor dapagliflozin in addition to their insulin treatment.	How to manage the DKA was added and clarification was made

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Sections	**Revision Summary**	**Reason for Revision**
5.3.3 Insulin Dosing Adjustment and Data Collection Guidelines	The underlined parts were added in the following paragraph; In part B, it is recommended that subjects reduce their daily insulin dose by up to 20% for both basal and bolus insulin after first dose of study drug to minimize the risk of hypoglycemia. It is at the discretion of the investigator to determine the extent to which to reduce the insulin doses. In some cases it may be necessary to reduce insulin (particular basal insulin) in advance of study drug administration. <u>If total daily insulin dose is reduced upon initiation of study medication, attempts must be made to titrate insulin back to baseline total daily insulin dose. It is not recommended to reduce total daily insulin dose by more than 20% compared to baseline at any time during the study unless medically indicated and close attention should be paid, especially in these subjects, to symptoms of, and risk factors for developing DKA (See also Section 5.3.2).</u> Subjects are to be instructed to document their daily individual insulin doses and at least 4-time self monitored glucose values (before breakfast, lunch, dinner, and bedtime) every day during the treatment period in part B and during the treatment period in part A. This information will be used to facilitate appropriate insulin dose adjustment and ensure subject safety. For the rest of the study period (both short-term and long-term), Subjects will be advised to continue self-monitoring their blood glucose as per local guidelines. Glucose control will be reviewed by the investigator at each visit. Insulin dose may be adjusted as deemed appropriate to be consistent with good medical practice according to SMBG readings, local guidance, and individual circumstances. The glycemic control goals may be individualized based upon a subject's personal target and stability of glycemic control at baseline.	How to adjust insulin dose was added and clarification was made
8.4.2 Secondary endpoints	From outcome measures for secondary objective (Part B), the parenthetic notes related to excluding/insulin up-titration were deleted.	After reconsideration, it was concluded that efficacy analyses should primarily be based on all available data regardless of insulin up-titration.

Version 3, 14th December 2016 **Changes to the protocol are summarised below.**		
Sections	**Revision Summary**	**Reason for Revision**
8.4.3 Exploratory Endpoints	The following exploratory endpoint of Part A was added; The relationship between changes in 7-point SMBG measurements, 24-hr urinary glucose excursion and total daily insulin dose will be explored.	Additional data collection of 7-point SMBG in the eCRF for Part A has been decided as follows; As for Part A, last subject has completed the study in June 2016 and analysis of the result was performed. Sponsor judged the 7-point SMBG data which has already been collected in the subject diary was necessary to interpret the result of the PD variables more precisely and decided to collect the data exploratively.
8.4.5 LOCF	The strike-through parts were deleted in the following paragraph; For LOCF, if no measurement is available at a time point, the last post-baseline measurement prior to the specific time-point will be used instead for analysis. ~~Unless otherwise specified, if a subject up-titrates the insulin dose, the last value taken on or before the first up-titration of insulin dose will be used for analysis.~~	After reconsideration, it was concluded that efficacy analyses should primarily be based on all available data regardless of insulin up-titration.
8.5.2. Analyses of secondary variable(s)	Clarified that efficacy analysis is primarily conducted based on available data regardless of insulin up-titration.	After reconsideration, it was concluded that efficacy analyses should primarily be based on all available data regardless of insulin up-titration.

Version 3, 14th December 2016 **Changes to the protocol are summarised below.**		
Sections	**Revision Summary**	**Reason for Revision**
8.5.3 Exploratory analyses	It is now clarified that analysis plan for exploratory endpoint will be documented in the SAP. The subsequent subsection number is changed accordingly.	Additional data collection of 7-point SMBG in the eCRF for Part A has been decided as follows; As for Part A, last subject has completed the study in June 2016 and analysis of the result was performed. Sponsor judged the 7-point SMBG data which has already been collected in the subject diary was necessary to interpret the result of the PD variables more precisely and decided to collect the data exploratively.
8.5.4 Interim Analyses	It was clarified the interim analyses occurs only after Part A and there will be no interim DBL for Part B.	Reconsideration of timeline/submission strategy

Version 2, 10th February 2016 **Changes to the protocol are summarised below.**		
Sections	**Revision Summary**	**Reason for Revision**
Synopsis/Study site(s) and number of subjects planned	The number of subjects for Part A was changed from 30 to 42.	The number of subjects planned for Part A has been changed as follows; Sponsor received a recall notice on tubes and confirmed that recalled tubes had been used for all 12 subjects who participated in Part A. As for the 12 subjects, plasma concentration might not be measured properly. Therefore, sponsor judged additional 12 subjects are necessary.
Synopsis/Study design	Number of subjects for Part A was changed from 30 to 42.	The number of subjects planned for Part A has been changed.

Version 2, 10th February 2016 **Changes to the protocol are summarised below.**		
Sections	**Revision Summary**	**Reason for Revision**
1.4.1 PK and PD evaluation part (Part A)	Number of subjects for Part A was changed from 30 to 42.	The number of subjects planned for Part A has been changed.
5.3.8 Resting 12-Lead ECG	A term "initiated", changed in the Clinical Study Protocol Amendment 1 as a typo, was changed back to "initialed".	Typo
8.2.1 PK and PD evaluation part (Part A)	Number of subjects for Part A was changed from 30 to 42.	The number of subjects planned for Part A has been changed.
	The underlined parts were added in the following paragraph; In terms of key PD evaluation (mean change in 24-hour urinary glucose [g/24h]), the half width of 95% confidence interval for treatment difference based on 10-14 evaluable patients/arm are estimated to be approximately 42-50 [g/24h], assuming the common standard deviation of 56 [g/24h].	The rationale for sample size estimation was added and clarification was made to explain why the number of subjects planned for Part A was changed.
	The following paragraph was added; In addition, PK-PD relationships will be evaluated exploratory to compare between those of Japanese T1DM patients and those of non-Japanese T1DM patients. For this evaluation, 10 patients per arm are considered sufficient. Originally, in the initial version of the Clinical Study Protocol issued at 9th July 2015, about 30 patients were planned to be randomized to the study. However, 12 patients in Part A were judged to be unevaluable for PK data due to issue related to sampling tube. It is considered that the revised sample size (randomization of about 42 patients) would lead to sufficient number of patients for evaluating PK profile, as well as exploratory evaluating PK-PD relationships, without the 12 patients.	The rationale for sample size estimation was added and clarification was made to explain why the number of subjects planned for Part A was changed.

Version 2, 10th February 2016 **Changes to the protocol are summarised below.**		
Sections	**Revision Summary**	**Reason for Revision**
10.5 Changes to the protocol and informed consent form	The following paragraph was amended as below (added part is indicated as underlined, deleted as ~~strike through~~); Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the ~~study protocol~~ Clinical Study Protocol to be amended, the ~~amendment~~ amended Clinical Study Protocol should be submitted to the Head of the Study Site. If the changes are of an administrative nature, it is submitted to the IRB. If the changes have a significant impact on the safety of the subjects, the scientific value of the study, the conduct and management of the study, and the quality of any investigational product used in the study, it should be approved by the IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If ~~a protocol amendment~~ the amended Clinical Study Protocol requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified by the Principal Investigator. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. ~~If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.~~	Due to the revision of the Japan template for the Clinical Study Protocol to reflect the updated Standard Operational Procedure, SOP, of the Sponsor
The whole document	List of abbreviations and definition of terms was updated.	Editorial changes due to updates.
	"gluccuronide" to "glucuronide" "glucemic" to "glycemic" "SMBG 4 point" to "4-point SMBG" "6 point SMBG" to "6-point SMBG"	Typo and editorial changes for the sake of terminology consistency

Administrative change 2, 5th January 2016
For changes to the protocol, refer to the document.

Amendment 2, 25th November 2015
For changes to the protocol, refer to the document.

Administrative change 1, 30th September 2015
For changes to the protocol, refer to the document.

Amendment 1, 12th August 2015
For changes to the protocol, refer to the document.

Version 1, 9th July 2015
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A clinical pharmacology and long term study to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of dapagliflozin therapy in combination with insulin in Japanese subjects with type 1 diabetes who have inadequate glycemic control

Principal Investigator

The names of the principal investigators are described in Japan Addendum - Investigators and Study Administrative Structure.

Study site(s) and number of subjects planned

Study Centres: Approximately 40 centres are planned for participation

Number of Subjects: [Part A] 42 randomized Japanese subjects. [Part B] 140 randomized Japanese subjects.

Study period		Phase of development
Estimated date of first subject enrolled	October 2015	Phase I/III
Estimated date of last subject completed	October 2017	

Study design

The study design of Part A is a randomized, single-blind, 3 arm, parallel-group, placebo-controlled design. Forty-two Japanese subjects in total will be randomized in a 1:1:1 ratio into one of the three single-blinded treatment arms; dapagliflozin 5 mg, dapagliflozin 10 mg or placebo.

The study design of Part B is a randomized, open-label, 2 arm, parallel-group design. One hundred forty Japanese subjects in total will be randomized in a 1:1 ratio into one of the two treatment arms; dapagliflozin 5 mg or dapagliflozin 10 mg.

Objectives

Primary Objective:	Outcome Measure:
[Part A] To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of 7 days repeated doses of dapagliflozin in Japanese patients with type 1 diabetes mellitus (T1DM) with inadequate glycemic control under standard insulin therapy.	PK variables: C_{max}, T_{max}, AUCτ for dapagliflozin and dapagliflozin 3-O-glucuronide, and ratio of dapagliflozin 3-O-glucuronide AUCτ to dapagliflozin AUCτ. PD variables: Change from baseline in 24-hour urinary glucose excretion on Day 7.
[Part B] To evaluate safety and tolerability of long-term treatment (52 weeks) of dapagliflozin 5mg and 10 mg in Japanese patients with T1DM with inadequate glycemic control under standard insulin therapy.	Adverse event (including AEs of hypoglycemia and diabetic ketoacidosis (DKA) events), physical examination, vital signs (blood pressure, heart rate), ECG, and clinical laboratory measures, urine test.

Secondary Objective:	Outcome Measure:
[Part A] To evaluate the PD of 7 days repeated doses of dapagliflozin in Japanese patients with T1DM with inadequate glycemic control under standard insulin therapy.	Change from baseline in fasting plasma glucose (FPG) on Day 7, daily insulin dose, Systolic blood pressure (SBP)
[Part A] To assess the safety and tolerability of 7 days repeated doses of dapagliflozin in Japanese patients with T1DM with inadequate glycemic control under standard insulin therapy.	Adverse event (including AEs of hypoglycemia and DKA events), physical examination, vital signs (blood pressure, heart rate), ECG and clinical laboratory measures, urine test.

Secondary Objective:	**Outcome Measure:**
[Part B] To assess the efficacy of long-term treatment (52 weeks) of dapagliflozin 5mg and 10 mg in Japanese patients with T1DM inadequately controlled on insulin therapy.	Change from baseline in HbA1c at Week 24 and 52 Change from baseline in GA at Week 24 and 52 Change from baseline in average glucose values measured by 6-point SMBG at Week 24 and 52 Change from baseline in postprandial glucose values measured by 6-point SMBG at Week 24 and 52 Percent change from baseline in total daily insulin dose at Week 24 and 52 Percent change from baseline in body weight at Week 24 and 52 Proportion of subjects with HbA1c reduction from baseline of at least 0.5% without severe hypoglycemia events at Week 24 and 52 Proportion of subjects with HbA1c reduction from baseline of at least 0.5% at Week 24 and 52 Proportion of subjects with HbA1c < 7.0% at Week 24 and 52 Change from baseline to Week 24 and 52 in seated SBP among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg

Safety Objective:	**Outcome Measure:**
Not applicable	Not applicable

Exploratory Objective:	**Outcome Measure:**
[Part A] Explore relationship between 7-point SMBG measurements and other PD variables	7-point SMBG measurements, 24-hr urinary glucose, total daily insulin dose and their changes from baseline
[Part B] The efficacy evaluation will be made by comparing subgroups BMI <25.0 kg/m^2 or BMI ≥ 25.0 kg/m^2.	Change from baseline in HbA1c, GA, average/post-prandial glucose values measured by 6-point SMBG, and percent change from baseline in body weight, total daily insulin dose by subgroup defined by BMI.

Target subject population

Patients are divided in two parts in this study.

[Part A]

Japanese male and female patients with T1DM and age 18 to 65 years, with inadequate glycemic control on insulin defined as HbA1c ≥ 7.0% and ≤ 10.0% at screening visit.

[Part B]

Japanese male and female patients with T1DM and age 18 to 75 years, with inadequate glycemic control on insulin defined as HbA1c ≥ 7.5% and ≤ 10.5% at screening visit.

[Part A and B]

Method of insulin administration (MDI or CSII) must have been unchanged for at least 3 months prior to the screening visit per subject report or medical records. Subjects must be on a total daily insulin dose of ≥ 0.3 U/kg/day for at least 3 months prior to the screening visit. In part A, CSII user are excluded.

Duration of treatment

[Part A]

The treatment period will be 7 days. Patients will have a screening period up to 14 days and a follow-up period of 7 days off of study medication. The 7 days follow-up period allows for a further understanding of any changes in physical signs and symptoms or laboratory parameters that can be potentially attributed to the use of the investigational product.

[Part B]

The treatment period will be 52 weeks. Patients will have a screening period of 14 days, a wash-out period of 7 days if needed, and a follow-up period of 4 weeks off of study medication. The 4 weeks follow-up period allows for a further understanding of any changes in physical signs and symptoms or laboratory parameters that can be potentially attributed to the use of the investigational product.

Investigational product, dosage and mode of administration

[Part A]

Each dose will be composed of 2 tablets. Investigational drug should be taken once daily in the morning.

dapagliflozin 5 mg dose: dapagliflozin 5 mg 1 tablet + dapagliflozin 10 mg placebo 1 tablet

dapagliflozin 10 mg dose: dapagliflozin 5 mg placebo 1 tablet + dapagliflozin 10 mg 1 tablet

placebo dose: dapagliflozin 5 mg placebo 1 tablet + dapagliflozin 10 mg placebo 1 tablet

[Part B]

Dapagliflozin 5 mg or 10 mg tablet administered orally once daily in much around the same time for the 52-week open-label treatment period. Study drug for 5 mg and 10 mg dose groups should be stated separately.

Statistical methods

[Part A]

PK: summary statistics for C_{max}, T_{max}, AUCτ for both dapagliflozin and its major metabolite dapagliflozin 3-O-glucuronide, and ratio of metabolite (MR) to parent AUCτ will be provided by arm. Geometric mean and CV (coefficient of variation) will be presented for C_{max}, AUCτ, and Ratio of metabolite to parent AUCτ. Medians and ranges will be presented for T_{max}.

PD: change from baseline to Day 7 in 24-hour urinary glucose will be summarized by arm. Also difference of dapagliflozin vs. placebo and 95%CIs will be summarized if appropriate. No formal statistical testing will be performed. For other PD parameters to be assessed by change from baseline (ie, FPG and SBP), similar analysis like 24-hour urinary glucose will be carried out. For PD parameters to be assessed by percent change from baseline (ie, daily basal insulin dose, daily bolus insulin dose, total daily dose of insulin), similar analysis will be carried out with exception that mean percent change from baseline will be calculated from the exponentiated values of estimates obtained on the natural logarithmic scale.

[Part B]

Adverse events (including hypoglycemia events and DKA events), serious adverse events (SAEs) and adverse event leading to discontinuation of study drug (DAEs) will be summarized by treatment group (dapagliflozin 5 mg or 10 mg).

Efficacy analyses on change from baseline in HbA1c, GA, average glucose values measured by 6-point SMBG and post-prandial glucose values measured by 6-point SMBG, are to be analysed by Mixed Model with Repeated Measures (MMRM) to provide point estimate and 95% confidence intervals (95% CIs) for each dapagliflozin group. Efficacy analyses on percent change from baseline in total daily insulin dose and body weight will be conducted by MMRM on log-transformed values. No confirmatory statistical testing is planned and hence no multiplicity adjustment will be done in this study.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUCτ	Area under the plasma concentration time curve from 0 to τ
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRF	Case Report Form (electronic/paper)
CSII	Continuous subcutaneous insulin infusion
DAE	Discontinuation of study drug
DBP	Diastolic blood pressure
DKA	Diabetic Ketoacidosis
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ET	End of Treatment
FAS-B	Full analysis set -Part B
FFA	Free Fatty Acid
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
GA	Glycoalbumin
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice' (ICH GCP) and the Japanese 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications' (GCP Ordinance).
GFR	Glomerular filtration rate

Abbreviation or special term	Explanation
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HCG	Human chorionic gonadotropin
HDL-C	High-density lipoprotein cholesterol
HDPE	High-density polyethylene
HR	Heart rate
HRT	Hormone replacement therapy
IATA	International Airline Transportation Association
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
Investigators	Principal Investigator + Sub-investigator
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
MDI	Multiple daily injections
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
MOA	Mechanism of Action
NGSP	National Glycohemoglobin Standardization Program
PD	Pharmacodynamics
PI	Principal Investigator
PD-A	Pharmacodynamic set -Part A
PK	Pharmacokinetics
PK-A	Pharmacokinetic set -Part A
QD	qd quaque die, once daily
SAE	Serious adverse event
SAF-A	Safety set -Part A
SAF-B	Safety set -Part B
SBP	Systolic blood pressure
SGLT	Sodium-glucose cotransporter

Abbreviation or special term	Explanation
SMBG	Self monitored blood glucose
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Telephone contact
TG	Triglycerides
T_{max}	Time to maximum plasma concentration
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
WBDC	Web Based Data Capture
α-GI	α-glucosidase inhibitor

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Unmet Medical Need in Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a serious chronic disorder that results in the destruction of insulin-producing pancreatic β-cells. T1DM accounts for approximately 5-10% of all cases of diabetes worldwide, and its incidence continues to increase (Daneman 2006). Patients with T1DM require lifelong insulin therapy due to their inability to produce endogenous insulin. Insulin requirements in these subjects vary widely and depend on several factors including body weight, activity level, and food intake.

People with T1DM must balance the goal of long-term glycemic control and reduction of complications of the disease with the day-to-day challenges of insulin therapy. The major limiting factor for restoring euglycemia is insulin-related hypoglycemia (Cryer 2002). Unfortunately, recent data suggest hypoglycemia remains a common event, with 11.8% of subjects in a clinic registry study experiencing at least one episode of severe hypoglycemia resulting in seizure or loss of consciousness within the past 12 months (Weinstock et al 2013). The occurrence of severe hypoglycemia did not appear to be related to hemoglobin A1c (HbA1c). However, the risk of recurrent hypoglycemia episodes in T1DM can be related to the degree of glycemic variability, which suggests that reducing the swings in glucose may be of importance in this population (Kilpatrick et al 2007b).

Intensive insulin therapy is also associated with weight gain and insulin resistance, as evidenced in the Diabetes Control and Complications Trial, where subjects in the intensive treatment arm gained an average of 4.6 kg more than the control group over the 5 year study (Tajima N, Morimoto A 2012, The Diabetes Control and Complications Trial Research Group 1993, Kilpatrick et al 2007a). It has been postulated that the weight gain associated with intensive insulin treatment is related to reductions in urinary glucose excretion, increased appetite, and the ingestion of excess calories to manage or avoid hypoglycemia. Weight gain and insulin resistance may have a significant deleterious impact upon cardiovascular risk factors, at least in some people with T1DM, and has recently contributed to the concept of ‘double diabetes’ (Ferriss et al 2006, Cleland et al 2013).

Average HbA1c values greater than 8% have been reported in several large studies in people with T1DM, suggesting a large proportion of the population are unable to achieve recommended glycemic levels with insulin alone because of the challenges associated with insulin therapy (Soedamah-Muthu et al 2008, Beck et al 2012). Novel therapies used as an adjunct to insulin that improve glycemic control and provide important secondary benefits, such as reductions in insulin dose, hypoglycemia and glycemic variability, and attenuation of weight gain associated with insulin, address important unmet needs for people with T1DM.

Reported incidence rate of T1DM among those below 15 years of age is 1.5-2.5 per 100000 (Tajima N, Morimoto A 2012). The figure is relatively lower than the rate in Europe and the US and calculated population of patients with T1DM including all ages is estimated as from

70000 to 80000. Despite advances in intensive insulin therapy including Multiple Daily Injection (MDI) and Continuous Subcutaneous Insulin Injection (CSII) for T1DM, the date revealed that most people with T1DM in Japan still fail to meet therapeutic target.

The national health insurance has been providing coverage for CSII since 2000 and this therapy has been used in clinical practice in Japan since then, but less frequently than in the U.S. due to several reasons such as financial burden on patients, concerns regarding operation and safety of the device, and slower introduction of newest devices. In addition, α-GI is only approved for T1DM as an oral hyperglycemic agent in Japan (used without insulin) (Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013), although SYMLIN® has been used for patients with T1DM with Insulin in the US since 2005. Thus, finding new possible medication for combination therapy with insulin for T1DM patients is required in Japan.

1.1.2 Introduction of dapagliflozin and Study Rationale

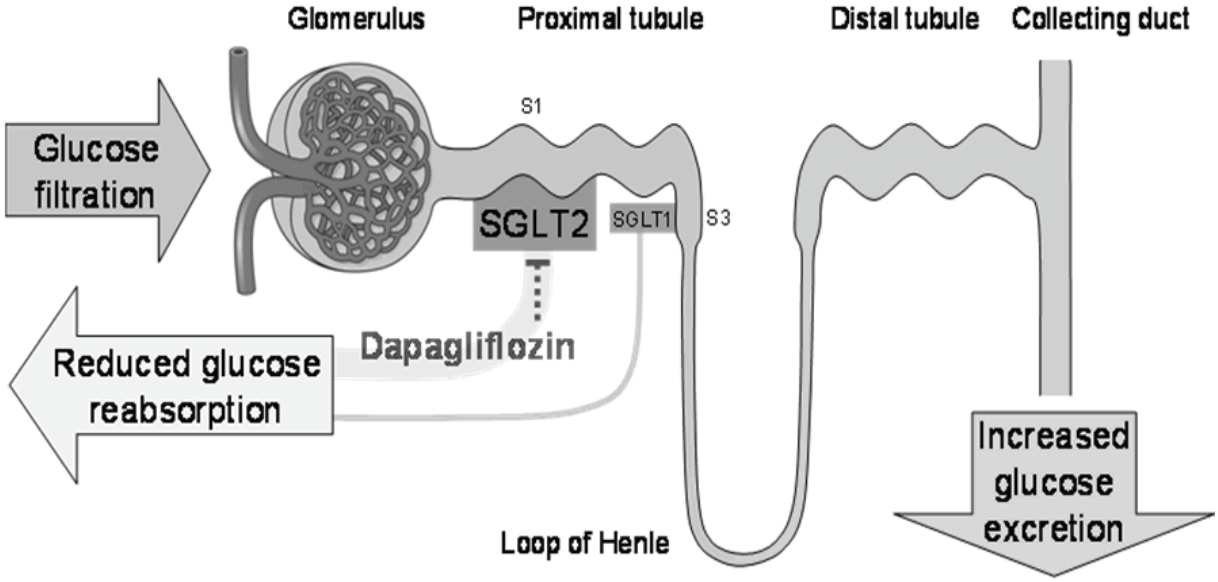
The study is designed to evaluate safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of dapagliflozin therapy in combination with insulin in Japanese subjects with T1DM who have inadequate glycemic control.

Dapagliflozin is a stable, competitive, reversible, highly selective, and orally active inhibitor of sodium glucose cotransporter 2 (SGLT-2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin has been approved for the treatment of type 2 diabetes mellitus (T2DM) in Japan on March 2014. Dapagliflozin is marketed in 40 countries/regions, including the European Union (EU; 5 or 10 mg dapagliflozin), United States (5 or 10 mg dapagliflozin), and Australia (10 mg dapagliflozin only), and is under investigation for marketing in numerous countries around the world.

The mechanism of action (MOA) for dapagliflozin is different from and complementary to the mechanisms of existing medications in other drug classes for T2DM, resulting in the direct, and insulin-independent, elimination of glucose by the kidney. Further, as SGLT-2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off-target (ie, non-kidney) effects. Therefore, no effects are observed on glucose and/or other carbohydrate transport or absorption in any other organs, including the gut, and no other transporters are affected. As such, dapagliflozin offers an important additional strategy for improving glycemic control as an add-on to insulin in patients with T1DM.

Urinary glucose excretion induced by dapagliflozin depends upon the amount of glucose filtered by the kidney (Figure 1). This filtered load is the product of the plasma glucose concentration and the glomerular filtration rate (GFR). Therefore, the action of dapagliflozin is dependent upon the patient's plasma glucose and renal function, and is independent of the patient's beta cell function or insulin sensitivity, which translates into a relatively low risk of hypoglycemia. Furthermore, because the mechanism reduces hyperglycemia independently of insulin secretion or action, this approach to anti-diabetic therapy provides an opportunity to achieve clinically important glycemic efficacy as an add-on to insulin in patients with T1DM.

Figure 1 How dapagliflozin Works (Mechanism of Action)



Currently, dapagliflozin as add on therapy to insulin is now being investigated as a potential treatment for patients with T1DM with inadequate glycemic control (defined as HbA1c ≥ 7.5%). Dapagliflozin may be a clinically relevant adjunctive therapy for patients with T1DM given its insulin-independent MOA. Because patients with T1DM are insulin deficient, insulin treatment is required for preventing ketoacidosis and ultimately for survival. Thus, dapagliflozin would not be a replacement for insulin therapy in the setting of T1DM. However, dapagliflozin reduces blood glucose levels by an insulin-independent mechanism and may be effective in improving glycemic control in patients with T1DM when used in combination with insulin. In the T1DM population, the inhibition of urinary glucose reabsorption via SGLT-2 inhibition is expected to produce a glucose lowering similar to that observed in the T2DM population, as well as the modest reductions in blood pressure and body weight. Furthermore, the amount of urinary glucose excreted following treatment with dapagliflozin is dependent upon the plasma glucose concentration, which may serve to blunt the excursions of glucose values over the course of the day (reduce glycemic variability) (Defronzo et al 2013).

The potential of dapagliflozin as a treatment option for the T1DM population was explored in a Phase 2a pilot study (MB102072) which was conducted in US. The MB102072 study was a randomized, double-blind, 5-arm, parallel-group, placebo-controlled exploratory trial to evaluate the safety, tolerability, PK and PD of dapagliflozin in subjects with T1DM who had inadequate glycemic control on insulin therapy. Subjects taking insulin monotherapy who met the central laboratory enrolment requirement of HbA1c ≥ 7.0% and ≤ 10.0% were randomly assigned in a 1:1:1:1:1 ratio to one of 5 blinded treatment arms: placebo, 1 mg, 2.5 mg, 5 mg, or 10 mg of dapagliflozin once daily. Subjects received dapagliflozin or matching placebo for

a total of 14 days and remained confined to the inpatient unit from Day -3 to Day 7, at which point they were discharged. Subjects then had outpatient visits on Day 10, Day 14, and a final visit on Day 21. In this pilot study, dapagliflozin was generally well tolerated at all doses in subjects with T1DM. Hypoglycemia events were frequent in this population during study treatment. Events were relatively balanced across treatment groups. Consistent with the known mechanism of action of dapagliflozin, dose-related increases in 24-hour urinary glucose were observed. Based upon the similar PK characteristics in subjects with T1DM compared to T2DM or healthy subjects, the exposure response relationship in terms of urinary glucose excretion appeared to be virtually identical in this T1DM population to that previously described in T2DM subjects, correcting for baseline differences in glycemic control and eGFR between the studies. Because dapagliflozin 5 mg was established as the minimally effective dose in T2DM and the marked similarities in the PK and PD response that drives efficacy, it is expected that dapagliflozin 5 mg will also be the minimally effective dose in subjects with T1DM.

In completed clinical studies in subjects with both T2DM and T1DM overseas, dapagliflozin was generally well-tolerated. No clinically relevant changes from baseline were seen in either renal function or serum electrolytes in subjects treated with dapagliflozin. In Phase 2/3 studies in subjects with T2DM, the frequency of overall adverse events (AEs) was similar to placebo. In the Phase 2 study in subjects with T1DM (MB102072), the frequency of overall AEs was similar to placebo. Compared to subjects with T2DM, hypoglycemia was more frequent in subjects with T1DM, but the frequency of hypoglycemia was relatively balanced across dapagliflozin treatment and placebo groups. Urine ketone tests revealed frequent positive urine ketones in this study, with a possibly slight increase in subjects receiving dapagliflozin 10 mg. No diabetic ketoacidosis (DKA) was observed during the study period (from the start of study drugs to the end of follow-up).

It is expected that dapagliflozin will exhibit an efficacy and safety profile in subjects with T1DM that will be similar to that observed in T2DM not only in the overseas but also in Japan. In fact, dapagliflozin may be a potentially novel adjunct to insulin therapy for the treatment of T1DM. Dapagliflozin potently decreases HbA1c and may provide important secondary benefits, such as reductions in total daily insulin dose, hypoglycemia, and glycemic variability and may attenuate the weight gain associated with insulin use to address important unmet needs for people with T1DM.

In Clinical Pharmacology studies, dapagliflozin exhibited similar PK and PD properties between Japanese and the US-based subjects both who were healthy and with T2DM. Study MB102072 conducted in the US studied dapagliflozin PK/PD in patients with T1DM at 1, 2.5, 5, and 10 mg. Comparing pooled exposure-response analysis of MB102072 to several T2DM studies showed that PK and exposure-response relationship after adjusting baseline parameters (fasting plasma glucose (FPG), urine glucose excretions (UGE) and eGFR) were virtually identical between patients with T1DM and T2DM in the US. All of the above results suggest that the PK/PD response to dapagliflozin in Japanese T1DM patients are expected to be similar to what were observed in T1DM patients in the US. Therefore, the protocol of Part A of this study such as endpoint, treatment period, major inclusion and exclusion criteria were

designed so that indirect comparison to results of Study MB102072 could be possible. The dose of dapagliflozin 5 and 10 mg were decided corresponding to the international Phase III study (MB102230). The objective of this Part A study of dapagliflozin to evaluate PK and PD in Japanese with T1DM then to prove our above hypothesis. With all of these understandings, we propose to conduct the PK/PD study in Japanese T1DM patients to both at 5 and 10 mg doses. In addition, we plan to add the data of this study to the previously pooled PK/PD data sets (T1DM and T2DM), in order to compare Japanese T1DM patients with T1DM patients in the US and T2DM patients as well. Furthermore, with the available model, we will be able to predict the PK/PD of other dose of dapagliflozin as needed in Japanese T1DM patients using all the data we collect. 24-hour urinary glucose excretion will be evaluated as primary variable for PD in PK/PD evaluation part of the study.

Part B study is designed to evaluate the long term safety of dapagliflozin in Japanese with T1DM.

The number of Japanese subjects with T1DM in Part B of this study was decided to ensure that ≥ 100 Japanese subjects in total (Japanese long-term + Global Phase III studies) received dapagliflozin for 1 year, whichever candidate is selected, in accordance with the ICH E1 guideline.

1.1.3 Product Development Background

Dapagliflozin has been designed as a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT-2. In the results from Japanese clinical studies for T2DM, it was demonstrated that dapagliflozin is associated with a significant reduction of HbA1c from baseline compared to placebo and dapagliflozin in combination with another antidiabetic agent is generally safe and well tolerated. Currently, the Phase IV study is ongoing in order to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of Japanese T2DM patients with inadequate glycemic control on insulin.

Besides data obtained from subjects with T2DM, results from MB102072, where dapagliflozin was added to insulin therapy in subjects with T1DM, showed that dapagliflozin 5 mg and 10 mg may improve glycemic control during a 2-week study period while reducing total daily insulin dose. In this pilot study, adverse events, including hypoglycemia and genitourinary infections, were generally balanced across treatment groups.

Additional clinical safety and efficacy information is available in the Investigator Brochure.

1.2 Rationale for study design, doses and control groups

1.2.1 Research Hypothesis

In Japanese subjects with T1DM that have inadequate glycemic control with insulin alone, the addition of dapagliflozin to adjustable insulin will result in a comparable PK and PD profile with non-Japanese patients in Part A, and long term safety of dapagliflozin in Part B.

1.3 Benefit/risk and ethical assessment

Dapagliflozin is being developed as a potential new therapy for hyperglycemia in subjects with T1DM. Considering the mechanism of action of dapagliflozin, the design features of this study (ie, the inclusion, exclusion, and discontinuation criteria), and the planned safety procedures, participation in this study presents a minimal risk.

As noted above, dapagliflozin has been effective at lowering glucose and HbA1c in subjects with T2DM, when studied as monotherapy, as well as in combination with insulin or oral anti-diabetic medications. In a recently concluded Phase 2a study (MB102072), the combination therapy of dapagliflozin with insulin when used in subjects with T1DM with inadequate glycemic control was assessed. In that study, dapagliflozin was found generally well-tolerated. Results from the study also suggested that treatment with dapagliflozin as add-on to insulin may have potential to reduce glucose levels, decrease glycemic variability, and reduce total daily insulin dose. Similar results were also reported in an 8-week study in which empagliflozin was added as an adjunct to insulin therapy in subjects with T1DM (Perkins et al 2014).

Potential risks

The potential risks associated with dapagliflozin have been identified based upon the mechanism of action, the preclinical results, and the extensive clinical experience to date, including a study combining it with insulin when used in subjects with T1DM. The benefits and risks associated with the investigational drug and insulin are well established and presented in their approved Investigator Brochure and prescribing information respectively. No study procedure will put subjects at a risk beyond those ordinarily encountered during the performance of routine medical examinations or tests.

Protection against risks

The present study has been designed with appropriate measures in place to monitor and minimize any of the potential health risks to participating subjects. In order to ensure the safety of all subjects participating in this study, the Sponsor will conduct a real-time review of all safety information from all ongoing clinical dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, AE reports, pre-clinical data, epidemiological studies and literature reports, and post-marketing reports to identify and characterize unrecognized safety risks or changes in those which are currently expected Adverse Drug Reactions. Any information that may affect the benefit-risk profile of dapagliflozin will be immediately communicated to relevant health authorities and appropriate actions will be taken regarding the clinical program as needed.

Given the potential increased risk of hypoglycemia when dapagliflozin is added on to insulin. In case of part A, the subjects would be observed carefully at the Investigator's site during the hospitalization period and communicate with the Investigators by regular telephone (fax or email) contact during outpatient following randomization to reduce the risk of hypoglycemia. In case of part B, it is recommended that subjects reduce their daily insulin doses by up to

20% for both basal and bolus insulin after the first dose of study drug on Day 1 following randomization to reduce the risk of hypoglycemia. In some cases it may be necessary to reduce insulin (particularly basal insulin) in advance of study drug administration. During the study, insulin dose may be adjusted as deemed appropriate to be consistent according to SMBG readings, local guidance and individual circumstances.

All studies which include dapagliflozin are subject to a carefully designed subject risk management plan. Investigators are also provided guidance on appropriate management of potential risks such as hypoglycemia, DKA, urinary tract infections and decreased renal function mentioned in the plan (see Section 5.3).

Potential benefits to subjects

As noted above, dapagliflozin added to background insulin therapy was well-tolerated in the Phase 2 study in subjects with T1DM (MB102072) and had a PK profile similar to the healthy and T2DM populations studied previously. Therefore, it is expected that the efficacy and safety profile of dapagliflozin in subjects with T1DM will be similar to that observed in T2DM subjects. Furthermore, because its mechanism is independent of insulin, dapagliflozin provides an opportunity to achieve clinically important glycemic efficacy in subjects with T1DM. In addition, all subjects will continue to receive insulin (dose can be adjusted) as active background therapy.

It is commonly observed that even subjects receiving placebo in diabetes studies show some improvement in glycemic control, likely due to their increased compliance to dietary and exercise counselling. This improvement is expected for subjects in this trial that participate in Part A.

Subjects are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes multiple clinic visits and physical examinations over the 52 week study in Part B. Subjects will also receive counselling on diet and exercise.

1.4 Study Design

The study is designed to evaluate safety, efficacy, PK and PD of dapagliflozin therapy in combination with insulin in Japanese subjects with T1DM who have inadequate glycemic control.

1.4.1 PK and PD evaluation part (Part A)

The study design of Part A is a randomized, single-blind, 3 arm, parallel-group, placebo-controlled design. Forty-two subjects will be randomized in a 1:1:1 ratio into one of the three blinded treatment arms.

Potential subjects will be assessed for eligibility criteria at the screening visit. On Day 1, subjects who meet all the protocol-specific enrolment and randomization inclusion criteria and meet none of the exclusion criteria will be randomized into one of the three single-blinded

treatment arms (dapagliflozin 5 mg QD, dapagliflozin 10 mg QD, or placebo QD) in a 1:1:1 ratio.

Subjects will receive dapagliflozin 5 mg QD, 10 mg QD, or placebo QD for 7 days, and a 1-week follow-up evaluation. Besides study medications, subjects will be treated with MDI (3 or more injections per day of basal and bolus insulin).

The randomized subject will be observed within 24 hours after first dose of study drug on Day 1 at the Investigator's site in order to adjust their daily insulin doses for both basal and bolus insulin to reduce the risk of hypoglycemia. Subjects will be monitored closely with regard to safety parameters, including vital signs, safety laboratory tests, and adverse events.

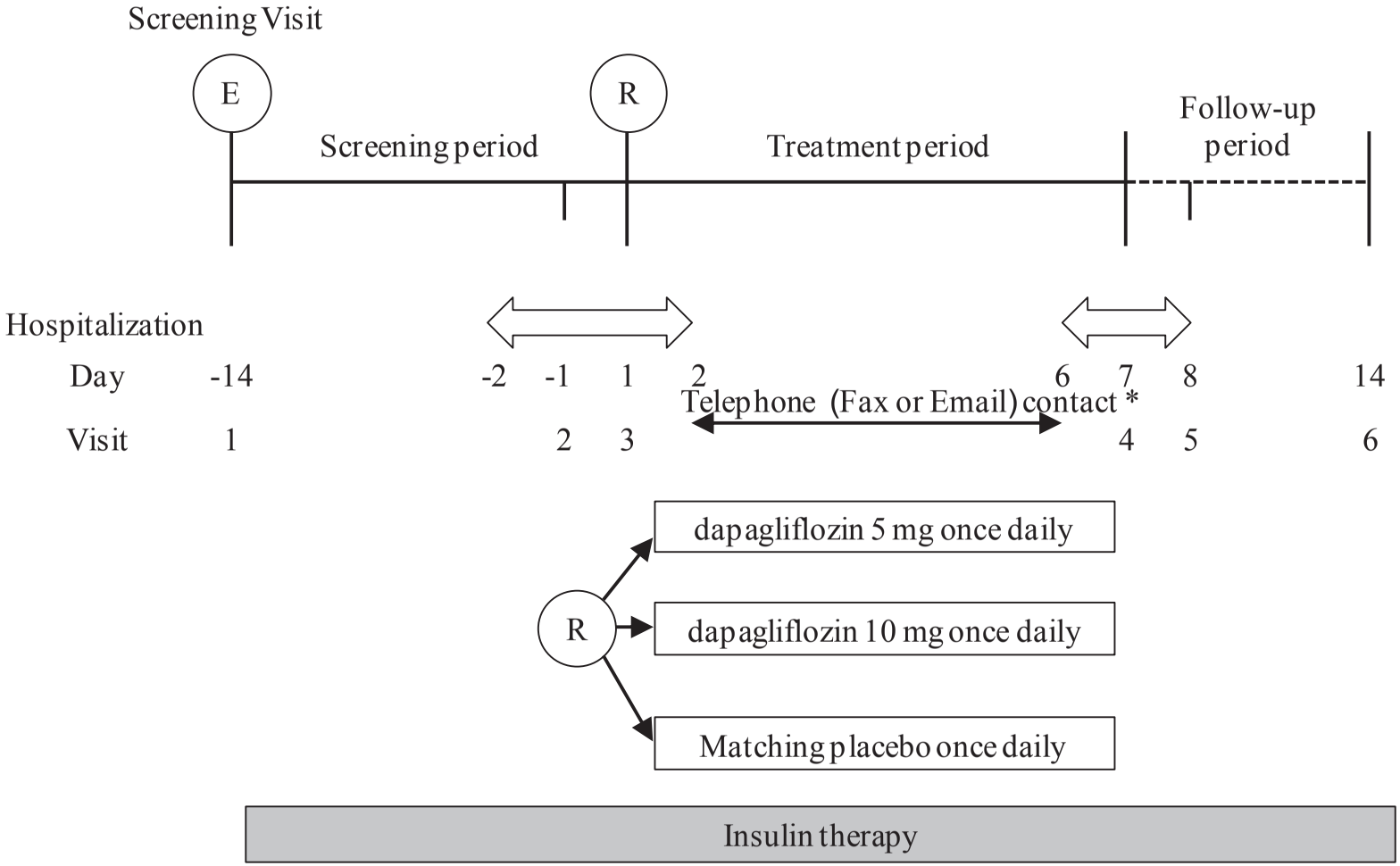
Because this is a short-term study, the primary goal for insulin adjustment is to avoid significant hyperglycemia or hypoglycemia, rather than strict glycemic control. Insulin adjustment is not performed to 'fine tune' glycemic control, but rather to ensure patient safety in the event that there is a significant change in insulin requirements. Maintaining the majority of blood glucose readings between 70 - 220 mg/dL is considered adequate glycemic control for subjects during the course of this study. In general, the goal was to maintain FPG between 70 - 140 mg/dL and postprandial blood glucose below 220 mg/dL, although these goals are individualized based upon a specific subject's personal targets and stability of glycemic control at baseline. The two main scenarios in which insulin adjustment was appropriate are unexpected events of either hypoglycemia or hyperglycemia. An unexpected event is defined as an event that could not be explained by circumstances such as dietary (missed or unusually high carbohydrate meal), strenuous exercise, error in insulin dosing, etc. In subjects with one or more unexpected events of hypoglycemia or hyperglycemia, insulin dosing is to be adjusted.

In the event insulin dose adjustment is deemed necessary, the Investigators will guide insulin dose changes, based upon review of the insulin and glucose logs, as well as potential circumstances that may have contributed to erratic glucose control (eg, insulin dosing errors, missed meals, unusual physical activity, etc). In addition, consultation with the subject and/or appropriate representatives of the subject's diabetes management team is strongly recommended

Subjects should self-monitor their blood glucose at least 7 times per day (generally before and after breakfast, lunch, dinner, and bedtime) during the treatment period, and in the occurrence of hypoglycemic symptoms, and to contact the Investigators in the event of an unusually high or low blood glucose value. In addition, study subjects should comply with the site's instructions with regard to self-monitoring of blood glucose and insulin adjustments accordingly and should report to the Investigators blood glucose values and/or signs and symptoms suggestive of a hypoglycemic episode.

The study design schematic is presented in Figure 2.

Figure 2 Study Design Schematic (Part A)



E: Enrolment, R; Randomization
* Subjects must report the values on Day 3 to 5 by telephone (fax or email) at least once a day.

1.4.2 Long term treatment part (Part B)

The study design of Part B is a randomized, open-label, 2 arms, and parallel-group design. One hundred forty subjects will be randomized in a 1:1 ratio into one of the two treatment arms.

Potential subjects who will join the study from part B will be assessed for eligibility criteria at the screening visit. A wash-out period is applicable only for subjects who received α-GI at enrolment or within one month before enrolment. Eligible subjects who are treated with insulin only, will skip the period and directly proceed to the randomization. On Day 1, subjects who meet all the protocol-specific enrolment and randomization inclusion criteria and meet none of the exclusion criteria will be randomized into one of the 2 open-label treatment arms (dapagliflozin 5 mg QD or dapagliflozin 10 mg QD) in a 1:1 ratio. Randomization will be stratified by the following factors to ensure equal representation across all treatment groups:

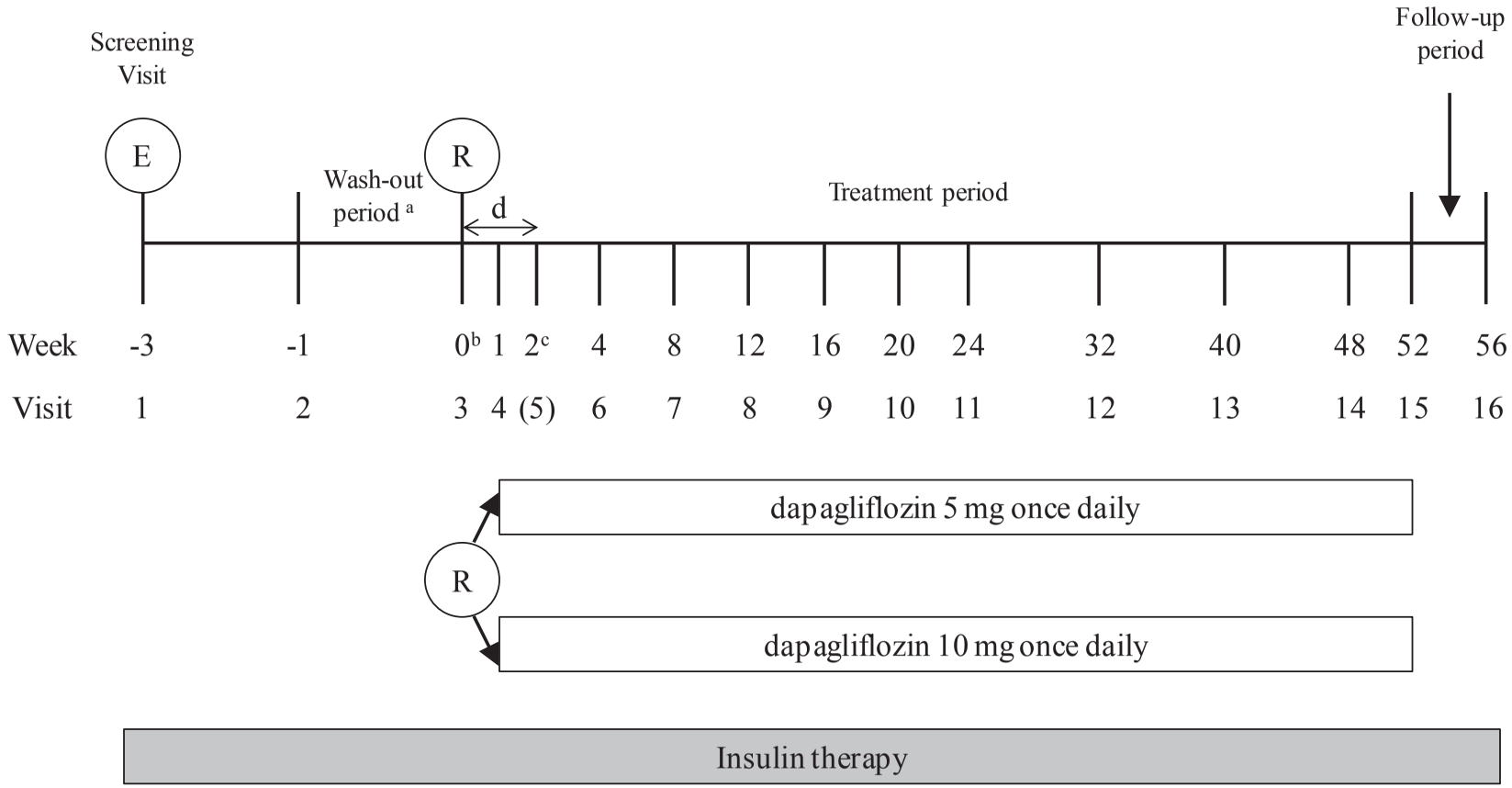
- HbA1c < 9.0% vs. ≥ 9.0% at screening visit

Subjects will receive dapagliflozin 5 mg QD or 10 mg QD for 52 weeks, and a 4-week follow-up evaluation. Besides study medications, subjects will be treated with MDI (3 or more injections per day of basal and bolus insulin) or CSII.

It is recommended that subjects reduce their daily insulin dose by up to 20% for both basal and bolus insulin after the first dose of study medication to minimize the risk of hypoglycemia. In some cases it may be necessary to reduce insulin (particular basal insulin) in advance of study drug administration. It is at the discretion of the Investigators to determine the extent to which to reduce the insulin doses. Throughout the study during the treatment period, insulin dose may be adjusted as deemed appropriate to be consistent according to SMBG readings, local guidance and individual circumstances. Subjects will be monitored closely with regard to safety parameters, including vital signs, safety laboratory tests, and adverse events.

The study design schematic is presented in Figure 3.

Figure 3 Study Design Schematic (Part B)



E: Enrolment, R; Randomization

a Wash-out period is applicable only for subjects who are on an α-GI at enrolment or within one month before enrolment. Subjects on insulin only as their diabetes treatment will skip the period and directly proceed to the Visit 3.

b Day 1 of Week 0 means the stating day of dapagliflozin.

c Either hospital visit or telephone (fax or email) contact is acceptable for visit at Week 2.

d On Day 2, 4 and 10 patients must contact the Investigators by phone (fax or email) and report the patient's condition (including glucose and ketone values from SMBG). The investigators must indicate appropriate insulin adjustment. There is time window ± 1 day for Day 4 and 10.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
[Part A] To evaluate the PK and PD of 7 days repeated doses of dapagliflozin in Japanese patients with T1DM with inadequate glycemic control under standard insulin therapy.	PK variables: C_{max}, T_{max}, AUCτ for dapagliflozin and dapagliflozin 3-O-glucuronide, and ratio of dapagliflozin 3-O-glucuronide AUCτ to dapagliflozin AUCτ. PD variables: Change from baseline in 24-hour urinary glucose excretion on Day 7.
[Part B] To evaluate safety and tolerability of long-term treatment (52 weeks) of dapagliflozin in Japanese patients with T1DM with inadequate glycemic control under standard insulin therapy.	Adverse event (including AEs of hypoglycemia and DKA events), physical examination, vital signs (blood pressure, heart rate), ECG, and clinical laboratory measures, urine test.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
[Part A] To evaluate the PD of 7 days repeated doses of dapagliflozin in Japanese patients with T1DM with inadequate glycemic control under standard insulin therapy.	Change from baseline in FPG on Day 7, daily insulin dose, SBP
[Part A] To assess the safety and tolerability of 7 days repeated doses of dapagliflozin in Japanese patients with T1DM with inadequate glycemic control under standard insulin therapy.	Adverse event (including AEs of hypoglycemia and DKA events), physical examination, vital signs (blood pressure, heart rate), ECG and clinical laboratory measures, urine test.

Secondary Objective:	Outcome Measure:
[Part B] To assess the efficacy of long-term treatment (52 weeks) of dapagliflozin 5mg and 10 mg in Japanese patients with T1DM inadequately controlled on insulin therapy.	Change from baseline in HbA1c at Week 24 and 52 Change from baseline in GA at Week 24 and 52 Change from baseline in average glucose values measured by 6-point SMBG at Week 24 and 52 Change from baseline in postprandial glucose values measured by 6-point SMBG at Week 24 and 52 Percent change from baseline in total daily insulin dose at Week 24 and 52 Percent change from baseline in body weight at Week 24 and 52 Proportion of subjects with HbA1c reduction from baseline of at least 0.5% without severe hypoglycemia events at Week 24 and 52 Proportion of subjects with HbA1c reduction from baseline of at least 0.5% at Week 24 and 52 Proportion of subjects with HbA1c < 7.0% at Week 24 and 52 Change from baseline to Week 24 and 52 in seated SBP among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg

2.3 Safety objectives

Safety Objective:	Outcome Measure:
Not applicable	Not applicable

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
[Part A] Explore relationship between 7-point SMBG measurements and other PD variables	7-point SMBG measurements, 24-hr urinary glucose, total daily insulin dose and their changes from baseline
[Part B] The efficacy evaluation will be made by comparing subgroups BMI <25.0 kg/m^2 or BMI ≥ 25.0 kg/m^2.	Change from baseline in HbA1c, GA, average/post-prandial glucose values measured by 6-point SMBG, and percent change from baseline in body weight, total daily insulin dose by subgroup defined by BMI.

3. SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Signed Written Informed Consent

   Subjects or their legally responsible representatives must be willing and able to give signed and dated written informed consent. In the case of the subject was under the age of 20, their legally responsible representatives must be willing and able to give signed, relationship and dated written informed consent.

2. Target Population

(a) Diagnosis of T1DM. In addition, the following criteria also needs to be met; Central laboratory test of C-peptide < 0.7 ng/mL

(b) Subject re-enrolment: This study does not permit the re-enrolment of a subject who has discontinued the study as a screen failure

3. Insulin use for at least 12 months prior to the enrolment per subject report or medical records and

(a) Method of insulin administration (MDI or CSII) must have been unchanged for at least 3 months prior to the enrolment per subject report or medical records. Subjects must be taking a total daily insulin dose of ≥ 0.3 U/kg/day for at least 3 months prior to the enrolment. In Part A, CSII users are excluded.

(b) If on MDI insulin administration subject must be on ≥ 3x injections per day.

4. Gender and reproductive Status

(a) Japanese men and women, inclusive

(b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

(c) Women must not be breastfeeding.

(d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with dapagliflozin.

Criteria for Part A

5. HbA1c eligibility criteria include:

(a) Screening Visit: Central laboratory HbA1c ≥ 7.0 % and ≤ 10.0 % (One repeat HbA1c test for subjects in screening if their initial test result was an HbA1c ± 0.2% of the cut off values)

6. BMI ≥ 20.0 kg/m², ≤ 35.0 kg/m² at Visit 1

7. Ages 18 to 65 years, inclusive

8. ≥ 18 years old and < 20 years old must have assent forms signed and dated by their parents or guardians

Criteria for Part B

9. HbA1c eligibility criteria include:

(a) Screening Visit: Central laboratory HbA1c ≥ 7.5% and ≤ 10.5% (One repeat HbA1c test for subjects in screening if their initial test result was an HbA1c ± 0.2% of the cut off values)

10. BMI ≥ 20.0 kg/m² at Visit 1

11. Age 18 to 75 years, inclusive

12. ≥ 18 years old and < 20 years old must have assent forms signed and dated by their parents or guardians

3.1.1 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In additional, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.*

* Females treated with hormone replacement therapy (HRT), are likely to have artificially suppressed FSH levels and may require a wash-out period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the Investigators should use their judgment in checking serum FSH levels. If the washout period exceeds 4 weeks, the subject must have all enrolment procedures and laboratory assessments repeated and all of these must meet enrolment eligibility criteria. The subject's number will however remain the same as initially assigned. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require wash-out periods as long as 6 months.

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Target Disease Exceptions

(a) History of T2DM

In cases where the subject has a history of T2DM and has a documented history of being auto-antibody positive for GAD65, tyrosine phosphatase IA-2/IA-2β, or Zinc Transporter 8 (ZnT8), or fasting c-peptide value below the lower limit of detection performed by local or central laboratory, the subject will be eligible for screening

(b) Maturity onset diabetes of young (MODY)

(c) Pancreatic surgery, chronic pancreatitis, or other pancreatic disorders that could result in decreased β-cell capacity (eg, pancreatogenous diabetes)

Criteria for Part A

(d) Any anti-hyperglycemic agent use, other than thiazolidinediones, or insulin, within 1 month prior to the screening visit.

(e) Use of thiazolidinediones within 6 months prior to the screening visit

Criteria for Part B

(f) Any anti-hyperglycemic agent use, other than α-GI or insulin, within 1 month prior to the enrolment.

α-GI users at the enrolment or within 1 month prior to the enrolment are permitted to enter this study, if subjects can conduct wash-out of the drug.

(g) Use of thiazolidinediones within 6 months prior to the enrolment

(h) History of DKA requiring medical intervention (eg, emergency room visit and/or hospitalization) within 1 month prior to the enrolment

(i) History of hospital admission for glycemic control (either hyperglycemia or hypoglycemia) within 1 month prior to the enrolment

(j) Frequent episodes of severe hypoglycemia as defined by more than one episode requiring medical assistance, emergency care (paramedics or emergency room care), and/or glucagon therapy administered by a third-party individual within 1 month prior to the enrolment

(k) Symptoms of poorly controlled diabetes that would preclude participation in this trial including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during the three months prior to the enrolment, or other signs and symptoms.

(l) History of Addison's disease or chronic adrenal insufficiency

(m) History of diabetes insipidus

2. Medical History and Concurrent Diseases

(a) Any of the following cardiovascular (CV) /vascular disease within 6 months of the enrolment:

1) Myocardial infarction
2) Cardiac surgery or revascularization (coronary artery bypass surgery [CABG]/percutaneous transluminal coronary angioplasty [PTCA])
3) Unstable angina
4) Unstable congestive heart failure (CHF)
5) New York Heart Association (NYHA) CHF Class III or IV
6) Transient ischemic attack (TIA) or significant cerebrovascular disease
7) Unstable or previously undiagnosed arrhythmia

(b) Renal disease:

1) History of unstable or rapidly progressing renal disease
2) Conditions of congenital renal glucosuria
3) Renal allograft

(c) Hepatic diseases:

1) Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency

(d) Hematological and oncological disease/conditions:

1) History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis
2) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus

3) Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of > 400 mL of blood during the 8 weeks prior to the enrolment
4) Malignancy within 5 years of the enrolment (with the exception of treated basal cell or treated squamous cell carcinoma)
5) History of bladder cancer
6) History of radiation therapy to the lower abdomen or pelvis at any time

(e) Unstable pre-proliferative and proliferative retinopathy (untreated or under treatment).

3. Physical and Laboratory Test Findings

(a) Aspartate aminotransferase (AST) > 3x upper limit of normal (ULN)

(b) Alanine aminotransferase (ALT) > 3x ULN

(c) Serum total bilirubin (TB) > 2.0 mg/dL (34.2 μmol/L)

(d) [Criteria for Part A only] Estimated GFR (eGFR) by the Japanese Society of Nephrology formula ≤ 60 mL/min/1.73m^2

[Criteria for Part B only] Estimated GFR (eGFR) by the Japanese Society of Nephrology formula ≤ 45 mL/min/1.73m^2

(e) Hemoglobin ≤ 11.0 g/dL (110 g/L) for men; hemoglobin ≤ 10.0 g/dL (100 g/L) for women.

(f) Positive for hepatitis B surface antigen or anti-hepatitis C virus antibody

(g) Abnormal Free T4

NOTE: Abnormal TSH value at enrolment will be further evaluated for free T4. Subjects with abnormal free T4 values will be excluded.

4. Allergies and Adverse Drug Reaction

(a) Allergies or contraindication to the contents of dapagliflozin tablets or insulin.

5. Sex and Reproductive Status

(a) Women who are pregnant

6. Other Exclusion Criteria

(a) Prisoners or subjects who are involuntarily incarcerated

(b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

(c) Subjects on a commercial weight loss program with ongoing weight loss, or on an intensive exercise program.

(d) History of bariatric surgery or lap-band procedure within 12 months prior to screening.

(e) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to the Day 1 visit

NOTE: Topical or inhaled corticosteroids are allowed

(f) Any unstable endocrine, psychiatric or rheumatic disorders as judged by the Investigators

(g) Volume depleted subjects. Subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics who cannot carefully monitor their volume status should be excluded from the study.

(h) Subject is, in the judgment of the Investigators, unlikely to comply with the protocol, or is unable to correctly self administer subcutaneous insulin injections and/or manage their insulin pump, or has any severe concurrent medical or psychological condition that may affect the interpretation of efficacy or safety data.

(i) Subject with any condition which, in the judgment of the Investigators, may render the subject unable to complete the study or which may pose a significant risk to the subject.

(j) Subject is currently abusing alcohol or other drugs or has done so within the last 6 months prior to the enrolment.

(k) Subject is a participating Investigators, study coordinator, employee of an investigator or immediate family member of any of the aforementioned.

(l) Employee of Bristol-Myers Squibb, AstraZeneca, or their relatives.

(m) Participation in other clinical study within 30 days of the enrolment.

(n) Previous use of SGLT2 inhibitor.

(o) No clinical conditions or clinically significant abnormalities, in any laboratory value(s) collected after screening and prior to randomization which, in the Investigator’s judgment, should preclude entry into the treatment period.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment and randomization

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject or their guardian/legal representative before any study specific procedures are performed.

2. Perform enrolment call in Interactive Web Response System (IWRS).

3. Assign potential subject a unique enrolment number "E43XXYYY", which is composed of 4 digits (43XX) of centre number and 3 digits (YYY) of consecutive number in order of enrolment registration at each study site.

4. Determine subject eligibility. See Sections 3.1 and 3.2.

5. Perform drug allocation call for randomization at visit 3 in IWRS.

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

Routines for this will be described in the IWRS user manual that will be provided to each centre.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigators should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigators regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

3.5.1 PK and PD evaluation part (Part A)

Following completion of the screening period, subjects who meet the criteria will be randomly assigned by the IWRS at the Day 1 Randomization visit, to one of the following 3 single-blind treatment arms in a 1:1:1 ratio using a centralized randomization schedule:

1. Blinded dapagliflozin 5 mg dose group

2. Blinded dapagliflozin 10 mg dose group

3. Blinded placebo dose group

Randomization schedules for subject treatment will be generated and kept by AstraZeneca.

3.5.2 Long term treatment part (Part B)

Following completion of the screening period or wash-out period, subjects who meet the criteria will be randomly assigned by the IWRS at the Day 1 Randomization visit, to one of the following 2 open-label treatment arms in a 1:1 ratio using a centralized randomization schedule:

Treatment allocation for patients randomized will be done by following procedure:

1. dapagliflozin 5 mg tablet, once daily

2. dapagliflozin 10 mg tablet, once daily

Randomization will be stratified by:

- HbA1c < 9.0% vs. ≥ 9.0% at screening visit

Randomization schedules for subject treatment will be generated and kept by AstraZeneca.

3.6 Methods for ensuring blinding (in Part A)

The Centralized Registration/ Randomization Center will assign the study material to be dispensed to each subject. Each dose will be identical and presented to ensure blinding of the medication.

3.7 Methods for unblinding (in Part A)

Since Part A is conducted with single blind, the methods for unblinding for the site is not needed.

For those personnel analysing the PK samples, the randomization code will be provided to ensure that only samples from patients who were on active study treatment are analysed. Samples from patients not dosed with the relevant active study treatment will only be analysed

on a "for cause" basis, for example if there is suspicion that a patient has been dosed incorrectly.

3.8 Restrictions

Subjects who join Part A

- Subjects who join the Part A should enter the hospital from Day -2 to Day 2 and Day 6 to Day 8.
- Subjects must abstain alcohol from Day -2 to discharge from hospital on Day 8.
- Subjects must abstain from excessive exercise from Day -2 to discharge from hospital on Day 8. Light work only is recommended.
- Subjects must abstain from sauna from Day -2 to discharge from hospital on Day 8.
- Subjects must be in a fasting state at least 10 hours prior to fasting blood sampling (however, drinking water is allowed). Permitted medications may be taken with water only.

Subjects who join Part A or Part B

- Subjects should not use tobacco/nicotine/alcohol within 8 hours prior to study visit with blood pressure and heart rate (HR) measurements.
- Subjects must make every attempt to adhere to the dietary and physical activity changes and goals as discussed with the Investigator(s).
- Women of child-bearing potential must immediately contact the Investigators if they suspect they might be pregnant and if they have changed, or plan to change their birth control method.
- Subjects must comply with their prescribed dosing regimen to preserve study integrity and ensure subject safety.
- Subjects should be cautioned that any new prescription medication or over-the-counter or herbal/nutritional therapies should be discussed thoroughly with the Investigators, as concomitant use could result in alterations to their glycemic control and may place them at risk for significant hypoglycemic episodes.

If a subject arrives for a visit without having followed the above instructions, the entire visit should be rescheduled (within the allowed visit-window, if possible).

3.9 Discontinuation of investigational product

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the Investigators) for any of the following reasons:

- Subject’s request to stop study treatment
- Withdrawal of informed consent (subject’s decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the Investigators, indicates that continued participation in the study is not in the best interest of the subject

- Unblinding a subject for any reason (emergency or non-emergency) (in Part A)
- Pregnancy
- Termination of the study by the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Estimated GFR (eGFR) by the Japanese Society of Nephrology formula < 30 mL/min/1.73m^2
  - If at any time the subject's eGFR (based on Japanese Society of Nephrology formula) falls below 30 mL/min calculated at the central laboratory and confirmed at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the subject should be discontinued from study medication.
  - If at any time the subject's eGFR (based on Japanese Society of Nephrology formula) falls below 30 mL/min calculated at local laboratory, a central laboratory eGFR should be obtained promptly. If the eGFR is confirmed by the central laboratory and persists at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the subject should be discontinued from study medication.
- Subjects experience at least one protocol-defined on Section 3.9.1.1 hypoglycemia episode that leads to a loss of consciousness and/or seizure as determined by the Investigators
- Change of insulin administration method (eg, switch from MDI to CSII or vice versa)
- Note: Subjects are not allowed to change their insulin administration methods (MDI or CSII) throughout the study. Under certain situations (eg, the replacement of an insulin pump), the subjects who are on CSII may be on temporary use of MDI. They should restart CSII administration as early as feasible. The period of time when a subject is on temporary use of MDI should not be more than 2 weeks.
- Subjects with a central laboratory ALT and/or AST > 3x ULN will be scheduled for a follow-up visit within 3 days following the receipt of the result (see Appendix D for further guidance). Subjects should be discontinued from study if the initial and repeat laboratory tests meet any of the following criteria:
  - ALT and/or AST are > 3x ULN and total bilirubin (TB) > 2x ULN
  - ALT and/or AST are > 5x ULN for ≥ 14 consecutive days, at any time after initial confirmatory results
  - ALT and/or AST are ≥ 10x ULN

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study (ie, investigational product and assessments – see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 4.4); diary cards and all study drugs should be returned by the subject.

If a subject is withdrawn from study, see Section 3.10.

3.9.1.1 Discontinuation Guidelines due to Protocol-Defined Hypoglycemia Episode or Recurrent Hypoglycemia Episodes

Subjects should not be discontinued from any treatment phase based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated (see the criteria below). The assessment of a single fingerstick or central laboratory glucose value should not be the sole assessment used to determine subject discontinuation due to hypoglycemia.

Subjects should be discontinued from study drug if they meet any of the following criteria:

- At least one hypoglycemia episode that leads to loss of consciousness and/or seizure
- Severe/recurrent hypoglycemia episodes where the possibility of down-titration of contributing concomitant medication(s) (other than single-blind study medication), and/or contributing factors (eg, excessive physical activity) have been evaluated and corrected.

NOTE: Dose titration is not permitted at any time during the treatment period in part A and Part B.

Section 5.3.1.2 provides additional guidance on management and reporting of hypoglycemia.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as ‘Incorrect Enrolment’ (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). If possible, they will be seen and assessed by an investigator. AEs

will be followed up (See Sections 6.3.2 and 6.4); diary, blood glucose/ketone meters and all study drugs should be returned by the subject.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study schedule for Part A

Period	**Screening**		**Treatment period[b]**				**Follow-up period [b, c]**
Week (Day)	**Week -2 (Day -14)**	**-1 (Day -1)**	**0 (Day 1)[a]**	**0 (Day 3 to Day 5)**	**1 (Day 7)**	**1 (Day 8)**	**2 (Day 14)**
Visit	**1**	**2**	**3**	**-**	**4**	**5**	**6**
Visit window (days)	**+7**	**-**	**0**	**-**	**+2**	**-**	**+2**
Eligibility Assessments							
Informed Consent	X [d]						
Review Inclusion/Exclusion	X	X	X				
Review Medical History	X	X	X				
General procedures							
Complete Physical Examination	X						
Brief Physical Examination		X	X		X	X	X
Vital Signs (BP, HR), Body Weight	X	X	X		X	X	X
Height	X						
12-lead ECG	X					X	X
Weight (BMI)	X		X			X	
Review concomitant medications/procedures	X	X	X		X	X	X
Provide Dietary and Exercise Counselling	X		X (Day 2)			X	
Dispense subject diaries, blood glucose/ketone meters and provide instructions	X					X	

Table 1 Study schedule for Part A

Period	**Screening**		**Treatment period[b]**				**Follow-up period [b, c]**
Week (Day)	**Week -2 (Day -14)**	**-1 (Day -1)**	**0 (Day 1)[a]**	**0 (Day 3 to Day 5)**	**1 (Day 7)**	**1 (Day 8)**	**2 (Day 14)**
Visit	**1**	**2**	**3**	**-**	**4**	**5**	**6**
Visit window (days)	**+7**	**-**	**0**	**-**	**+2**	**-**	**+2**
Review subject diaries		X	X (Day 2)		X	X	X
Adjust Insulin Dose, as needed	←	―	―	―	―	―	→
Hospitalization		← (From Day -2)	― (Discharge at Day 2)			(From Day 6) →	
Telephone (fax or email) contact				X (at least once a day)			
Safety Assessments							
Assess Adverse Events	←	―	―	―	―	―	→
Assess Hypoglycemia Episodes	←	―	―	―	―	―	→
Assess Diabetic Ketoacidosis	←	―	―	―	―	―	→
7-point SMBG		←	―	―	→		
Laboratory Assessments							
Blood Standard Safety Laboratory Test	X		X			X	X
Urine Standard Safety Laboratory Test	X		X			X	X

Table 1 Study schedule for Part A

Period	**Screening**		**Treatment period[b]**				**Follow-up period [b, c]**
Week (Day)	**Week -2 (Day -14)**	**-1 (Day -1)**	**0 (Day 1)[a]**	**0 (Day 3 to Day 5)**	**1 (Day 7)**	**1 (Day 8)**	**2 (Day 14)**
Visit	**1**	**2**	**3**	**-**	**4**	**5**	**6**
Visit window (days)	**+7**	**-**	**0**	**-**	**+2**	**-**	**+2**
Pregnancy test (serum) WOCBP only	X						
Pregnancy test (urine) WOCBP only			X			X	X
Urine (dipstick)	X		X			X	X
Microscopic urinalysis	X		X			X	X
24-hour urine collection for Glucose, Sodium, Uric Acid and Creatinine [e]		X	X		X	X	
Blood sampling for pharmacokinetics [e]			X		X	X	
FPG			X		X	X	
C-peptide	X						
Hepatitis Screen Panel	X						
TSH	X						
HbA1c	X		X				
Study Drug Supply							
Randomize			X				
Dispense Study Drug			X				

Table 1 Study schedule for Part A

Period	**Screening**		**Treatment period[b]**				**Follow-up period [b, c]**
Week (Day)	**Week -2 (Day -14)**	**-1 (Day -1)**	**0 (Day 1)[a]**	**0 (Day 3 to Day 5)**	**1 (Day 7)**	**1 (Day 8)**	**2 (Day 14)**
Visit	**1**	**2**	**3**	**-**	**4**	**5**	**6**
Visit window (days)	**+7**	**-**	**0**	**-**	**+2**	**-**	**+2**
Contact IWRS	X		X			X	
Review study drug dosing			X	X	X		

a Day 1 of Week 0 means the stating day of dapagliflozin. The previous day of Day 1 is shown as "Day -1"
b The results of urine glucose (dipstick, spot urine and 24-hour collection urine) at central laboratory are blinded for subjects during the treatment period.
c If a patient meet any study discontinuation criteria, the patient should receive the 1 week follow-up evaluation (Tests and evaluations of Visit 4 are unnecessary).
d If a patient performed Informed Consent only, it is to allowed be out of visit window.
e The detail is referred to Table 2.

Table 2 Time schedule of PK and PD sample collection (Part A)

Date	Time after administration (hour)	Blood sampling for PK	Urine sampling for PD
Day -1			24-hour sampling
Day 1	Pre dose of dapagliflozin	X	
Day 7	Pre dose (60 minutes prior to dapagliflozin dose, ±5 minutes)	X	
	0 (dapagliflozin dose)		24-hour sampling
	0.5 (±5 minutes)	X	
	1 (±10 minutes)	X	
	2 (±10 minutes)	X	
	3 (±10 minutes)	X	
	4 (±20 minutes)	X	
	6 (±30 minutes)	X	
	8 (±40 minutes)	X	
	12 (±60 minutes)	X	
Day 8	24 (±60 minutes)	X	

Table 3 Study schedule (Part B)

Period	**Screening**	**Wash-out[a]**	**Treatment period**											**Follow-up period[d]**
Week	**-3**	**-1**	**0[b]**	**1**	**2[c]**	**4**	**8**	**12**	**16**	**20**	**24**	**32, 40, 48**	**52**	**56**
Visit	**1**	**2**	**3**	**4**	**(5)**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14**	**15**	**16**
Visit window (days)	**-7**	**±3**	**0**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**
Eligibility Assessments														
Informed Consent [e]	X													
Review Inclusion/Exclusion	X	X	X											
Review Medical History	X	X	X											
General procedures														
Telephone (fax or email) contact (TC) [f]			←	—	→									
Complete Physical Examination	X													
Brief Physical Examination		X	X			X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR), Body Weight	X	X	X			X	X	X	X	X	X	X	X	X
Height	X													
12-lead ECG	X										X		X	X
Weight (BMI)	X	X	X			X	X	X	X	X	X	X	X	X

Table 3 Study schedule (Part B)

Period	**Screening**	**Wash-out[a]**	**Treatment period**											**Follow-up period[d]**
Week	**-3**	**-1**	**0[b]**	**1**	**2[c]**	**4**	**8**	**12**	**16**	**20**	**24**	**32, 40, 48**	**52**	**56**
Visit	**1**	**2**	**3**	**4**	**(5)**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14**	**15**	**16**
Visit window (days)	**-7**	**±3**	**0**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**
Review concomitant medications/ procedures	X	X	X	X		X	X	X	X	X	X	X	X	X
Provide Dietary and Exercise Counselling	X	X	X			X	X	X	X	X	X	X	X	
Dispense subject diaries, blood glucose/ketone meters and provide instructions	X	X	X			X	X	X	X	X	X	X	X	
Review subject diaries		X	X	X		X	X	X	X	X	X	X	X	X
Adjust Insulin Dose, as needed	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Safety Assessments														
Assess Adverse Events	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Assess Hypoglycemia Episodes	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Assess Diabetic Ketoacidosis	←	←	←	←	←	←	←	←	←	←	←	←	←	→
4-point SMBG			←	←	←	←	←	←	←	←	←	←	←	

Table 3 Study schedule (Part B)

Period	**Screening**	**Wash-out[a]**	**Treatment period**											**Follow-up period[d]**
Week	**-3**	**-1**	**0[b]**	**1**	**2[c]**	**4**	**8**	**12**	**16**	**20**	**24**	**32, 40, 48**	**52**	**56**
Visit	**1**	**2**	**3**	**4**	**(5)**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14**	**15**	**16**
Visit window (days)	**-7**	**±3**	**0**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**
Laboratory Assessments														
C-peptide	X													
Hepatitis Screen Panel	X													
TSH	X													
Blood Standard Safety Laboratory Panel	X		X			X	X	X	X	X	X	X	X	X
Urine Standard Safety Laboratory Panel	X		X			X	X	X	X	X	X	X	X	X
Pregnancy test (serum) WOCBP only	X													
Pregnancy test (urine) WOCBP only			X			X	X	X	X	X	X	X	X	X
Urine (dipstick)	X		X			X	X		X		X	X	X	X
Microscopic urinalysis	X		X								X	X	X	X
6-point SMBG, Self-Monitored Blood Ketone			X[g]					X[g]			X[g]		X[g]	
HbA1c, GA	X		X			X	X	X	X	X	X	X	X	
Study Drug Supply														

Table 3 Study schedule (Part B)

Period	**Screening**	**Wash-out[a]**	**Treatment period**											**Follow-up period[d]**
Week	**-3**	**-1**	**0[b]**	**1**	**2[c]**	**4**	**8**	**12**	**16**	**20**	**24**	**32, 40, 48**	**52**	**56**
Visit	**1**	**2**	**3**	**4**	**(5)**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14**	**15**	**16**
Visit window (days)	**-7**	**±3**	**0**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**
Randomization			X											
Dispense Study Drug			X			X	X	X	X	X	X	X		
Contact IWRS	X		X								X		X	
Review study drug dosing				X	X	X	X	X	X	X	X	X	X	

a Wash-out period is applicable only for subjects who received α-GI until enrolment. Subjects not taking other anti-hyperglycemic drugs other than insulin skip the period and directly proceed to the Treatment period.
b Day 1 of Week 0 means the stating day of dapagliflozin. The previous day of Day 1 is shown as "Day -1"
c Either hospital visit or telephone (fax or email) contact is acceptable on Week 2.
d If a patient meet any study discontinuation criteria, the patient should receive the Week 52 and follow-up evaluation.
e If a patient performed Informed Consent only, it is to allowed be out of visit window.
f On Day 2, 4 (± 1 day) and 10 (± 1 day) patients must contact the Investigators by phone (fax or email) and report the patient's condition (including glucose and ketone values from SMBG). The Investigators must indicate appropriate insulin adjustment.
g It will be performed on any 3 days within a week before each visit.

4.1 Enrolment/screening period (2weeks)

Japanese male and female subjects with T1DM will be enrolled into the study. Subjects should be on insulin for at least 12 months prior to screening per subject report or medical records.

Subjects will be instructed to continue their current insulin and if applicable any ongoing therapy during enrolment period.

Patients for part B on α-GI use currently (see exclusion criteria 1-(f)) of enrolment on top of insulin mono-therapy need to undergo a 1-week wash-out period prior to randomization.

4.1.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within any single screening will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Retesting is limited to HbA1c as described in Section 3.1.

4.1.1.1 Study Materials

Sponsor will supply the sites with the following materials.

- Blood glucose/ketone meters. One (1) meter will be provided to each study subject at screening period and 1 meter will be provided to each investigative site. SMBG: see Section 5.3.1.1.
- Glucose and ketone test strips
- Lancets
- Glucose control solutions
- eCRFs [SAE Forms, Pregnancy Surveillance Forms, Events of Special Interest]
- Subject Alert Cards
- Study Drug inventory control forms
- Site File
- Subject Diary:
  - Full Diary review by site staff is required for this study
  - Use of subject diaries are mandatory for the study and will be maintained by each study subject for documentation and SMBGs, insulin doses, study medication dosing, ketone testing, DKA symptoms, and hypoglycemia episodes.

- Subjects are to be instructed to document their insulin dose in their study diaries during the protocol defined time period as outlined in Section 5.3.3. The eCRF pages will be provided to the sites so they can record the data obtained from the diaries in the study database.

    - Subjects who have not recorded all of their insulin doses should be assessed by the study staff for their ability to comply with the protocol. The diaries are to be maintained to ensure subject safety and must be completed by the subject throughout the study. Compliance with prescribed insulin administration and diary completion should be assessed and re-enforced at every visit.

- The dates, time, and number of tablets of study medication taken by the subject are to be recorded in the study diary. The eCRF pages will be provided to the sites so they can record the data obtained from the diaries in the study database (Part A only)

- Subjects are to record any hypoglycemic symptoms they may experience and SMBG values if they conducted the test when they have symptoms in their diaries. All events recorded in subject diary to be reviewed by site staff according to Section 5.3.1.

- Any ketone testing performed by the subject, symptoms potentially associated with DKA, and relevant events (Section 5.3.2) are to be recorded in the diary. All results recorded in subject diary will be reviewed by site staff.

The central laboratory will provide all laboratory-related materials including home pregnancy testing kits for WOCBP to the study sites.

4.2 Wash-out period only for part B (1 week, it is applicable exclusively for subjects receiving α-GI on top of insulin)

Subjects, who are previously treated with insulin only but have not been treated with any anti-hyperglycemic agent except insulin within 1 month prior to screening visit (see exclusion criteria 1-(f)), can skip wash-out period. Washout means to stop taking anti-hyperglycemic agent except insulin.

Subjects will receive a glucose and ketone meter and a patient diary, testing supplies and instruction on their use. Testing supplies will be provided to allow for blood glucose and ketone testing for the duration of the study.

Subjects will be advised to continue self-monitoring their blood glucose as per local guideline, and in the occurrence of hypoglycemic symptoms, and to contact the Investigators in the event of an unusually high or low blood glucose value. In addition, study subjects should comply with the site's instructions with regard to self-monitoring of blood glucose and insulin

adjustments accordingly and should report to the Investigators blood glucose values and/or signs and symptoms suggestive of a hypoglycemic episode.

Subjects who meet the eligibility criteria at visit 1 and visit 2 are eligible to entry into the treatment period at Visit 3.

4.3 Treatment period

4.3.1 PK and PD evaluation part (Part A)

Subjects who meet all the protocol-specific enrolment and randomization inclusion criteria and meet none of the exclusion criteria will be randomized into one of the three single-blind treatment arms (dapagliflozin 5 mg QD, dapagliflozin 10 mg QD, or placebo QD) in a 1:1:1 ratio.

Duration of hospitalization:

- First hospitalization: From evening (before dinner, approximately 18:00) on Day -2 to morning (approximately 10:00) on Day 2 (4 days and 3 nights) and
- Second hospitalization: From evening (before dinner, approximately 18:00) on Day 6 to morning (approximately 10:00) on Day 8 (3 days and 2 nights)

Recommendation of calorie control during hospitalization:

- Calculation of adequate calories;
  - Adequate calorie intake for each patient is calculated by mean of formula as followed,
    - Calorie intake = (basal metabolic standard [kcal/kg]) x (standard body weight [kg])
    - Basal metabolic standard is 20-30 kcal/kg for inpatients.
    - Standard body weight (kg) = Height (m) x Height (m) x 22
  - Total calories and proportion of carbohydrate should be similar between two hospitalization periods.

Recommendation of calorie control during outpatient:

Patients are recommended to do “light work (desk workers, housewives, etc)” only during outpatient (Day 2 to 6). Total calories and proportion of carbohydrate should be stable as much as possible (basal metabolic standard is 25-35 kcal/kg for outpatients). The investigators must instruct the management of excise and diet during the outpatient period before discharge from hospital.

Subjects should self-monitor their blood glucose (see Section 5.3.1.1).

The randomized subject will be observed within 24 hours after first dose of study drug on Day1 at the investigator’s site in order to adjust their daily insulin doses for both basal and

bolus insulin to reduce the risk of hypoglycemia. It is at the discretion of the Investigators to determine the extent to which to reduce the insulin doses. In some cases it may be necessary to reduce insulin (particularly basal insulin) in advance of study drug administration.

4.3.2 Long term treatment part (Part B)

Subjects who meet all the protocol-specific enrolment and randomization inclusion criteria and meet none of the exclusion criteria will be randomized into one of the 2 open-label treatment arms (dapagliflozin 5 mg QD or dapagliflozin 10 mg QD) in a 1:1 ratio.

Subjects should self-monitor their blood glucose (see Section 5.3.1.1).

It is recommended that subjects reduce their daily insulin dose by up to 20% for both basal and bolus insulin after the first dose of study drug to minimize the risk of hypoglycemia. It is at the discretion of the investigator to determine the extent to which to reduce the insulin doses. In some cases it may be necessary to reduce insulin (particularly basal insulin) in advance of study drug administration.

4.4 Follow-up period

4.4.1 PK and PD evaluation part (Part A)

Subjects will stop taking investigational products at Visit 4 and will be re-evaluated 1 week later for AEs and laboratory parameters. Subjects who discontinue study medication during the treatment period will also be re-evaluated 1 week later for AEs and laboratory parameters and tests and evaluation of Visit 4 are unnecessary. Open-label use of anti-diabetic agents are permitted during the follow-up period within approved dose range and regimen in Japan.

4.4.2 Long term treatment part (Part B)

Subjects will stop taking investigational products at Visit 15 (end of treatment period) and will be re-evaluated 4 weeks later for AEs and laboratory parameters. Subjects who discontinue study medication during the treatment period will also be re-evaluated 4 weeks later for AEs and laboratory parameters. Open-label use of anti-diabetic agents are permitted during the follow-up period within approved dose range and regimen in Japan.

4.5 Supplemental Visits

4.5.1 Early Treatment Discontinuation Visit

Subjects discontinued from the treatment period

Any subject who discontinues study medication during the treatment period in Part B is to have the end of treatment visit (Visit 15 in part B) completed. The ET visit eCRF will also need to be completed and the ET visit laboratory kit will need to be used to collect ET Visit blood and urine samples. The IWRS must be called to record the subject status (ie, discontinuation status). In case of ET in part A, the patient would not need tests and evaluation of Visit 4.

4.5.2 Other Supplemental (Unscheduled) Visits

At any time during the trial, the investigator may at his/her discretion arrange for a subject to have an unscheduled (supplemental) assessment(s), especially in the case of AEs that require follow-up. If a subject is seen for an unscheduled assessment, the appropriate Supplemental Pages of the eCRF must be completed.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Efficacy assessments

The laboratory parameters that will be measured to assess efficacy in Part B are displayed in Table 4 by visit. There is not applicable parameter in part A.

Table 4 Efficacy laboratory variables in part B

Visit	**1**	**2**	**3**	**4**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14**	**15**	**16**
Week	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**32, 40, 48**	**52/ET**	**56/ET+4 weeks**
6-point SMBG			X				X			X		X	
HbA1c, GA	X		X		X	X	X	X	X	X	X	X	

5.1.2 HbA1c and glycoalbumin

HbA1c is the assessment for the determination of glycemic efficacy accepted referred by The Japanese Guideline for Clinical Evaluation of Oral Hypoglycaemic Agents 2010. HbA1c will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation. The measurement of HbA1c is National Glycohemoglobin Standardization Program (NGSP).

Glycoalbumin (GA) will be also analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation. GA is a well established measure of glycemic efficacy and considered to be an acceptable secondary objective.

5.1.3 6-point SMBG profiles

Subjects will be instructed to perform 6-point SMBG profiles as described below. Subjects must use the meter provided by the Sponsor.

Profiles will be obtained on any 3 days within a week before the Day 1 visit, Week 12 visit, and Week 24 visit, week 52 visit according to the schedules presented in study flow chart/time and event schedule (see Section 5.1). Each separate 6-point SMBG profile encompasses 1 day within one week before the scheduled visits, with three glucose measurements obtained preprandially (prior to meal) and three glucose measurements obtained postprandially (1.5 - 2 hours after the start of the meal) for the three main meals of the day. Subjects will be provided with a diary to record these SMBG measurements and mealtimes, and eCRFs will available for the investigator sites to capture these results.

If a subject fails prior to the randomization, the 6-point SMBG profile will not be required within one week prior to Day 1 visit.

If a randomized subject terminates the study any time prior to the Week 52 visit, the 6-point SMBG profile will not be required for the early termination visit.

5.1.4 Weight and height

The subject's weight will be recorded in kilogram (kg) to one decimal place, with light clothing and no shoes. The subject's height will be recorded in centimetres, with no shoes. All readings should be recorded as accurately as possible and the same scale should be used for all assessments for a given subject.

5.1.5 Blood pressure

As BP is both efficacy and safety variable in this study, measurement of BP is described in Section 5.3.7.

5.2 PD assessment (Part A only)

5.2.1 Analysis of 24-hour urinary glucose excretion

The 24 -hour urinary glucose excretion is an assessment linked to the mechanism of action of Dapagliflozin. It is measured based on 24 -hour urine collections. Urine is collected over a 24-hour period on Days -1 and 7.

The 24-hour period is defined from morning of one day to morning of the next day. Therefore, in the morning, on the day that the 24-h urine collection is started, the first morning void is not included in the 24-h collection. The date and time of the first urine should be recorded on the urine collection log as the start of the 24-h urine collection. All subsequent urinations

throughout the entire day and night and into the following day should be collected. The first voided urine of the subsequent day should be included in the 24-hr urine collection. The urine collection ends after 24 hrs and the stop time should equal the start time of the previous day. The stop date and time should be recorded on the urine collection log.

5.2.2 FPG

FPG is the secondary glycemic parameter. FPG is measured on Days 1, 7 and 8.

5.3 Safety assessments

Safety assessments will include adverse event reporting, as well as marked abnormalities in clinical laboratory tests. Please refer to Section 5.5 for details on central laboratory assessments.

The procedures described in the sections that follow will also be completed to ensure subject's safety.

5.3.1 Self Monitored Blood Glucose (SMBG) and Guidance on Management and Reporting of Hypoglycemia Episodes

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the investigator as per standard medical/clinical judgment.

5.3.1.1 Self Monitored Blood Glucose (SMBG)

Combination glucose and ketone meters will be supplied to each study site. At the screening visit, subjects will receive a glucose and ketone meter, supplies and instruction on their use. Testing supplies will be provided to allow for blood glucose and ketone testing for the duration of the study. Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly and for review of SMBG results. Subjects may keep the glucose meters at the end of the study.

In part A, subjects should self-monitor their blood glucose whenever possible at least 7 times per day (before and after each meal and before going to bed) from Day -1 to Day 7 and in the occurrence of hypoglycemic symptoms, and contact the Investigators in the event of an unusually high or low blood glucose value. Study sites will review these diary entries and record these data on the eCRF. In addition, study subjects should comply with the site's instructions with regard to self-monitoring of blood glucose and insulin adjustments accordingly and should report to the investigator blood glucose values and/or signs and symptoms suggestive of a hypoglycemic episode. Subjects must report the values to the investigator on Day 3 to 5 by telephone (fax or email) at least once a day.

In part B, subjects should self-monitor their blood glucose whenever possible at least 4 times per day (generally before breakfast, lunch, dinner, and bedtime) during the treatment period (until Visit 15), and in the occurrence of hypoglycemic symptoms, and contact the Investigators in the event of an unusually high or low blood glucose value. In addition, study

subjects should comply with the site's instructions with regard to self-monitoring of blood glucose and insulin adjustments accordingly and should report to the investigator blood glucose values and/or signs and symptoms suggestive of a hypoglycemic episode.

The glucose values should be reviewed by the site to identify any unusual high or low values, and to confirm that the values (from the glucose and ketone meter's memory and/or from the subject's hypoglycemia portion in the diary) were obtained from the subject. If fingerstick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose and ketone meter should be tested and the procedure for using it reviewed with the subject.

5.3.1.2 Guidance on Management and Reporting of Hypoglycemia Episodes

Hypoglycemia may be an expected event in subjects who are treated for diabetes. Subjects and their family members must be aware of the possibility that hypoglycemia may occur and the dangers associated with low blood sugar.

Study subjects must be properly instructed on the recognition and management of hypoglycemia. Subjects should record in their diaries any hypoglycemic symptoms. They should be encouraged to measure, when possible, their blood glucose values when they have symptoms of hypoglycemia. Subjects should carry with them easily ingestible forms of carbohydrate at all times in order to treat an event of hypoglycemia should it occur.

During clinical trials, subjects frequently report symptoms of hypoglycemia when asked, even when treated with placebo or medications not otherwise associated with hypoglycemia. As hypoglycemia is an important event associated with diabetes therapy, all episodes which could be consistent with the clinical definition of hypoglycemia as assessed by the investigator should be documented and reported on the appropriate eCRF page.

The following definitions of hypoglycemia will be used:

- **Severe hypoglycemia:** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- **Documented symptomatic hypoglycemia:** An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).
- **Asymptomatic hypoglycemia:** An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).

- **Probable symptomatic hypoglycemia:** An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL [3.9 mmol/L]). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as "probable" hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they should be reported.
- **Relative hypoglycemia:** An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration > 70 mg/dL (3.9 mmol/L). This category reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels > 70 mg/dL (3.9 mmol/L) as plasma glucose concentrations decline toward that level. Though causing distress and interfering with the patient's sense of well-being, and potentially limiting the achievement of optimal glycemic control, such episodes probably pose no direct harm and therefore may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they should be reported.

Hypoglycemia eCRF pages will be used to document all reported episodes of hypoglycemia. The Investigator is responsible for questioning the subject about all symptoms reported on the hypoglycemia portion of the diary and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values deemed by the Investigator to meet the definition of hypoglycemia should be reported on the hypoglycemia eCRF pages. Signs and symptoms of hypoglycemia, hypoglycemia episode or discontinuation due to hypoglycemia should not be reported on the AE eCRF page, unless the event fulfils protocol criteria for a SAE (see Section 6.2), in which case an SAE form must be completed in addition to the hypoglycemia eCRF pages for hypoglycemia.

5.3.2 Self-Monitored Blood Ketone Testing and Guidance on Management and Reporting of Diabetic Ketoacidosis (DKA) Episodes

DKA is an expected event in subjects with T1DM. Subjects and their family members must be aware of the possibility that DKA may occur and the dangers associated with DKA.

Dapagliflozin reduces blood glucose by urinary excretion of glucose, thus representing a daily removal of a substantial amount of carbohydrate from the body. We estimate (from insulin:carbohydrate ratios) that the amount of glucose excreted in the urine in subjects on dapagliflozin may correspond to the glycemic effect achieved from as much as 20% of a subject's total daily insulin dose and, therefore, insulin dose reductions will have opposite glycemic effects compared to those of dapagliflozin. Furthermore, since DKA is caused by gross insulin deficiency and is mechanistically unrelated to glucose levels per se (as can be seen in euglycemic DKA), reductions in insulin doses of more than 20% are not recommended regardless of glucose values. If subjects have repeatedly low blood glucose and could

otherwise not avoid a 20% reduction in total daily insulin dose, their carbohydrate intake should be re-valuated and those who have insufficient amount of carbohydrate are recommended to increase their daily dietary carbohydrate intake. Similarly, subjects should be reminded that during/after elevated physical activity/exercise, dapagliflozin continues to remove glucose in addition to what is being consumed by the physical activity. Therefore, additional (re-) fueling with carbohydrates is important and should generally be preferred over higher than usual reductions in subjects' insulin doses.

As noted above, subjects will receive a combined glucose and ketone meter and sufficient supplies for testing at the screening period. Subjects will also be trained in the procedure of conducting blood ketone testing according to the manufacture's specifications. Subjects will be advised to measure their blood ketones using the glucose and ketone meter provided by the Sponsor when they have potential symptoms/signs of DKA, including but not limited to, (excessive thirst, nausea and vomiting, frequent urination, weakness or fatigue, fever, fruity-scented breath, confusion, and/or consistently elevated blood glucose), and/or during acute illness. Blood ketone test results, symptoms potentially associated with DKA and relevant risk factors (eg, missed insulin injection, insulin pump malfunction, infection, heart attack, etc) should be recorded in the subject diary.

In part B, subject will measure their blood ketones using the meter provided by the Sponsor when they measure the blood glucose of each before breakfast at 6-point SMBG profiles (see Section 5.1.3), and will record the results on the patient diary. The Investigators will review these diary entries and record the results on the eCRF.

Study subjects must be properly instructed on the recognition and management of DKA. Subjects should contact the site for assistance with diabetes management in the event that the blood ketone reading is 0.6 mmol/L or above according to the glucose/ketone meter user guide. Investigator(s) is recommended to advise the subject to take extra insulin and extra carbohydrate if elevated ketones are registered and continue to measure blood ketones. If deemed necessary, dosing of study medication should be interrupted during sick days. The action, follow-up, and monitoring plan will be at the discretion of the investigator and will depend on his/her judgment of severity based on signs/symptoms of DKA, risk factors, relevant contributing factors, and blood glucose (with the caveat that the blood glucose may be lower than would be otherwise expected given elevated ketone levels). It is recommended that for subjects who report elevated ketones/ketosis, investigator(s) considers re-education concerning DKA at the next scheduled visit, at an un-scheduled visit or by telephone contact, as appropriate. Subjects must also be instructed that if attempts to contact the investigator are unsuccessful and if they are in urgent need of medical attention, e.g. sings/symptoms, that they should seek medical attention. They should provide information to the health care provider on their participation in a placebo controlled clinical study evaluating the effects of the SGLT2 inhibitor dapagliflozin in addition to their insulin treatment.

The blood ketone values should be reviewed by the site to identify any unusual high values, and to confirm that the values (from the glucose and ketone meter's memory and/or from the subject's diary) were obtained from the subject. If fingerstick blood values are discordant

from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose and ketone meter should be tested and the procedure for using it reviewed with the subject. Investigators will examine if any of the elevated ketone values from the subject's diary are associated with a DKA event. If yes, investigators will document all DKA related symptoms, relevant risk factors, and available laboratory test results (including blood ketone values and blood glucose values measured by the glucose/ketone meter) on the DKA eCRF pages and report this event to the Sponsor.

In addition the Sponsor will utilize Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) based on a list of pre-defined terms in MedDRA to identify potential DKA events. The list of these terms is included in the Data Monitoring Committee Charter. Investigators will further evaluate these cases and if the event is determined to be DKA, the investigator will complete the DKA eCRF.

Regarding the reporting of DKA events, it is important to distinguish ketosis from DKA. Low levels of ketosis, in which blood or urine ketone values are elevated, can occur in individuals who follow a low-carbohydrate, high-fat diet (eg, dietary ketosis) or after prolonged periods of fasting. However, ketosis is a benign condition in symptoms are absent and the blood pH remains buffered within normal limits (eg, no acidosis). In contrast, DKA episode may be confirmed when subjects have potential symptoms/signs of DKA (polyuria, polydipsia, weight loss, vomiting, abdominal pain, signs of volume depletion on physical examination), marked hyperglycemia, elevated blood/urine ketone values, and a metabolic acidosis characterized by low arterial blood pH values and decreased serum bicarbonate with an increased anion gap). The combination of specific symptoms/signs of DKA and elevated blood/urine ketone values may be suggestive of DKA, recognizing that some subjects may not have lab test results (eg, blood gas measurement) to confirm acidosis.

During clinical trials, subjects frequently report symptoms of DKA when asked, even when treated with placebo or medications not otherwise associated with DKA. The Investigator is responsible for questioning the subject about all DKA related symptoms reported on the subject diary and for determining if they meet the clinical definition of DKA. Only the episodes deemed by the investigator to meet the definition of DKA should be reported on the DKA eCRF pages. Signs and symptoms of DKA, DKA episode or discontinuation due to DKA should not be reported on the AE eCRF page, unless the event fulfils protocol criteria for a SAE (see Section 6.2), in which case an SAE form must be completed in addition to the DKA eCRF pages. If a DKA episode occurs in a subject that fails screening, the DKA eCRF pages do not need to be completed. However, if the event meets the protocol criteria for an SAE, the SAE form must be completed.

A DKA Adjudication Committee, blinded to the treatment of the subjects, will independently adjudicate all the DKA events reported by investigators during the study period. A separate Adjudication Manual will define and describe the procedure for the handling, reporting, and classification of these cases.

The key goals of treating DKA include correcting dehydration, hyperglycemia, and electrolyte imbalance, and identifying and appropriately treating comorbid precipitating events. Subjects

with DKA should be carefully monitored until significant improvement in the symptoms, normalization of blood acidity (eg, pH > 7.3), and improvement/absence of ketones in blood or urine.

5.3.3 Insulin Dosing Adjustment and Data Collection Guidelines

Adjustment of a subject's pre-existing insulin dosing regimen may be required during the conduct of this study, due to changes in diet, activity, emotional stress during the study as well as potential effects of dapagliflozin to reduce blood glucose and thereby insulin requirements.

During the screening and wash-out period, subjects will be advised to self-monitor their blood glucose consistent with local treatment guidelines. The method of documentation for glucose results to be based on local clinic practice. Glucose control will be reviewed by the investigator at each visit. Insulin dose may be adjusted as deemed appropriate to be consistent according to SMBG readings, local guidance and individual circumstances.

In part A, the randomized subject will be observed within 24 hours after first dose of study drug on Day1 at the investigator's site in order to adjust their daily insulin doses for both basal and bolus insulin to reduce the risk of hypoglycemia. It is at the discretion of the investigator to determine the extent to which to reduce the insulin doses. In some cases it may be necessary to reduce insulin (particularly basal insulin) in advance of study drug administration.

In part B, it is recommended that subjects reduce their daily insulin dose by up to 20% for both basal and bolus insulin after first dose of study drug to minimize the risk of hypoglycemia.

It is at the discretion of the investigator to determine the extent to which to reduce the insulin doses. In some cases it may be necessary to reduce insulin (particular basal insulin) in advance of study drug administration. If total daily insulin dose is reduced upon initiation of study medication, attempts must be made to titrate insulin back to baseline total daily insulin dose. It is not recommended to reduce total daily insulin dose by more than 20% compared to baseline at any time during the study unless medically indicated and close attention should be paid, especially in these subjects, to symptoms of, and risk factors for developing DKA (See also Section 5.3.2). Subjects are to be instructed to document their daily individual insulin doses and at least 4-time self monitored glucose values (before breakfast, lunch, dinner, and bedtime) every day during the treatment period in part B and during the treatment period in part A. This information will be used to facilitate appropriate insulin dose adjustment and ensure subject safety. For the rest of the study period (both short- term and long-term), Subjects will be advised to continue self-monitoring their blood glucose as per local guidelines. Glucose control will be reviewed by the investigator at each visit. Insulin dose may be adjusted as deemed appropriate to be consistent with good medical practice according to SMBG readings, local guidance, and individual circumstances. The glycemic control goals may be individualized based upon a subject's personal target and stability of glycemic control at baseline.

Subjects are not allowed to change their insulin administration methods (MDI or CSII) throughout the study unless a subject using an insulin pump needs to replace the pump. Under this situation, the subject may temporarily use MDI and should restart CSII administration as early as feasible. The period of time a subject is on temporary use of MDI should not be more than two weeks.

Insulin Dosing Recording in part A

At the following time periods the subjects will be instructed to record all their individual doses of (basal and bolus) insulin in their study diary.

- Day-3 visit to Day 14

Insulin Dosing Recording in part B

At the following time periods the subjects will be instructed to record all their individual doses of (basal and bolus) insulin in their study diary.

- 2 weeks prior to randomization
- Day 1 visit after randomization to Day 14 (Week 2)
- Week 10 to Week 12 visit
- Week 22 to Week 24 visit
- Week 50 to Week 52 visit

The Investigators will review these diary entries and record the total basal, total bolus, and total pre-mix (if applicable), daily dose of insulin the subject received on the eCRF. For statistical analysis purposes the total daily dose is defined as the sum of all these individual doses of insulin (both basal and bolus) during a 24-hour period.

Subject's daily individual insulin doses and self monitored glucose values collected from Day 1 visit (after randomization) to Week 2 will be used to facilitate appropriate insulin dose adjustment and ensure patient safety.

At the following time periods subjects will be instructed to record the minimum and maximum total daily insulin dose range (basal plus bolus) taken for each week in their study diary:

- Week 2 visit to Week 10
- Week 12 visit to Week 22
- Week 24 visit to Week 50
- Week 52 visit to Week 56 visit

The Investigators will review these diary entries and record the weekly ranges subject received of insulin on the eCRF.

5.3.4 Guidance on Assessment of Urinary Infections & Hematuria

5.3.4.1 Guidance on Assessment of Urinary Infections

The following is presented to assist in the classification and management of urinary tract infections. It is not intended to supplant investigators' clinical judgment: It is at the discretion of an investigator to determine whether and when to send an initial urine culture.

Study drug should be withheld in subjects with clinical evidence of urinary tract infection or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred.

It is recommended that a urine culture be obtained by local laboratory within 7 days of clinical recovery from all treated urinary tract infections. Whether or not additional therapy is prescribed because of culture results should be determined by Investigator judgment, after consultation with the Medical Monitor.

It is the Investigator's responsibility to report, as applicable based on the Investigator's judgment and subject's medical history, related adverse events as defined in Section 6.1. Additional information, including but not limited to completion of supplemental eCRFs or questionnaires may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

Asymptomatic Bacteriuria

During enrolment, treatment and follow-up of subjects in this trial, the investigator may discover a subject with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guidelines from the US nor Europe recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients (Nicolle et al 2005, US Preventative Services Taskforce 2004, European Association of Urology 2008). In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

5.3.4.2 Guidance on Assessment of Hematuria

During the course of the study, hematuria should be investigated according to local standards and best clinical practices for a possible cause.

If **NO** common cause is identified, subjects should be further investigated based on American Urological Association (AUA) guidelines or equivalent local standard of care and best practices which could include referral to an urologist and undergoing evaluation that may include abdominal computed tomography (CT), urine cytology, and NMP-22 urine test. The subject should continue to be randomized/receive investigational product treatment during these investigations (unless otherwise contraindicated).

It is the investigator's responsibility to report, as applicable based on the investigator's judgment and subject's medical history, related adverse events as defined in Section 6.1. Additional information, including but not limited to completion of supplemental eCRFs or questionnaires may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

5.3.5 Guidance on Assessment of Hepatic Laboratory Abnormalities

An independent Hepatic Adjudication Committee, blinded to the treatment of the subjects, will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities, included, but not limited to:

- AST and/or ALT > 3x ULN and TB > 2x ULN (within 14 days of the AST and/or ALT elevation)
- Hepatic events timely related to death (within 30 days before death)
- AST and/or ALT > 10x ULN

These events should be reported as SAEs.

Hepatic disorders leading to discontinuation from study drug and/or death

Liver laboratory abnormalities such as elevated AST and/or ALT with or without TB Elevations

A separate Adjudication Charter will define and describe the procedure for the handling, reporting and classification of these cases.

The following is presented to assist in the evaluation and management of hepatic laboratory values. It is not intended to supplant the investigator’s clinical judgment. Subjects who experience ALT and/or AST values > 3x ULN confirmed with a repeated test will have the following performed within 3 days of the confirmed laboratory results:

- AE assessment
- Physical examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
  - Use of suspect concomitant medication [including over-the-counter (ie, acetaminophen/paracetamol), herbal and vitamin preparations]
  - Recent alcohol consumption or recreational drug/narcotic use
  - Recent unaccustomed physical exertion
  - Occupational or environmental exposure to hepatotoxins
  - Other conditions which may cause liver diseases or which may cause abnormal test results

- Specialized Liver Laboratory Panel (see Appendix D)

Additional information, including but not limited to completion of supplemental eCRFs or questionnaires, may be requested for certain adverse events and/or laboratory abnormalities which are reported /identified as part of the hepatic safety surveillance.

For subjects who are discontinued from study medication as a result of sustained elevated liver safety abnormalities, as described in Section 3.9, additional blood sampling must be done within 3 days of the confirmed laboratory results (see Appendix D), in conjunction with an Early Treatment Discontinuation (End-of-Treatment) visit, in addition to the procedures noted above. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained. Any additional tests and/or examinations should be carried out at the discretion of the Investigator. Any further investigations and laboratory results for subjects with abnormal laboratory values at the follow-up visit should be made available to the Sponsor upon request.

5.3.6 Physical Examination

- A brief physical examination should include cardiovascular, lungs, abdomen, and extremities, and any organ systems pertinent to the subject's signs, symptoms, or adverse events
- A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform this procedure.

Baseline data is collected at Visit 3, and new findings discovered on subsequent physical examinations should be recorded as changes from baseline.

5.3.7 Blood Pressure and Heart Rate

Blood pressure (BP) and heart rate (HR) measurements must be taken consistently throughout the study. Only use either the right or the left arm when measuring these parameters. Document which arm was used along with the observer's initials; the same arm should be used at each visit. The subject should be in a seated position allowing at least 5 minutes of rest before measurement. BP should be measured with the subject's arm resting on a table, and with subject's back supported and feet flat on the floor.

BP and HR will be determined from 3 replicate measurements obtained at least 1 minute apart. The average BP and HR will be determined from these 3 replicate measurements and reported in the eCRF.

5.3.8 Resting 12-Lead ECG

A 12-Lead ECGs will be performed at noted in Section 5.3.8. The investigator should review and assess all ECGs for any clinically significant abnormalities, and initial and date the report. The screening ECG must be assessed, and initialed and dated by the investigator prior to

randomizing the subject. In preparation for the ECG, ensure there is minimal interference between the skin surface and the electrode. Use alcohol to prepare the skin at each electrode site. Thick chest hair should be shaved to ensure sufficient contact. Before attaching electrodes to pick-up points, spread the electrode with electrode gel. Place the electrodes on bony areas, avoiding large muscle masses, to achieve better tracings as described below. The subject must be supine and should refrain from movement during the ECG recording. Ensure that the subject and the electrodes (including the neutral electrode) are not exposed to conducting objects, even if grounded.

- RL: On the right leg (inside calf, midway between knee and ankle)
- LL: On the left leg (inside calf, midway between knee and ankle)
- RA: Right arm (on the inside)
- LA: Left arm (on the inside)
- V1: 4th intercostal space, at right sternal margin
- V2: 4th intercostal space, at left sternal margin
- V3: Midway between V2 and V4
- V4: 5th intercostal space at left midclavicular line
- V5: Same transverse level at V4, at anterior axillary line
- V6: Same transverse level at V4, at left midaxillary line

Keep one original ECG print-out, assessed, initialled and dated by the investigator, in the medical chart. In addition, ensure a copy is maintained in the source documents for the study regarding the print-out such as thermal recording paper that could not be preserved for a long time.

5.3.9 Guidance on Volume Depletion

Dapagliflozin has a modest diuretic effect. The risk of volume depletion is enhanced when two diuretics are used in combination and in subjects that otherwise are at risk for volume depletion. Therefore, caution should be exercised when administering dapagliflozin to subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. These subjects should be carefully monitored for of volume status, electrolytes, and renal function.

5.3.10 Other safety assessments

Self-monitored blood glucose, keton, hypoglycemic and DKA events will be collected in a subject diary and reviewed by the investigator at each visit.

5.4 Other assessments

5.4.1 Height and Body Mass Index (BMI)

- Measurement of height should be performed with the subject's shoes removed. The subject's knees should be straightened, head held erect and eyes forward.

- BMI is used as an index of obesity and is a method of defining normal body weight and excess body fat. BMI is determined by weight (kg) divided by height (m) squared.

Method of BMI calculation:

- Use actual height and weight.
- To calculate BMI:

  BMI = (weight in kg) / (height in meter) ^{2}

5.4.2 Diet and Exercise Counselling

Starting at entry into the screening visit, subjects will be instructed on a diet and an exercise program in accordance with the ADA or similar local guidelines to be followed for the study duration.

A registered dietitian, registered nurse, physician, certified diabetes educator (CDE), nutritionist, or other qualified member of the study team who has appropriate documented training, will provide this counselling.

5.5 Results of Central Laboratory Assessments

Blood and urine samples will be obtained at specified time points for laboratory evaluations (see Table 5 and Table 6). The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. The central laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples.

Spot urine for glucose, 24-hour collection urine and urine dipstick will be masked for the patients during the treatment period in part A.

The following laboratory variables will be measured.

Table 5 Safety laboratory variables (Part A)

Week (Day)	**-2 (Day -14)**	**-1 (Day -1)**	**0 (Day 1)**	**1 (Day 7)**	**1 (Day 8)**	**2 (Day 14)**
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Blood Standard Safety Laboratory Test	X		X		X	X
Urine Standard Safety Laboratory Test	X		X		X	X
Pregnancy test (serum) WOCBP only	X					
Pregnancy test (urine) WOCBP only			X		X	X

Table 5 Safety laboratory variables (Part A)

Week (Day)	**-2 (Day -14)**	**-1 (Day -1)**	**0 (Day 1)**	**1 (Day 7)**	**1 (Day 8)**	**2 (Day 14)**
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Urine (dipstick) Urine glucose	X		X		X	X
Microscopic urinalysis	X		X		X	X
Hepatitis Screen Panel	X					
TSH	X					

Table 6 Safety laboratory variables (Part B)

Week	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**32, 40, 48**	**52**	**56**
Visit	**1**	**2**	**3**	**4**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14**	**15**	**16**
Blood Standard Safety Laboratory Panel	X		X		X	X	X	X	X	X	X	X	X
Urine Standard Safety Laboratory Panel	X		X		X	X	X	X	X	X	X	X	X
Pregnancy test (serum) WOCBP only	X												
Pregnancy test (urine) WOCBP only			X		X	X	X	X	X	X	X	X	X
Urine (dipstick) Urine glucose	X		X		X	X		X		X	X	X	X
Microscopic urinalysis	X		X							X	X	X	X
Hepatitis Screen Panel	X												
TSH	X												

Regarding Efficacy and PK/PD laboratory variables (see Section 4) except SMBG and self monitoring Blood Ketone variables, the central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests.

5.5.1 Blood Standard Safety Laboratory Panels:

5.5.1.1 Hematology

- Hemoglobin (g/dL, g/L)
- Hematocrit (%, v/v)
- Red blood cell (RBC) ($x10^6$/UL, $x10^{12}$/L)

RBC count indices:

- Mean Cell Volume (MCV) (fL)
- Mean Cell Hemoglobin (MCH) (pg/cell)
- Mean Cell Hemoglobin Concentration (MCHC) (gHb/dL, gHb/L)
- White blood cell Count and Differential
- Platelet count (x 10^9/L)

5.5.1.2 Serum Chemistry

- AST (IU/L)
- ALT (IU/L)
- ALK-P (IU/L)
- CK/CPK (IU/L)
- Total Bilirubin (mg/dL, µmol/L), Reflex test for direct bilirubin when TB is elevated >1.5ULN
- Serum Creatinine (mg/dL, µmol/L). Creatinine Clearance will be calculated by the Central Laboratory
- Blood Urea Nitrogen (mg/dL, mmol/L)
- Albumin (g/dl, g/L)
- Bicarbonate (mEq/L, mmol/L)
- Sodium (mEq/L, mmol/L)
- Potassium (mEq/L, mmol/L)
- Chloride (mEq/L, mmol/L)
- Calcium (mg/dL, mmol/L)
- Magnesium (mEq/L, mmol/L)
- Phosphorus (mg/dL, mmol/L)
- Total Protein (g/dL, g/L)
- Uric acid (mg/dL, µmol/L)
- Total ketone (µmol/L), acetoacetic acid (µmol/L), 3-hydroxybutyric acid (µmol/L); Part A only
- GA (%); Part B only

5.5.1.3 Urine Analyses

Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L; performed at site or at home). If a urine HCG test is positive, a blood specimen will be obtained and a serum pregnancy test will be performed by the central laboratory for confirmation.

Urine standard safety laboratory panel (without microscopy):

- Spot Urine for glucose, albumin, and creatinine quantification and determination of glucose : creatinine and albumin : creatinine ratios
- Calculated Urinary albumin : creatinine ratio (UACR)

5.5.2 Screening-Specific Safety Panel

- Thyroid stimulating hormone (TSH)
  - Reflex Testing: abnormal TSH value at enrolment will be further evaluated by free T4.
  - Hepatitis Screen Panel:
    - Anti-hepatitis C virus antibody
- Reflex Testing: Low positive results require confirmation.
- Hepatitis B surface antigen
- Serum Pregnancy test for women of childbearing potential

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a subject shows an AST or ALT ≥ 3x ULN or total bilirubin ≥ 2x ULN please refer to Appendix D, for further instructions.

5.6 Pharmacokinetics (PK) in part A

5.6.1 Collection of samples

Blood samples for determination of dapagliflozin and dapagliflozin 3-O-Glucuronide in plasma will be taken at the times presented in the study plan Table 1 and Table 2.

Samples will be collected, labeled stored and shipped as detailed in the Laboratory Manual.

5.6.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by a suitable bioanalytical laboratory on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.7 Pharmacodynamics (Not Applicable)

5.8 Pharmacogenetics (Not Applicable)

5.9 Biomarker analysis (Not Applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including wash-out periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, treatment, wash-out, follow-up) even if no study treatment has been administered, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from the start of the treatment period throughout the treatment period (Part A: Visit 3 to 5, Part B: Visit 3 to 15) and including the follow-up period (Part A: Visit 6, Part B: Visit 16).

AEs which occurred and resolved before the randomization will be record only the original documents and the data will not be entered into eCRF excluding SAEs.

SAEs will be recorded from the time of informed consent is obtained until the end of follow-up period (Part A: Visit 6, Part B: Visit 16).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigators for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)

- Causality assessment in relation to other medication
- Description of AE.

Maximum intensity will be graded according to the following definitions:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product, or require the subject to receive specific corrective therapy.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination or ECG evaluation as compared with the baseline assessment will be reported as an AE.

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

6.3.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigators to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigators or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigators/study site personnel how to proceed.

6.5 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study and/or metformin and/or glimepiride may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The PREGREP module in the eCRF is used to report the pregnancy. This module in the eCRF should be completed by the investigator and the AstraZeneca representative will forward the information to the AstraZeneca Patient Safety data entry site using the same procedure as for SAE reporting. An AstraZeneca paper Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

6.7 Management of IP related toxicities and dose Reductions- Not Applicable

6.8 Study governance and oversight

6.8.1 Hepatic Adjudication Committee

An Independent Adjudication Committee, blinded to the treatment of the subjects, will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities, including but not limited to:

- AST and/or ALT > 3 x ULN and TB >2x ULN (within 14 days of the AST and/or ALT elevation)
- Hepatic events timely related to death (within 30 days before death)
- AST and/or ALT > 10 x ULN

A separate Adjudication Charter will define and describe the procedure for the handling, reporting, and classification of these events.

6.8.2 DKA Adjudication Committee

A DKA Adjudication Committee, blinded to the treatment of the subjects, will independently adjudicate all the DKA events reported by the Investigators during the study period.

A separate Adjudication Manual will define and describe the procedure for the handling, reporting, and classification of these cases.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Dapagliflozin (BMS-512148) tablets are packed into high-density polyethylene (HDPE) bottle and are supplied by AstraZeneca or their designee. For details of the identity of the investigational product see below.

Table 7 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
dapagliflozin 5 mg tablet	Film coated tablet 5 mg, green, plain, diamond shaped	AstraZeneca
dapagliflozin 10 mg tablet	Film coated tablet 10 mg, green, plain, diamond shaped	AstraZeneca
Matching placebo for dapagliflozin 5 mg tablet	Film coated tablet 5 mg placebo, green, plain, diamond shaped	AstraZeneca
Matching placebo for dapagliflozin 10 mg tablet	Film coated tablet 10 mg placebo, green, plain, diamond shaped	AstraZeneca

7.2 Dose and treatment regimens

7.2.1 PK and PD evaluation part (Part A)

Dapagliflozin tablet 5 mg, 10 mg or matching placebos administered orally for the 7 days single-blind treatment period.

Each dose will be composed of 2 tablets according to Table 8. Investigational drug should be taken once daily in the morning.

Table 8 Composition of dose and number of tablets

Dose	Investigational product
5 mg dose	5 mg 1 tablet + 10 mg placebo 1 tablet
10 mg dose	5 mg placebo 1 tablet + 10 mg 1 tablet
Placebo dose	5 mg placebo 1 tablet + 10 mg placebo 1 tablet

7.2.2 Long term treatment part (Part B)

Dapagliflozin tablet 5 mg or 10 mg administered orally for the 52-week open-label treatment period.

The investigational product dapagliflozin should be taken once daily in much around the same time as directed by the Investigators.

Table 9 Drug dispensing scheme

Visit ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Number of bottles to dispense dapagliflozin 5 mg or 10 mg	0	0	1	0	0	1	1	1	1	1	2	2	2	1	0	0

7.2.3 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products. Sponsor(s) will not be supplying other medications than dapagliflozin and placebo.

In this protocol, non-investigational product is insulin

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practise (GMP) and local regulatory guidelines. Label text will be written in local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the document explaining 'Procedures for drug accountability'.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

Each time study medication is dispensed, compliance will be reinforced. When study medication is returned, compliance will be assessed based upon subject's interview and a count of the tablets returned. Compliance should be between ≥ 80% and ≤ 120%. The investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, as well as document reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF. If the subject is not ≥ 80% compliant the period of non compliance should be noted as a protocol deviation and the Sponsor should be notified. The subject should be re-educated regarding treatment compliance and/or recording dose.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The Investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

7.7 Concomitant and other treatments

7.7.1 Prohibited and/or Restricted Treatments

Once enrolled, subjects must not receive any of the following for the duration of the screening (qualification period), wash-out, and treatment periods:

- Anti-hyperglycemic medication (other than protocol required medication)
- Weight loss medication

- Newly initiated treatment with any systemic corticosteroid therapy that will involve ≥ 5 days of therapy (inhaled and topical are allowed)

7.7.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Post Study Access to Study Treatment

At the end of the study treatment period, AstraZeneca will not continue to supply study drug to subjects/investigators unless AstraZeneca chooses to extend the study. The Investigators should ensure that the subject receives appropriate standard of care to treat the condition under study.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All the analyses for Part A and Part B will be separately conducted.
- Analyses will be performed by AstraZeneca or its representatives.
- Further details will be specified in Statistical Analysis Plan.

8.2 Sample size estimate

8.2.1 PK and PD evaluation part (Part A)

Approximately 42 patients are to be randomized to placebo, dapagliflozin 5 mg or dapagliflozin 10 mg in ratio 1:1:1.

Although in view of purpose of Part A being purely exploratory, sample size is not based on statistical power calculation, 6 - 8 patients per arm are generally considered sufficient to assess the pharmacokinetic profile, as done in Japan Phase I studies.

In terms of key PD evaluation (mean change in 24-hour urinary glucose [g/24h]), the half-width of 95% confidence interval for treatment difference based on 10-14 evaluable patients/arm are estimated to be approximately 42-50 [g/24h], assuming the common standard deviation of 56 [g/24h].

In addition, PK-PD relationships will be evaluated exploratory to compare between those of Japanese T1DM patients and those of non-Japanese T1DM patients. For this evaluation, 10 patients per arm are considered sufficient.

Originally, in the initial version of the Clinical Study Protocol issued at 9th July 2015, about 30 patients were planned to be randomized to the study. However, 12 patients in Part A were judged to be unevaluable for PK data due to issue related to sampling tube. It is considered that the revised sample size (randomization of about 42 patients) would lead to sufficient

number of patients for evaluating PK profile, as well as exploratory evaluating PK-PD relationships, without the 12 patients.

8.2.2 Long term treatment part (Part B)

The number of patients in the Long term treatment part was decided according to the ICH E1 guideline (1994), "The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions". The number of patients in the Part B was designed so that approximately 100 Japanese T1DM patients treated by dapagliflozin 5 mg and 10 mg for 52 weeks are secured in total, when summed up with Japanese T1DM patients randomized in study MB102230, where about 160 Japanese T1DM patients are to be randomized to dapagliflozin 5 mg, 10 mg or placebo in ratio 1:1:1.

With 140 patients randomized to dapagliflozin 5 mg or 10 mg in Part B of this study, approximately 59 patients/arm are expected to complete 52-week dapagliflozin treatment in this study, assuming drop-out rate of 15%.

8.3 Definitions of analysis sets

Analysis sets for Part A and Part B will be separately determined.

8.3.1 PK and PD evaluation part (Part A)

Pharmacokinetic set -Part A (PK-A): The PK set will consist of all randomized subjects who had at least one dose of randomized study medication for Part A and had an evaluable plasma concentration data of dapagliflozin and/or its major metabolite dapagliflozin 3-O-glucuronide.

Pharmacodynamic set -Part A (PD-A): The PD set will be consist of all randomized subjects who received at least one dose of randomized study medication for Part A, and who have a non-missing baseline value and at least one post-baseline value for at least one pharmacodynamic variable.

Safety set -Part A (SAF-A): The safety analysis set will include all subjects who received at least one dose of randomized study medication for Part A and who provide any safety records. Subjects will be analysed according to the treatment group for which they received medication.

8.3.2 Long term treatment part (Part B)

Safety set -Part B (SAF-B): The safety analysis set will include all subjects who received at least one dose of randomized study medication for Part B and who provide any safety records. Subjects will be analysed according to the treatment group for which they received medication.

Full analysis set -Part B (FAS-B): The full analysis set will include all randomized subject who received at least one dose of randomized study medication for Part B, and who have a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable. The subjects will be analysed according to the treatment group to which they were randomized, regardless of the actual treatment taken.

8.4 Outcome measures for analyses

The outcome measures for the primary, secondary and exploratory objectives are as described in Sections 2.1 to 2.4.

8.4.1 Primary Endpoints

Part A

Primary variables for Part A would include following PK/PD variables

- PK variables: C_{max}, T_{max}, AUCτ for dapagliflozin and dapagliflozin 3-O-glucuronide, and ratio of dapagliflozin 3-O-glucuronide AUCτ to dapagliflozin AUCτ.
- PD variables: Change from baseline in 24-hour urinary glucose excretion on Day 7.

Part B

Adverse events (including hypoglycemia / DKA), Serious adverse events (SAEs) and Adverse event leading to discontinuation of study drug (DAEs), vital signs (blood pressure, heart rate), ECG, and clinical laboratory measures, urine test will be summarized by treatment group (dapagliflozin 5 mg or 10 mg).

8.4.2 Secondary Endpoints

Part A

- Secondary PD variables: Change from baseline in FPG on Day 7, daily insulin dose, SBP
- Safety variables: Adverse event (including hypoglycemia events and DKA events), physical examination, vital signs (blood pressure, heart rate), ECG and clinical laboratory measures, urine test.

Part B

- Change from baseline in HbA1c at Week 24 and 52
- Change from baseline in GA at Week 24 and 52
- Change from baseline in average glucose values measured by 6-point SMBG at Week 24 and 52
- Change from baseline in post-prandial glucose values measured by 6-point SMBG at Week 24 and 52
- Percent change from baseline in total daily insulin dose at Week 24 and 52
- Percent change from baseline in body weight at Week 24 and 52
- Proportion of subjects with HbA1c reduction from baseline of at least 0.5% without severe hypoglycemia at Week 24 and 52
- Proportion of subjects with HbA1c reduction from baseline of at least 0.5% at Week 24 and 52
- Proportion of subjects with HbA1c < 7.0% at Week 24 and 52

- Change from baseline to Week 24 and 52 in seated SBP among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg

8.4.3 Exploratory Endpoints

Part A

The relationship between changes in 7-point SMBG measurements, 24-hr urinary glucose excursion and total daily insulin dose will be explored.

Part B

The efficacy evaluation will be made by comparing subgroups BMI < 25.0 or BMI ≥ 25.0, as measured by the change from baseline in HbA1c, GA, average/post-prandial glucose values measured by 6-point SMBG, and percent change from baseline in body weight, total daily insulin dose.

8.4.4 Baseline value

For each subject, baseline value of a parameter (eg, efficacy/pharmacodynamic laboratory parameter, safety laboratory test, ECG or physical measurement) is defined as the last assessment on or prior to the date of the first dose of the randomized study medication.

8.4.5 LOCF

For LOCF, if no measurement is available at a time point, the last post-baseline measurement prior to the specific time-point will be used instead for analysis.

8.4.6 Calculation of eGFR

The following Japan guideline recommended equation will be used to calculate eGFR.

$eGFR\ (mL/min/1.73m^2) = 194 \times (SCr)^{-1.094} \times (age)^{-0.287}$ (x 0.739 if female)

8.5 Methods for statistical analyses

Analyses for Part A and Part B will be separately conducted.

In both Parts, there will be no confirmatory hypothesis to be tested and hence no multiplicity issues occur. Pharmacodynamic variable in Part A and efficacy variables in Part B will be presented mainly descriptively. Ninety-five percent confidence intervals will be calculated, where appropriate, as measures of study precision.

8.5.1 Analysis of the primary variable (s)

Part A

All PK/PD analysis for Part A will be carried out for PK-A and PD-A.

PK : summary statistics for C_{max}, T_{max}, AUCτ for both dapagliflozin and its major metabolite dapagliflozin 3-O-glucuronide, and ratio of metabolite to parent AUCτ will be provided by

arm. Geometric mean and CV (coefficient of variation) will be presented for C_{max}, AUCτ and ratio of metabolite to parent AUCτ. Medians and ranges will be presented for T_{max}.

PD: change from baseline to Day 7 in 24-hour urinary glucose will be summarized by arm. Also difference of dapagliflozin vs. placebo and 95%CIs will be summarized if appropriate. No formal statistical testing will be performed.

The dapagliflozin plasma concentrations obtained by sampling of individual subjects will be used to build a population PK (PPK) model to estimate PK parameters (eg, oral clearance (CL/F), apparent volume of distribution (Vd/F), and absorption rate constant (ka)). Possible covariate effects on PK parameters may be identified and quantified. The estimated parameters will be used to derive individual exposure measures (eg, AUC, C_{min}). Relationships between observed exposures, and/or these model based estimates of exposures, and efficacy/safety endpoints (eg, changes from baseline in HbA1c, average daily glucose, hypoglycemia) will be explored as needed. The PK data and efficacy endpoint responses derived from this study may also be pooled with similar data from other studies to refine the model-based exposure-response relationship. Listings and summary statistics will be reported for the sampled pharmacokinetic measurements. The PPK and exposure-response analyses will be specified in Statistical Analysis Plan in details, and described in a separate report.

Part B

All safety analysis for Part B will be carried out for SAF-B.

The incidence of adverse events and of marked abnormalities in clinical laboratory tests will be summarized by treatment group.

The proportion of subjects with at least one hypoglycemic event will be summarized by treatment group and by the severity of the events. The frequency of the hypoglycemia will also be summarized. Subjects with adjudicated DKA events will also be summarized by treatment group.

All SAEs or DAEs will be described in depth. Changes from baseline at each of the scheduled time points in each clinical laboratory parameter will be summarized by treatment group.

Changes from baseline at each of the scheduled time points in each selected safety clinical laboratory parameters, physical examinations, vital signs and ECG data will be summarized by treatment group.

8.5.2 Analysis of the secondary variable(s)

Part A

All the pharmacodynamic (PD) evaluation will be conducted on PD-A.

For secondary PD parameters to be assessed by change from baseline (ie, FPG and SBP), similar analysis like primary PD variable of 24-hour urinary glucose will be carried out. For

PD parameters to be assessed by percent change from baseline (ie, daily basal insulin dose, daily bolus insulin dose, total daily dose of insulin), similar analysis will be carried out with exception that mean percent change from baseline will be calculated from the exponentiated values of estimates obtained on the natural logarithmic scale.

All safety analysis for Part A will be carried out for SAF-A.

The incidence of adverse events and of marked abnormalities in clinical laboratory tests will be summarized by treatment group.

The proportion of subjects with at least one hypoglycemic episode will be summarized by treatment group and by the severity of the events. The frequency of the hypoglycemia will also be summarized. Subjects with adjudicated DKA events will also be summarized by treatment group.

All SAEs or DAEs will be described in depth. Changes from baseline at each of the scheduled time points in each clinical laboratory parameter will be summarized by treatment group.

Changes from baseline at each of the scheduled time points in each selected safety clinical laboratory parameters, physical examinations, vital signs and ECG data will be summarized by treatment group.

Part B

All efficacy analyses for Part B will be carried out for FAS-B.

Unless otherwise specified, all available efficacy data obtained up to Week 52 or premature discontinuation of study drug (regardless of insulin uptitiration) will be included in the analysis. For the selected efficacy variables (eg, Change from baseline in HbA1c, Percent change from baseline in body weight), analyses excluding data after insulin up-titration may also be performed supportively.

- Change from baseline in HbA1c at Week 24 and 52
- Change from baseline in GA at Week 24 and 52
- Change from baseline in average glucose values measured by 6-point SMBG at Week 24 and 52
- Change from baseline in post-prandial glucose values measured by 6-point SMBG at Week 24 and 52
- Percent change from baseline in total daily insulin dose at Week 24 and 52
- Percent change from baseline in body weight at Week 24 and 52
- Change from baseline to Week 24 and 52 in seated SBP among subjects with hypertension at baseline, defined as seated SBP $\geq$ 140 mmHg and/or seated DBP $\geq$ 90 mmHg

Efficacy analyses on change from baseline in HbA1c, GA, average glucose values measured by 6-point SMBG, post-prandial glucose values measured by 6-point SMBG and SBP are to be analysed by Mixed Model with Repeated Measures (MMRM). Point estimate an 95%CI for each treatment by time point will be presented from the model. For analysis for change from baseline, model will include the change from baseline as a response variable and treatment, stratification factor, visit as a fixed categorical effects and baseline value as a fixed continuous covariate and interactions for treatment x visit and baseline x visit. For within subject correlation, unstructured covariance matrix (UN) will be assumed.

Efficacy analyses on percent change from baseline in total daily insulin dose, and body weight are to be analysed by the similar model using the log transformed values. Point estimate an 95%CI for percentage change from baseline will be calculated by exponentiating the estimates obtained from the model and will be presented by treatment and time point.

- Proportion of subjects with HbA1c reduction from baseline of at least 0.5% without severe hypoglycemia at Week 24 and 52
- Proportion of subjects with HbA1c reduction from baseline of at least 0.5% at Week 24 and 52
- Proportion of subjects with HbA1c < 7.0% at Week 24 and 52

Number and proportion of subjects meeting each criterion will be summarized descriptively. 95%CIs will also be provided if appropriate.

8.5.3 Exploratory analyses

Detail will be documented in the separate statistical analysis plan.

8.5.4 Interim Analyses

Interim database locks/analysis occurs once after completion of Part A

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a training record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Direct access to source data in Japan

The Head of the study site and the Principal Investigator/ Investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

9.2.3 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in October, 2015 and to end by October, 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin.

9.4 Data management by AstraZeneca

Data management will be performed [redacted] according to the Data Management Plan.

Data will be entered into the WBDC system Rave at the study site. Trained site staff will be entering the data as specified in the protocol and according to the eCRF instructions. Data entered into the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified, reviewed, queried and updated as needed.

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the Data Management Centre.

The Principal Investigator is responsible for signing the eCRF and this may be delegated to a trained Investigator.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study is completed.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Management of genotype data

Not applicable in this study.

Data associated with human biological samples

Not applicable in this study.

Management of external data

Data Management determines the format of the data to be received from external vendors. External data reconciliation will be done with the clinical database as applicable.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as the IRB written approval to AstraZeneca and the Principal Investigator before enrolment of any subject should into the study.

The IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification

provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the Principal Investigator with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the Clinical Study Protocol to be amended, the amended Clinical Study Protocol should be submitted to the Head of the Study Site. If the changes are of an administrative nature, it is submitted to the IRB. If the changes have a significant impact on the safety of the subjects, the scientific value of the study, the conduct and management of the study, and the quality of any investigational product used in the study, it should be approved by the IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If the amended Clinical Study Protocol requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified by the Principal Investigator. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements (see Section 10.1). The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C New York Heart Association (NYHA) Classification

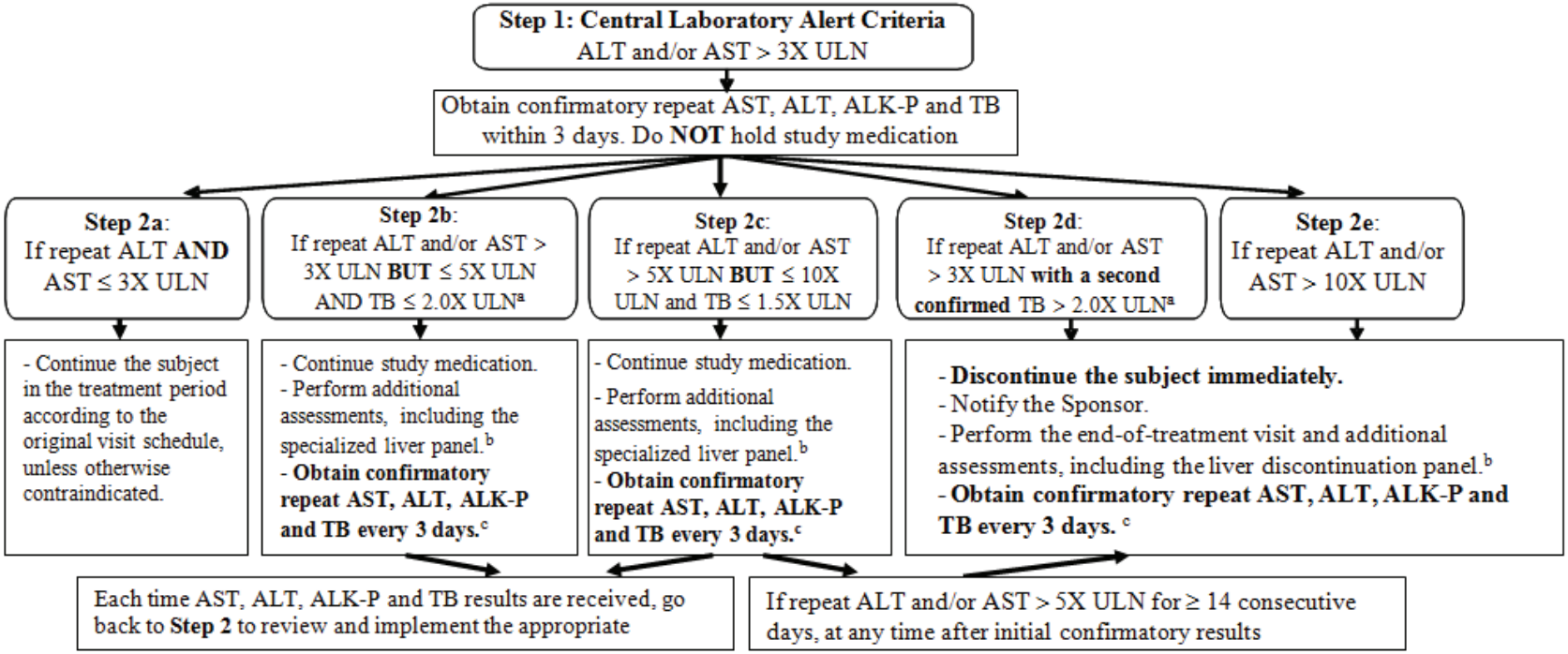
NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The NYHA classification will be based on the following definitions:

Class I	No limitation: Ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations.
Class II	Slight limitation of physical activity: Comfortable at rest but ordinary activity results in fatigue, palpitations, dyspnoea.
Class III	Marked limitation of physical activity: Comfortable at rest but less than ordinary activity results in symptoms.
Class IV	Unable to carry out any physical activity without discomfort: Symptoms of congestive heart failure are present even at rest with increased discomfort with any physical activity.

Appendix D Sustained Elevated Liver Safety Abnormalities Flow Chart

Figure 4 Sustained elevated liver safety abnormalities flow chart



a In subjects with repeat ALT or AST > 3X ULN but ≤ 10X ULN, only patient with TB ≤ 2.0X ULN at Step 1 should be followed according to Step 2b. Subjects with an initial TB and confirmatory repeat TB > 2.0X ULN should be followed according to Step 2d.

b Refer to next page for details on additional assessments to be performed (AE assessment, review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel])

c Confirmatory repeat AST, ALT, ALK-P and TB should be obtained every 3 days following receipt of prior laboratory results, until the ALT and AST are ≤ 2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic.

Specialized Liver Panel:

For subjects who are being monitored frequently as a result of confirmed AST and/or ALT > 3X ULN, additional central laboratory tests will be performed within 3 days of receipt of confirmatory results. These laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Hepatitis A IgM
- Hepatitis BsAg
- Hepatitis B Core Ab IgM
- Hepatitis C virus RNA or RIBA
- Hepatitis C Ab
- Hepatitis E IgM
- Epstein-Barr Virus (EBV) IgM Ab
- Lactate Dehydrogenase (LDH)
- Gamma-glutamyl-transpeptidase (GGT)
- Carbohydrate deficient transferrin (CDT)
- Prothrombin time (PT/INR)
- Iron Panel - iron, ferritin, total iron binding capacity (TIBC)
- Immunology Panel including Antinuclear Antibody (ANA), Anti-Smooth Muscle Antibody (SMA) and Anti-Liver/Kidney Microsomal Antibody (Anti-LKM)
- Anti-tissue Transglutaminase Antibody

Liver Discontinuation Panel:

For subjects who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of Early Termination (End-of-Treatment) visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Cytomegalovirus (CMV) IgM Ab
- Herpes Simplex Virus (HSV) 1 and 2

- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin

For specific details regarding the Specialized Liver Panel and the Liver Discontinuation Panel laboratory tests, refer to the Central Laboratory Manual for this study.