

STATISTICAL ANALYSIS PLAN

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Multicenter, Randomized, Open-label Study of Diabetes Treatment Support System
(BAP0527 and Blood Glucose Meter) in Patients with Type 2 Diabetes Mellitus

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Astellas Pharma Inc.

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
DCT	Decentralized Clinical Trial
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol 5 Dimension 5-level
FAS	Full Analysis Set
HbA1c	Hemoglobin A1c
HLS-14	14-item health literacy scale
ICH	International Council for Harmonisation of technical requirements for pharmaceuticals for human use
IWRS	Interactive Web Response System
IMDRF	International Medical Device Regulators Forum
IRT	Interactive Response Technology
MAR	Missing at Random
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
QOL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings and Figures
VAS	Visual Analogue Scale

List of Key Terms

Terms	Definition of terms
BMI	Body Mass Index (kg/m ²) BMI = Body mass (kg)/height (m ²)
Follow-up period	The period after the treatment period, from the end of assessment at visit 9 to the end of assessment at visit 12
Study end date	The date when assessment of all participants has ended (the date when all periods of the study, including final assessment, are complete)
Screening period	The period after registration, from visit 1 to randomization at visit 2
Treatment period	The period after the screening period, from randomization at visit 2 to the end of assessment at visit 9
Registration date	The date of obtaining informed consent
This product	The diabetes mellitus treatment support system (BAP0527 and blood glucose meter)
Randomization date	The date when a participant is assigned to the BAP0527 group or usual treatment group
Baseline	Visit 2

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data. The SAP is finalized and signed prior to the day that the first participant is randomized.

Changes from the planned analyses in the SAP finalized before randomization that impact the statistical analyses will be justified in the Clinical Study Report (CSR).

2 OBJECTIVES AND STUDY DESIGN

2.1 Objectives

The objective of this study is to assess the efficacy and safety of the use of this product in combination with usual treatment in patients with type 2 diabetes mellitus aged ≥ 18 years not receiving treatment with insulin preparations.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess efficacy based on the change in HbA1c level.	Change from baseline in HbA1c level at Week 24 (central lab measurement)
Secondary	
To assess efficacy based on blood glucose-related indices.	- Change from baseline in HbA1c level at each assessment time point (except Week 24) (central lab measurement) - Percentage of participants with a baseline HbA1c level $\geq 8.0\%$ who achieved an HbA1c level $< 8.0\%$ at Week 24 (central lab measurement) - Change from baseline in fasting blood glucose level and fasting insulin level at Week 24 (central lab measurement) - Percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 24, relative to antidiabetic use at baseline - Percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 24, relative to antidiabetic use at baseline
To assess the persistence of the effect based on the change in HbA1c level in the follow-up period.	- Change from baseline in HbA1c level at each assessment time point in the follow-up period (central lab measurement) - Change from Week 24 in HbA1c level at each assessment time point in the follow-up period (central lab measurement) - Percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 12 of the follow-up

Objectives	Endpoints
	- period, relative to antidiabetic use at Week 24 - Percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24
To assess safety.	AEs, deficiencies, laboratory test values (hematology, blood biochemistry, urinalysis), vital signs
Exploratory	
To assess efficacy based on the change in HbA1c level in participants with no change in hypoglycemics.	Change from baseline in HbA1c level at Week 24 (central lab measurement)
To assess the effect on other efficacy endpoints.	- Percentage of participants who achieved an HbA1c level <7.0% at Week 24 (central lab measurement) - Percentage of participants with a baseline HbA1c level $\geq 8.0\%$ who achieved an HbA1c level <8.0% at each assessment time point (except Week 24) (central lab measurement) - Change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point (except Week 24) (central lab measurement) - Change from baseline in tests related to complications of diabetes mellitus (vital signs, lipid levels) at each assessment time point - Percentages of each EQ-5D-5L level at each assessment time point - Change from baseline in DTSQ at each assessment time point
To assess the effect on the number of unscheduled visits during the treatment period.	The number of unscheduled visits up to Week 24
To assess the relationship between the state of use of this product and effects.	- The BAP0527 access rate and blood glucose level data input rate - The relationship between the BAP0527 access rate and blood glucose level data input rate and the effect improving HbA1c level

DTSQ: diabetes treatment satisfaction questionnaire; EQ-5D-5L: EuroQol 5 dimension 5-level; HbA1c: hemoglobin A1c

2.2 Study Design

This study is a Japanese multicenter, randomized, open-label study of this product with a usual treatment group as a comparator group. The blood glucose meter that will be used in

combination with BAP0527 is Accu-Chek Guide Me from Roche DC Japan K. K. (certification number: 303AABZX00007000). After a screening period of up to 4 weeks, participants will be randomized in a 1:1 ratio to the group using this product in combination with usual treatment (below, “the BAP0527 group”) and the usual treatment group. To address bias, the HbA1c level (central lab measurement: $<8.5\%$, $\geq 8.5\%$) and BMI level ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$) at screening have been selected as assignment factors. During the 24-week treatment period, participants in the BAP0527 group will use this product in addition to usual treatment. After the end of the treatment period, use of this product will not be allowed. After the end of the treatment period, usual treatment will be administered in a 12-week follow-up period in both the BAP0527 group and the usual treatment group. From visit 2 to the end of the follow-up period, changing medication to hypoglycemics other than insulin preparations will be allowed if it is considered particularly necessary (for example, if there is a tendency towards markedly increased HbA1c levels or if there are reasons for concern about safety such as hypoglycemia). The use of insulin preparations will be prohibited. After the end of the study, participants will transition to usual healthcare.

2.3 Randomization

Randomization will be performed using the IRT system. When the study site staff perform case registration in the IRT system, participants will be randomized in a 1:1 ratio to the BAP0527 group and usual treatment group. To address bias, stratified assignment will be performed using the HbA1c level (central lab measurement: $<8.5\%$, $\geq 8.5\%$) and BMI level ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$) at screening as assignment factors. The specific procedures for randomization via the IRT system will be included in the IWRS operation procedure.

This study will be conducted as a multicenter study, and no particular restrictions will be set on the number of participants registered at each site.

3 SAMPLE SIZE

For the primary endpoint, which is the change from baseline in HbA1c level, the difference between the BAP0527 group and the usual treatment group is presumed to be 0.44% and the standard deviation common to both is presumed to be 1.0%. In this case, with a two-sided significance level of 0.05 and a power of 90%, using a 2-sample t test, the sample size necessary to detect a statistically significant difference in the BAP0527 group relative to the usual treatment group is 110 participants per group, or a total of 220 participants. Assuming a discontinuation rate of approximately 10% before measurement of the efficacy endpoint in the treatment period, and accounting for discontinuations, a sample size for randomization of approximately 240 participants is required. The intergroup difference of 0.44% has been selected with reference to sources including the opinion of the medical expert, considering that the design allows changes of concomitant hypoglycemics during the study period.

4 ANALYSIS SETS

Analysis will be performed using the following analysis sets based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines E3 and E9.

4.1 Registered Analysis Set

All participants who sign the informed consent form.

4.2 Randomized Analysis Set

All participants who complete the screening and are randomized. Participants will be analyzed according to the treatment group to which they are randomized.

4.3 Full Analysis Set (FAS)

All participants who are randomized and have at least one post-baseline HbA1c measurement. Participants will be analyzed according to the treatment group to which they are randomized. Participants who are randomized to the BAP0527 group and do not use BAP0527 will be handled as those in the BAP0527 group.

4.4 Full Analysis Set for Follow-up Analysis (FAS2)

Participants in the FAS for whom follow-up was started, and who have at least one measured value for HbA1c level from Week 24 onwards. Participants will be analyzed according to the treatment group to which they are randomized.

4.5 Safety Analysis Set (SAF)

All participants who complete the screening and are randomized. Participants will be analyzed according to the treatment group to which they are randomized. Participants who are randomized to the BAP0527 group and use BAP0527 will be handled as those in the BAP0527 group.

5 ENDPOINTS

5.1 Efficacy

5.1.1 Primary Endpoint

- The change from baseline in HbA1c level at Week 24 (central lab measurement) is defined by the formula below.
 - $\text{HbA1c level at visit 9} - \text{HbA1c level at visit 2}$

5.1.2 Secondary Endpoints

- The change from baseline in HbA1c level at each assessment time point (except Week 24) (central lab measurement) is defined by the formula below.
 - $\text{HbA1c level at each assessment time point (visits 4 to 8)} - \text{HbA1c level at visit 2}$

- The percentage of participants with a baseline HbA1c level $\geq 8.0\%$ who achieved an HbA1c level $< 8.0\%$ at Week 24 (central lab measurement) is defined by the formula below.
 - $(\text{Number of participants with an HbA1c level } \geq 8.0\% \text{ at visit 2 and an HbA1c level } < 8.0\% \text{ at visit 9}) / (\text{Number of participants with an HbA1c level } \geq 8.0\% \text{ at visit 2})$
- The change from baseline in fasting blood glucose level and fasting insulin level at Week 24 (central lab measurement) is defined by the formula below.
 - Fasting blood glucose level at visit 9 – Fasting blood glucose level at visit 2
 - Fasting insulin level at visit 9 – Fasting insulin level at visit 2
- The percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 24, relative to antidiabetic use at baseline, is defined by the formula below. “A decreased dose of antidiabetics or reduced number of antidiabetics” is defined as cases where the dose of antidiabetics is decreased or the number of antidiabetics is reduced at least once between visits 3 and 9 compared with the dose or number of antidiabetics at visit 2.
 - $(\text{Number of participants who use antidiabetics at baseline and then have a decreased dose of antidiabetics or reduced number of antidiabetics by visit 9 relative to antidiabetic use at baseline}) / (\text{Number of participants who use antidiabetics at baseline})$
- The percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 24, relative to antidiabetic use at baseline, is defined by the formula below. “An increased dose of antidiabetics or newly started hypoglycemics” is defined as cases where the dose of antidiabetics is increased at least once or a hypoglycemic is added at least once between visits 3 and 9 compared with the dose of antidiabetics or the number of hypoglycemics at visit 2.
 - $(\text{Number of participants in the FAS with an increased dose of antidiabetics or newly started hypoglycemics by visit 9 relative to antidiabetic use at baseline}) / (\text{Number of participants in the FAS})$
- The change from baseline in HbA1c level at each assessment time point in the follow-up period (central lab measurement) is defined by the formula below.
 - $\text{HbA1c level at each assessment time point (visits 10 to 12)} - \text{HbA1c level at visit 2}$
- The change from Week 24 in HbA1c level at each assessment time point in the follow-up period (central lab measurement) is defined by the formula below.
 - $\text{HbA1c level at each assessment time point (visits 10 to 12)} - \text{HbA1c level at visit 9}$
- The percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24, is defined by the formula below. “A decreased dose of antidiabetics or reduced number of antidiabetics” is defined as cases where the dose of antidiabetics is decreased or the number of antidiabetics is reduced at least once between visits 10 and 12 compared with the dose or number of antidiabetics at visit 9.
 - (Number of participants who start the follow-up, use antidiabetics at visit 9, and have a decreased dose of antidiabetics or reduced number of antidiabetics between

visits 10 and 12 relative to antidiabetic use at visit 9) / (Number of participants who start the follow-up and use antidiabetics at visit 9)

- The percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24, is defined by the formula below. “An increased dose of antidiabetics or newly started hypoglycemics” is defined as cases where the dose of antidiabetics is increased at least once or a hypoglycemic is added at least once between visits 10 and 12 compared with the dose of antidiabetics or the number of hypoglycemics at visit 9.
 - (Number of participants in the FAS2 with an increased dose of antidiabetics or newly started hypoglycemics between visits 10 and 12 relative to antidiabetic use at visit 9) / (Number of participants in the FAS2)

5.1.3 Exploratory Endpoints

The exploratory endpoints are listed below.

- The change from baseline in HbA1c level at Week 24 (central lab measurement) in participants with no changes in hypoglycemics is defined by the formula below. Participants “with no change in hypoglycemics” are defined as those who never changed the type or dose of hypoglycemics between baseline and visit 9.
 - $\text{HbA1c level at visit 9} - \text{HbA1c level at visit 2}$
- The percentage of participants with a baseline HbA1c level $\geq 7.0\%$ who achieved an HbA1c level $< 7.0\%$ at Week 24 (central lab measurement) is defined by the formula below.
 - $(\text{Number of participants with an HbA1c level } \geq 7.0\% \text{ at visit 2 and an HbA1c level } < 7.0\% \text{ at visit 9}) / (\text{Number of participants with an HbA1c level } \geq 7.0\% \text{ at visit 2})$
- The percentage of participants with a baseline HbA1c level $\geq 8.0\%$ who achieved an HbA1c level $< 8.0\%$ at each assessment time point (except Week 24) (central lab measurement) is defined by the formula below.
 - $(\text{Number of participants with an HbA1c level } \geq 8.0\% \text{ at visit 2 and an HbA1c level } < 8.0\% \text{ at each assessment time point [visits 4 to 8 and 10 to 12]}) / (\text{Number of participants with an HbA1c level } \geq 8.0\% \text{ at visit 2})$
- The change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point (except Week 24) (central lab measurement) is defined by the formula below.
 - $\text{Fasting blood glucose level at each assessment time point (visits 4 to 8 and 10 to 12)} - \text{Fasting blood glucose level at visit 2}$
 - $\text{Fasting insulin level at each assessment time point (visits 4 to 8 and 10 to 12)} - \text{Fasting insulin level at visit 2}$
- The change from baseline in tests related to complications of diabetes mellitus (vital signs, lipid levels) at each assessment time point will be assessed. Vital signs will include systolic and diastolic blood pressure (mmHg) at rest in a sitting position, pulse rate (beats/minute), and body temperature, and lipid levels will include total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol.
- Percentages of each EQ-5D-5L level at each assessment time point (visits 2 and 4 to 12)

- EQ-5D-5L

EQ-5D-5L is an internationally standardized scale for describing and assessing health status that can be applied to any disease. EQ-5D-5L is a questionnaire consisting of five questions and a visual analogue scale (VAS). Each question is rated on a 5-point scale. The VAS is a vertical line with “the best imaginable health state” anchored at 100 and “the worst imaginable health state” anchored at 0. Participants themselves will select a point on the scale that represents their health status, and the corresponding score will be recorded.
- The change from baseline in VAS score at each assessment time point (visits 4 to 12) is defined by the formula below.
 - VAS score at each assessment time point (visits 4 to 12) – VAS score at visit 2
- The change from baseline in DTSQ at each assessment time point is defined by the formula below.
 - DTSQ score at each assessment time point (visits 4 to 12) – DTSQ score at visit 2
 - DTSQ

DTSQ has been developed specifically for diabetes mellitus as a questionnaire for the level of satisfaction with treatment, and is currently used in countries around the world as a method for quantifying the level of satisfaction with treatment. The DTSQ used in this study is a questionnaire consisting of eight questions. The sum of scores selected by the participant in response to questions 1, 4, 5, 6, 7, and 8 is used as the level of treatment satisfaction. The total score ranges from 0 to 36 points, with higher scores indicating higher levels of treatment satisfaction. To assess the influence of this product on the level of satisfaction with diabetes mellitus treatment, the change from baseline in DTSQ total score and the scores of questions 2 and 3 will be calculated at each assessment time point.
- The total number of unscheduled visits up to Week 24 will be counted for each treatment group. The number of visits entered as unscheduled visits in the EDC will be counted.
- The BAP0527 access rate and blood glucose level data input rate are defined on the basis of the input data listed in Table 2.

Table 2 Data Used for Access Rate and Blood Glucose Level Data Input Rate

Parameter	Data set	Access rate	Blood glucose level data input rate
Blood glucose level entry	ELogBGEntry	X	X
Blood pressure entry	ELogBPEntry	X	
Mean content and dietary target entry	ELogFoodItem, CustomFood, PatientMeal, ELogMiscellaneous, PatientCarbTarget, ELogCarbsEntry	X	
Body weight and weight goal entry	ELogWeightEntry, WeightGoal	X	
Blood glucose level and blood pressure target entry	PatientBloodGlucoseTargets, PatientTargetSegment	X	
Weekly challenge entry	PatientWeeklyChallenge	X	
Laboratory test result entry	PatientLabTestResult	X	
Basic information entry	PatientHeight, UserDetail	X	
Comment entry	ELogCommentEntry	X	
Exercise entry	ELogExerciseEntry	X	
Medicine administration and prescription entry	MedAdministration, MedPrescription	X	
Smoking habit entry	PatientSmokingHabit	X	
Sleep entry	SleepEntry	X	
Completion of educational contents	PatientCurriculumCourseProgress	X	

- Access rate: The percentage of days that the app is used in each 28-day interval during the treatment period, relative to the day of visit 2

The day that the app is used represents the day that any input or record is made for the data used for the access rate in Table 2. The number of days that the app is used will be counted on the basis of the dates that an input is made. Specifically, any input of multiple days' data on a single day will be counted as single-day access. As defined below, the percentage of days that any input or record is made will be calculated during each observation interval of 28 days. If the last observation interval is <14 days, data observed during this interval will be excluded from analysis. If the last observation interval is ≥14 days to <28 days, the percentage of days that any input or record is made will be calculated on the basis of the number of days until the end date of observation.

 - (Number of days that any input or record is made) / 28
- Blood glucose level data input rate: The percentage of days that blood glucose levels are recorded in each 28-day interval during the treatment period, relative to the day of visit 2

The percentage of days that blood glucose levels are recorded will be calculated in each 28-day interval. The number of days that blood glucose levels are recorded will be counted on the basis of the dates that blood glucose levels are measured. Specifically, if multiple days' blood glucose levels are entered on a single day, only the blood glucose levels measured on separate days will be counted. As defined below, the percentage of days that blood glucose levels are recorded will be calculated during each observation interval of 28 days. If the last observation

interval is <14 days, data observed during this interval will be excluded from analysis. If the last observation interval is ≥ 14 days to <28 days, the percentage of days that blood glucose levels are recorded will be calculated on the basis of the number of days until the end date of observation.

- (Number of days that blood glucose levels are entered) / 28
- To determine the relationship between the BAP0527 access rate or blood glucose level data input rate and the effect improving HbA1c level, the BAP0527 access rate and blood glucose level data input rate throughout the treatment period are defined below.
 - Access rate throughout the treatment period: Percentage of days that the app is used during the treatment period

The day that the app is used represents the day that any input or record is made for the data used for the access rate in Table 2. The number of days that the app is used will be counted on the basis of the dates that an input is made. Specifically, any input of multiple days' data on a single day will be counted as single-day access. As defined below, the percentage of days that any input or record is made throughout the treatment period will be calculated. For participants who discontinue the study during the treatment period, the percentage will be calculated on the basis of the treatment period calculated by the formula: (Day of discontinuation – Day of randomization at visit 2 + 1).

 - (Number of days that any input or record is made) / (Number of days during the treatment period)
 - Blood glucose level data input rate throughout the treatment period: Percentage of days that blood glucose levels are recorded during the treatment period

The number of days that blood glucose levels are recorded will be counted on the basis of the dates that blood glucose levels are measured. Specifically, if multiple days' blood glucose levels are entered on a single day, only the blood glucose levels measured on separate days will be counted. As defined below, the percentage of days that blood glucose levels are recorded throughout the treatment period will be calculated. For participants who discontinue the study during the treatment period, the percentage will be calculated on the basis of the treatment period calculated by the formula: (Day of discontinuation – Day of randomization at visit 2 + 1).

 - (Number of days that blood glucose levels are entered) / (Number of days during the treatment period)
- The access count and blood glucose level data input count are defined on the basis of the input data listed in Table 3.

Table 3 Data Used for Access Count and Blood Glucose Level Data Input Count

Parameter	Data set	Access count	Blood glucose level data input count
Blood glucose level entry	ELogBGEntry	X	X
Blood pressure entry	ELogBPEntry	X	
Mean content and dietary target entry	ELogFoodItem, CustomFood, PatientMeal, ELogMiscellaneous, PatientCarbTarget, ELogCarbsEntry	X	
Body weight and weight goal entry	ELogWeightEntry, WeightGoal	X	
Blood glucose level and blood pressure target entry	PatientBloodGlucoseTargets, PatientTargetSegment	X	
Weekly challenge entry	PatientWeeklyChallenge	X	
Laboratory test result entry	PatientLabTestResult	X	
Basic information entry	PatientHeight, UserDetail	X	
Comment entry	ELogCommentEntry	X	
Exercise entry	ELogExerciseEntry	X	
Medicine administration and prescription entry	MedAdministration, MedPrescription	X	
Smoking habit entry	PatientSmokingHabit	X	
Sleep entry	SleepEntry	X	
Completion of educational contents	PatientCurriculumCourseProgress	X	

- Access count: Number of times the app is used in each 28-day interval during the treatment period, relative to the day of visit 2 and throughout the treatment period
The number of times the app is used represents the total number of times any input or record is made for the data used for the access count in Table 3. The number of times any input or record is made will be counted during each observation interval of 28 days. Any multiple data observed simultaneously (in seconds) in the same data set will be handled as a single input or record. If the last observation interval is <14 days, data observed during this interval will be excluded from analysis. If the last observation interval is ≥14 days to <28 days, the total number of times during this interval will be prorated to a 28-day equivalent.
- Blood glucose level data input count: Number of times blood glucose levels are recorded in each 28-day interval during the treatment period, relative to the day of visit 2 and throughout the treatment period
The total number of times blood glucose levels are recorded will be counted during each observation interval of 28 days. Any multiple data observed simultaneously (in seconds) in the same data set will be handled as a single record. If the last observation interval is <14 days, data observed during this interval will be excluded from analysis. If the last observation interval is ≥14 days to <28 days, the total number of times during this interval will be prorated to a 28-day equivalent.

5.1.4 Other Endpoints

- The percentage of participants with no changes in hypoglycemics by Week 24, relative to hypoglycemic use at baseline, is defined by the formula below.
 - $$\frac{\text{(Number of participants in the FAS with no changes in the dose of hypoglycemics and no addition of hypoglycemics at all time points up to visit 9 compared with baseline)}}{\text{(Number of participants in the FAS)}}$$
- To investigate the health literacy of participants as participant background information, HLS-14 will be performed. Questions 1 to 5 are related to functional health literacy, questions 6 to 10 are related to communicative health literacy, and questions 11 to 14 are related to critical health literacy. Each question is rated on a 5-point scale from 5 (highest) to 1 (lowest), and a total score ranging from 14 to 70 points is used to assess health literacy. Higher scores indicate higher health literacy.
- The percentage of participants with newly started hypoglycemics by Week 24 is defined by the formula below. “Newly started hypoglycemics” is defined as cases where a hypoglycemic is added at least once between visits 3 and 9. The percentage of such participants will also be calculated for each hypoglycemic.
 - $$\frac{\text{(Number of participants in the FAS with newly started hypoglycemics by visit 9)}}{\text{(Number of participants in the FAS)}}$$
- The percentage of participants with an increased dose of hypoglycemics by Week 24, relative to hypoglycemic use at baseline, is defined by the formula below. “An increased dose of hypoglycemics” is defined as cases where the dose of hypoglycemics is increased at least once between visits 3 and 9 compared with the dose of hypoglycemics at visit 2. The percentage of such participants will also be calculated for each hypoglycemic.
 - $$\frac{\text{(Number of participants in the FAS with an increased dose of hypoglycemics by visit 9 relative to hypoglycemic use at baseline)}}{\text{(Number of participants in the FAS)}}$$
- The percentage of participants with first started hypoglycemics by Week 24 is defined by the formula below. “First started hypoglycemics” is defined as cases where a hypoglycemic is added at least once between visits 3 and 9 in participants who use no hypoglycemics at baseline.
 - $$\frac{\text{(Number of participants in the FAS who use no hypoglycemics at baseline and first start hypoglycemics by visit 9)}}{\text{(Number of participants in the FAS who use no hypoglycemics at baseline)}}$$
- The percentage of participants with first started hypoglycemics during the follow-up period is defined by the formula below. “First started hypoglycemics” is defined as cases where a hypoglycemic is added at least once during the follow-up period in participants who use no hypoglycemics at Week 24.
 - $$\frac{\text{(Number of participants in the FAS2 who use no hypoglycemics at Week 24 and first start hypoglycemics during the follow-up period)}}{\text{(Number of participants in the FAS2 who use no hypoglycemics at Week 24)}}$$

5.2 Safety

The safety endpoints are listed below.

- AEs
- Deficiencies
- Laboratory test values
- Vital signs (systolic and diastolic blood pressure [mmHg] at rest in a sitting position, pulse rate [beats/minute], and body temperature)

5.3 Pharmacokinetics

Not applicable.

5.4 Pharmacodynamics

Not applicable.

5.5 Others

- Duration of use of this product
End date of use of this product – Start date of use of this product + 1
- Treatment duration (days)
Completion date or discontinuation date of the treatment period – Date of randomization at visit 2 + 1
- Follow-up duration (days)
 - Participants who do not enter the follow-up period: 0 (days)
 - Participants who enter the follow-up period:
Completion date or discontinuation date of the follow-up period – Day following the completion day of the treatment period + 1
If the completion date or discontinuation date of the follow-up period matches the completion date or discontinuation date of the treatment period, the follow-up duration is 1 day.
- Treatment duration + follow-up duration (days)
Completion date or discontinuation date of the study – Day of randomization at visit 2 + 1
- BMI (kg/m²)
Body mass (kg)/height (m²)
- The total duration of administration of hypoglycemics during the treatment period is defined as the total number of days from the start date to the stop date of hypoglycemics during the treatment period. If the start date of hypoglycemics is earlier than the randomization date, the randomization date will be used instead. If hypoglycemics are not stopped at the completion date of the treatment period, the completion date of the treatment period will be used instead of the stop date of hypoglycemics. The total duration of administration of all hypoglycemics during the treatment period is defined as the total number of days on which at least one hypoglycemic is used during the treatment period.

- The total duration of administration of hypoglycemics during the follow-up period is defined as the total number of days from the start date to the stop date of hypoglycemics during the follow-up period. If the start date of hypoglycemics is earlier than the start date of the follow-up period, the start date of the follow-up period will be used instead. If hypoglycemics are not stopped at the completion date of the follow-up period, the completion date of the follow-up period will be used instead of the stop date of hypoglycemics. The total duration of administration of all hypoglycemics during the follow-up period is defined as the total number of days on which at least one hypoglycemic is used during the follow-up period.

6 STATISTICAL ANALYSES

6.1 General Considerations

- Summary statistics of continuous data will include the number of participants (N), mean, standard deviation (SD), median, minimum, maximum, first quartile (Q1), and third quartile (Q3). Categorical data will be summarized by frequencies and percentages. Percentages will be calculated on the basis of the number of participants with no missing data.
- Unless otherwise noted, the mean, SD, median, first quartile, and third quartile will be rounded off and displayed to one more digit than the number of digits of data recorded in the case report form. The minimum and maximum will be displayed to the same number of digits as the input data. The percentage (%) of frequencies and its confidence interval will be rounded off and displayed to the first decimal place.
- AEs and complications by SOC and PT will be analyzed using the MedDRA.
- Deficiencies will be analyzed using the International Medical Device Regulators Forum (IMDRF) deficiency terminology.
- Previous and concomitant medications will be analyzed using the Iyakuhinmei Data File of Iyaku-Joho-Kenkyujo, Inc.
- Unless otherwise noted, the data will be analyzed according to the actual treatment groups. The data that can only be obtained from the BAP0527 group such as the access rate will be analyzed only in the BAP0527 group.
- All data summarization and analyses will be performed using SAS® Version 9.4 or higher on Red Hat Enterprise Linux. The specifications for tables, figures, and data listing formats can be found in the TLF specifications.
- HbA1c levels used as reference data will be excluded from the analysis and presented only in data listings. Other test values will also be included in the analysis even if they are used as reference data.

6.2 Study Participants

6.2.1 Participant Disposition

The number of participants in the following categories will be counted:

Table 4 Analysis of Participant Disposition

Participants for analysis	Group	Participants to be counted	Parameters to be calculated
Participants who have consented	Overall	- Participants who have consented - Rescreened participants - Participants who discontinue the study before randomization - Randomized participants	Number of participants relative to participants who have consented
Participants who have consented	Overall	- Participants who complete the screening - Participants who complete or discontinue the screening	- Percentage of participants among participants who have consented - Percentage of discontinued participants for each reason for discontinuation
Randomized participants	- BAP0527 group - Usual treatment group - Overall	- Randomized participants - Participants who use this product - Participants who do not use this product - SAF - FAS	Percentage of participants among randomized participants in each group
Participants who complete the treatment period	- BAP0527 group - Usual treatment group - Overall	- Participants who start the follow-up - FAS2	Percentage of participants among participants who start the follow-up in each group
Randomized participants	- BAP0527 group - Usual treatment group - Overall	- Study discontinuation (treatment period) - Main reason for study end (treatment period) - Protocol-specific reason for discontinuation	- Percentage of completed or discontinued participants among randomized participants - Percentage of discontinued participants for each reason for discontinuation - Percentage of discontinued participants for each protocol-specific reason for discontinuation
Participants who start the follow-up	- BAP0527 group - Usual treatment group - Overall	- Study discontinuation (follow-up period) - Main reason for study end (follow-up period)	- Percentage of completed or discontinued participants among participants who start the follow-up - Percentage of discontinued participants for each reason for discontinuation
Randomized participants	- BAP0527 group - Usual treatment group - Overall	Participants excluded from the FAS	Percentage of excluded participants among randomized participants for each reason for exclusion
FAS	- BAP0527 group - Usual treatment group - Overall	Participants excluded from the FAS2	Percentage of excluded participants among those in the FAS for each reason for exclusion
Randomized participants	- BAP0527 group - Usual treatment	Participants excluded from the SAF	Percentage of excluded participants among

Participants for analysis	Group	Participants to be counted	Parameters to be calculated
	group ● Overall		randomized participants for each reason for exclusion

6.2.2 Protocol Deviations

In the Randomized analysis set, the number and percentage of participants with major protocol deviations will be calculated by treatment group and overall. The results will be output by study site and overall. Participants deviating from a criterion more than once will be counted once for the corresponding criterion. Participants with more than one major protocol deviation will be counted once in the overall summary.

The following major protocol deviations will be included:

PD1 - Inclusion / Exclusion

PD2 - Withdrawal Criteria

PD3 - Study Intervention

PD4 - Excluded Concomitant Medications

PD5 - Informed Consent

PD6 - Safety Reporting

PD7 - Procedures/Tests

6.2.3 Demographic and Other Baseline Characteristics

In the FAS, SAF, and Randomized analysis set, frequency tabulations will be presented for categorical data and summary statistics will be calculated for continuous data, by treatment group and overall.

Table 5 Demographic Data (FAS, SAF, and Randomized Analysis Set)

Characteristic	Analysis method
Sex	- Number and percentage of participants - Male - Female
Age (at the time of obtaining informed consent) (years)	- Summary statistics - Number and percentage of participants ≥18 to <65 years ≥65 to <75 years ≥75 years
Body weight (at screening) (kg)	Summary statistics
Height (at screening) (cm)	Summary statistics
BMI (at screening) (kg/m ²)	- Summary statistics - Number and percentage of participants <25 kg/m² ≥25 kg/m² - Number and percentage of participants <18.5 kg/m² ≥18.5 kg/m² to <25 kg/m² ≥25 kg/m²
HbA1c (at screening) (%)	- Summary statistics - Number and percentage of participants <8.5% ≥8.5% - Number and percentage of participants <8.0% ≥8.0% to <9.0% ≥9.0% to <10.0% ≥10.0%
HbA1c (at baseline) (%)	- Summary statistics - Number and percentage of participants <8.0% ≥8.0%
HLS-14	- Summary statistics - Total score - Functional health literacy - Communicative health literacy - Critical health literacy
DCT	- Number and percentage of participants - Participants who receive assessment and intervention related to the study in the DCT - Participants who receive assessment and intervention at usual study sites
Diet and exercise restrictions	- Number and percentage of participants - Participants who have complications requiring diet and exercise restrictions - Participants who do not have complications requiring diet and exercise restrictions

In the FAS2, frequency tabulations will be presented for categorical data primarily at Week 24 and summary statistics will be calculated for continuous data, by treatment group and overall.

Table 6 Demographic data (FAS2)

Characteristic	Analysis method
Age (at the time of obtaining informed consent) (years)	- Summary statistics - Number and percentage of participants ≥18 to <65 years ≥65 to <75 years ≥75 years
Sex	- Number and percentage of participants - Male - Female
Height (at screening) (cm)	Summary statistics
Body weight (at screening) (kg)	Summary statistics
BMI (at screening) (kg/m ²)	- Summary statistics - Number and percentage of participants <18.5 kg/m² ≥18.5 kg/m² to <25 kg/m² ≥25 kg/m²
HbA1c (at Week 24) (%)	- Summary statistics - Number and percentage of participants <8.0% ≥8.0% to <9.0% ≥9.0% to <10.0% ≥10.0%
DCT	- Number and percentage of participants - Participants who receive assessment and intervention related to the study in the DCT - Participants who receive assessment and intervention at usual study sites
Diet and exercise restrictions	- Number and percentage of participants - Participants who have complications requiring diet and exercise restrictions - Participants who do not have complications requiring diet and exercise restrictions

In the SAF, the number and percentage of participants who have complications by SOC and PT will be calculated by treatment group and overall.

6.2.4 Previous and Concomitant Medications

Previous treatments are defined as treatments used before the day of randomization, and concomitant treatments are defined as treatments used from the day of randomization to the completion day of the treatment period + the follow-up period. Previous therapies are defined as therapies used before the day of randomization, and concomitant therapies are defined as therapies used from the day of randomization to the completion day of the treatment period + the follow-up period. Treatments (therapies) that start prior to and continue after the day of

randomization will be counted as both previous and concomitant treatments (therapies). Hypoglycemics and other medications will be summarized separately in previous and concomitant treatments.

The following frequency tabulations will be presented by treatment group and overall. The FAS and SAF will be used as the analysis sets.

- The number and percentage of participants who use or do not use previous or concomitant treatments other than hypoglycemics will be calculated.
- The number and percentage of participants who use or do not use previous or concomitant treatments with hypoglycemics will be calculated.
- The number and percentage of participants who use previous or concomitant treatments other than hypoglycemics will be calculated for each drug name and each route of administration.
- The number and percentage of participants who use previous or concomitant treatments with hypoglycemics will be calculated for each drug name.

The following frequency tabulations will be presented by treatment group and overall. Hypoglycemics used during the treatment period will be included to summarize hypoglycemics during the treatment period, and hypoglycemics used during the follow-up period will be included to summarize hypoglycemics during the follow-up period. The FAS will be used as the analysis set to summarize hypoglycemics during the treatment period, and the FAS2 will be used as the analysis set to summarize hypoglycemics during the follow-up period.

- The number and percentage of participants who use hypoglycemics will be calculated for each drug name, separately, during the treatment period and follow-up period.
- Summary statistics of the total duration of administration of each hypoglycemic will be calculated separately during the treatment period and follow-up period.

6.3 Investigational Device

6.3.1 Status of Use of This Product and Follow-up Status

The status of use of this product and the follow-up status will be analyzed on the SAF.

- Summary statistics of the duration (days) of use of this product will be calculated. The number of participants with the following categories of product use duration as well as the percentage of these participants in the SAF will be calculated:
 - ≥ 1 to < 29 days
 - ≥ 29 to < 57 days
 - ≥ 57 to < 85 days
 - ≥ 85 to < 113 days
 - ≥ 113 to < 141 days
 - ≥ 141 to < 169 days
 - ≥ 169 days
- Summary statistics of the treatment duration, follow-up duration, and treatment duration + follow-up duration (days) will be calculated.

- The number and percentage of participants with the following categories of treatment duration and follow-up duration (days) will be calculated:
 - Treatment duration:
 - Day 1 ~ Day 28
 - Day 29 ~ Day 56
 - Day 57 ~ Day 84
 - Day 85 ~ Day 112
 - Day 113 ~ Day 140
 - Day 141 ~ Day 168
 - Day 169 ~
 - Follow-up duration:
 - Day 0
 - Day 1 ~ Day 28
 - Day 29 ~ Day 56
 - Day 57 ~ Day 84
 - Day 85 ~

6.3.2 Investigational Device Compliance

Compliance with the investigational device will be analyzed on the FAS.

- In participants in the BAP0527 group, the BAP0527 access rate and blood glucose level data input rate during the treatment period will be summarized by time period. The BAP0527 access rate and blood glucose level data input rate throughout the treatment period will also be summarized.
- In participants in the BAP0527 group, the BAP0527 access count and the blood glucose level data input count during the treatment period will be summarized by time period. The BAP0527 access count and blood glucose level data input count throughout the treatment period will also be summarized.

6.4 Efficacy

Efficacy will be analyzed on the FAS unless otherwise stated.

6.4.1 Primary Endpoint

6.4.1.1 Primary Analysis

Since the treatment effect will be assessed under the assumption that the study treatment assigned to all participants is continuing, MAR will be assumed for any missing data. In the FAS, the change from baseline in HbA1c level at Week 24 of the treatment period in the BAP0527 group and usual treatment group will be compared using an MMRM. A two-sided 0.05 significance level will be used. The MMRM will include the change from baseline in HbA1c level at each time point as the response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), baseline levels, time point, interaction of treatment group and time point, and interaction of baseline and time point as explanatory variables. An unstructured covariance structure shared across treatment groups will be used to model the within-patient errors. The Kenward-Roger

approximation will be used to estimate denominator degrees of freedom and adjust standard errors. This analysis will use a restricted maximum likelihood-based repeated-measures approach. If the algorithm does not converge, a Toeplitz covariance structure will be used first. If the algorithm still does not converge, a compound symmetry covariance structure will be used. Subsequent MMRM analyses will use the same covariance structure, method for estimating denominator degrees of freedom and adjusting standard error, and covariance structures used in the case of convergence failure.

For the comparison between the BAP0527 group and the usual treatment group, the difference in least squares mean values and the two-sided 95% confidence interval and p-value will be calculated.

6.4.1.2 Sensitivity Analysis for the Primary Endpoint

6.4.1.2.1 Simplified MMRM

The change from baseline in HbA1c level at Week 24 of the treatment period will be analyzed using a simplified MMRM, with the treatment group, time point, baseline level, interaction of treatment group and time point, and interaction of baseline level and time point as explanatory variables.

6.4.1.2.2 Multiple Imputation Method Based on the Reason for Discontinuation

The MMRM used for the primary endpoint analysis assumes MAR. Specifically, it is assumed that the changes in HbA1c levels over time in participants who discontinue the study early are the same as the changes in HbA1c levels over time observed in the same group, and this model will be effective as long as this assumption is valid.

Multiple imputation (MI) based on the reason for discontinuation will be used to investigate the sensitivity of the primary analysis results to deviations from the assumption and assess whether the data from participants who discontinue the study early follow the pattern of missing not at random (MNAR).

For participants in the BAP0527 group who discontinue the study because of AEs, missing data will be imputed using the MI. If less than five participants discontinue the study because of AEs in the BAP0527 group, this analysis will not be performed. This analysis will be implemented using the common three processes of MI [O’Kelly and Ratitch, 2014]:

1. In the imputation phase, the MI will be implemented using sequential modeling of the “Jump to Reference” algorithm. If the “Jump to Reference” algorithm is implemented by sequential modeling, only baseline values will be used to impute missing data from participants in the BAP0527 group who discontinue the study because of AEs. In the imputation phase, M imputation data sets will be created (M=30).
2. In the analysis phase, the MMRM analysis of the primary endpoint specified in “6.4.1.1 Primary Analysis” will be performed for each of the M data sets with imputed missing data.
3. Rubin’s rules will be used to generate an overall set of pooled results which combines the analysis results from the M imputed datasets.

Based on the approach above, the following results will be presented in the pooled analysis:

- Least squares mean change from baseline to Week 24 in the BAP0527 group, SE, and two-sided 95% confidence interval
- Comparison between the BAP0527 group and the usual treatment group:
 - Difference in least squares mean change from baseline to Week 24, SE, and two-sided 95% confidence interval
 - A two-sided p-value in the comparison between the BAP0527 group and the usual treatment group will be calculated using the difference in least squares mean change.
- Summary statistics at Week 24 will be derived using the mean value of M imputation data sets.

6.4.2 Secondary Endpoints

- The change from baseline in HbA1c level (central lab measurement) at each assessment time point (except Week 24) will be analyzed using the MMRM described in “6.4.1.1 Primary Analysis.”
- For the percentage of participants with a baseline HbA1c level $\geq 8.0\%$ who achieved an HbA1c level $< 8.0\%$ at Week 24 (central lab measurement), the following two analyses will be performed:
 - If the HbA1c level at Week 24 is missing, the imputed HbA1c level under the assumption of MAR will be used. Missing data will be imputed using the MI. The details can be found in “6.11.1.2 Imputation of HbA1c levels.”
The logistic regression model will include whether or not participants achieve an HbA1c level $< 8.0\%$ at Week 24 as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($< 25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), and baseline HbA1c level as explanatory variables.
 - For participants with no missing HbA1c levels at Week 24, the percentage of participants who have achieved the target HbA1c level will be calculated.
- The change from baseline in fasting blood glucose level and fasting insulin level at Week 24 (central lab measurement) will be analyzed using the MMRM. The MMRM will include the change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($< 25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), baseline level, time point, interaction of treatment group and time point, and interaction of baseline and time point as explanatory variables.
- The percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 24, relative to antidiabetic use at baseline, will be analyzed with a logistic regression model. The logistic regression model will include whether or not participants have a decreased dose of antidiabetics or reduced number of antidiabetics by Week 24, relative to antidiabetic use at baseline, as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($< 25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), and baseline HbA1c level as explanatory variables.
- The percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 24, relative to antidiabetic use at baseline, will be analyzed with

a logistic regression model. The logistic regression model will include whether or not participants have an increased dose of antidiabetics or newly started hypoglycemics by Week 24, relative to antidiabetic use at baseline, as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), and baseline HbA1c level as explanatory variables.

- The change from baseline in HbA1c level at each assessment time point in the follow-up period (central lab measurement) will be analyzed using the MMRM described in “6.4.1.1 Primary Analysis.” The FAS2 will be used as the analysis set.
- The change from Week 24 in HbA1c level at each assessment time point in the follow-up period (central lab measurement) will be analyzed using the MMRM. The MMRM will include the change from Week 24 in HbA1c level at each time point after Week 24 as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), HbA1c level at Week 24, time point, interaction of treatment group and time point, and interaction of HbA1c level at Week 24 and time point as explanatory variables. The FAS2 will be used as the analysis set.
- The percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24, will be analyzed with a logistic regression model. The logistic regression model will include whether or not participants have a decreased dose of antidiabetics or reduced number of antidiabetics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24, as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), baseline HbA1c level, and HbA1c level at Week 24 as explanatory variables.
- The percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24, will be analyzed with a logistic regression model. The logistic regression model will include whether or not participants have an increased dose of antidiabetics or newly started hypoglycemics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24, as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), baseline HbA1c level, and HbA1c level at Week 24 as explanatory variables.

6.4.3 Exploratory Endpoints

- In participants with no changes in hypoglycemics, the change from baseline in HbA1c level at Week 24 will be analyzed using the MMRM described in “6.4.1.1 Primary Analysis.”
- For the percentage of participants who achieved an HbA1c level $<7.0\%$ at Week 24 (central lab measurement), the following two analyses will be performed:
 - If the HbA1c level at Week 24 is missing, the imputed HbA1c level under the assumption of MAR will be used. Missing data will be imputed using the MI. The details can be found in “6.11.1.2 Imputation of HbA1c levels.” The logistic regression model will include the percentage of participants who achieved an HbA1c level $<7.0\%$ at Week 24 as a response variable and treatment group (BAP0527

- group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), and baseline HbA1c level as explanatory variables.
- For participants with no missing HbA1c levels at Week 24, the percentage of participants who have achieved the target HbA1c level will be calculated.
- For the percentage of participants with a baseline HbA1c level $\geq 8.0\%$ who achieved an HbA1c level $< 8.0\%$ at each assessment time point (except Week 24) (central lab measurement), the following two analyses will be performed:
 - If the HbA1c level at the relevant assessment time point is missing, the imputed HbA1c level under the assumption of MAR will be used. Missing data will be imputed using the MI. The details can be found in “6.11.1.2 Imputation of HbA1c levels.” The logistic regression model will include whether or not participants achieve an HbA1c level $< 8.0\%$ at the relevant assessment time point as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), and baseline HbA1c level as explanatory variables.
 - For participants with no missing HbA1c levels at each assessment time point, the percentage of participants who have achieved the target HbA1c level will be calculated.
- The change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point (except Week 24) (central lab measurement) will be analyzed using the MMRM. The MMRM will include the change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), baseline level, time point, interaction of treatment group and time point, and interaction of baseline and time point as explanatory variables.
- The change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point in the follow-up period (central lab measurement) will be analyzed using the MMRM. The MMRM will include the change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), baseline level, time point, interaction of treatment group and time point, and interaction of baseline and time point as explanatory variables. The FAS2 will be used as the analysis set.
- Summary statistics of the change from baseline in tests related to complications of diabetes mellitus (vital signs, lipid levels) at each assessment time point will be calculated for each treatment group.
- For each level and for each item of EQ-5D-5L at each assessment time point, the frequencies and percentages will be calculated for each treatment group. Summary statistics of the change from baseline in VAS score at each assessment time point will also be calculated for each treatment group.
- Summary statistics of the change from baseline in DTSQ at each assessment time point will be calculated for each treatment group. The frequencies and percentages for each item will be calculated for each treatment group.

- The number of unscheduled visits up to Week 24 will be summarized and the mean number will be calculated for each treatment group.
- The BAP0527 access rate and blood glucose level data input rate will be calculated in the BAP0527 group. The details can be found in “6.3.2 Investigational Device Compliance.”
- To assess the relationship between the BAP0527 access rate or blood glucose level data input rate and the effect improving HbA1c level, summary statistics of HbA1c levels and changes from baseline at each assessment time point in the BAP0527 group will be calculated by access rate throughout the treatment period (<50%, ≥50% to <90%, ≥90%) and the blood glucose level data input rate throughout the treatment period (<25%, ≥25% to <50%, ≥50% to <75%, ≥75%).

6.4.4 Other Endpoints

- The percentage of participants with no changes in hypoglycemics by Week 24, relative to hypoglycemic use at baseline, will be analyzed with a logistic regression model. The logistic regression model will include whether or not participants have a change in antidiabetics by Week 24, relative to antidiabetic use at baseline, as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening (<25 kg/m², ≥25 kg/m²), and baseline HbA1c level as explanatory variables.
- The change from baseline in HbA1c level at Week 24 will be summarized at each study site. If there is an unacceptably large difference between sites, then add an analysis that includes sites as a model variable. Study sites with small numbers of randomized participants will be integrated to assess the impacts of study sites. If there are multiple study sites with less than four participants within the same region block, those sites will be integrated within the same region block and handled as an integrated site. The region blocks will include the following seven regions: Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku/Shikoku, and Kyushu/Okinawa.

The consistency of the observed effects between sites will be checked using a multivariate regression model. The change from baseline in HbA1c level at Week 24 will be the outcome variable, and treatment, site, BMI level at screening (<25 kg/m², ≥25 kg/m²), HbA1c level at screening, and interaction of treatment and site will be the explanatory variables. If an HbA1c level at Week 24 is missing, the Last Observation Carried Forward method will be used to impute the missing value using the HbA1c level measured on the latest day among the HbA1c levels measured from the day following the day of randomization until the last day of the treatment period. Statistical significance of interaction items (two-sided significance level 0.15) will indicate that the observed effects are not uniform between sites.

If the observed effects are not homogeneous among sites, site (or post-integration site if sites are integrated) will be added as an explanatory variable of the MMRM of the primary endpoint and used for analysis.

- The percentage of participants with newly started hypoglycemics by Week 24 will be analyzed with a logistic regression model. The logistic regression model will include whether or not participants have newly started hypoglycemics by Week 24 as a response

- variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), and baseline HbA1c level as explanatory variables.
- The percentage of participants with an increased dose of hypoglycemics by Week 24, relative to hypoglycemic use at baseline, will be analyzed with a logistic regression model. The logistic regression model will include whether or not participants have an increased dose of hypoglycemics by Week 24, relative to hypoglycemic use at baseline, as a response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), and baseline HbA1c level as explanatory variables.
 - The percentage of participants with first started hypoglycemics by Week 24 will be calculated.
 - The percentage of participants with first started hypoglycemics during the follow-up period will be calculated. The FAS2 will be used as the analysis set.

6.5 Safety

The following analyses will be performed on the SAF:

6.5.1 Adverse Events and Deficiencies

The number and percentage of participants with the following AEs and AEs for which a relationship with this product cannot be ruled out will be calculated by period (treatment period, follow-up period, and treatment period + follow-up period). The number and percentage of participants will also be calculated by SOC and PT. AEs observed after randomization, within the treatment period and follow-up period, will be defined as TEAEs. All TEAEs recorded by the investigator to have a causal relationship with this product will be defined as product-related TEAEs. A participant with multiple occurrences of an AE at differing severity levels will be counted once with the worst severity.

- Treatment-emergent adverse events (TEAEs)
- TEAEs by severity
- Product-related TEAEs
- Product-related TEAEs by severity
- TEAEs due to deficiencies
- Serious TEAEs
- Serious product-related TEAEs
- TEAEs leading to death
- Product-related TEAEs leading to death
- TEAEs leading to study discontinuation
- Product-related TEAEs leading to study discontinuation
- TEAEs reported by $\geq 5\%$ of participants in either group
- Non-serious TEAEs reported by $\geq 5\%$ of participants in either group
- Deaths

The number and percentage of participants with the following deficiencies will be calculated by product (BAP0527, Accu-Chek Guide Me).

- All deficiencies
- Deficiencies that may cause serious TEAEs
- Deficiencies that cause TEAEs

The number of deficiencies not linked to participants will be counted and presented in a data listing.

6.5.2 Laboratory Test Values

Baseline is defined as visit 2. Continuous data recorded as “<X” or “≤X” will be treated as “X” and continuous data recorded as “>Y” or “≥Y” will be treated as “Y” for analysis. The laboratory values will be analyzed only using the results of central lab measurement. The measurement results at study sites will be presented only in data listings.

- For continuous data, summary statistics of measured values and changes from baseline will be calculated at each assessment time point.
- For continuous data, a box plot of measured values will be created at each assessment time point.
- For categorical data, frequency tabulations will be presented at each assessment time point.
- For continuous data, changes from baseline to Week 24 over time will be summarized.

The reported ranges for urinalysis were changed after the request on June 10, 2024, due to the relocation of the central laboratory SRL.

- The reported range of specific gravity was changed from “1.000 to 1.999” to “1.000 to 1.049, ≥1.050.”
- The reported range of pH was changed from “5.0 to 8.5” to “5.0 to 9.0.”
- The reported range of glucose was changed from “–, +–, +, +2, +3” to “–, +–, +, +2, +3, +4.”
- The reported range of protein was changed from “–, +–, +, +2, +3” to “–, +–, +, +2, +3, +4.”
- The reported range of urobilinogen was changed from “+–, +, +2, +3” to “+–, +, +2, +3, +4.”

The data of specific gravity, pH, and glucose in urinalysis will be analyzed using the following methods:

- Specific gravity values of 1.050 to 1.999 measured before the change will be handled as 1.050 for analysis. Specific gravity values of ≥1.050 measured after the change will be handled as 1.050 for analysis.
- pH values of 8.5 to 9.0 measured after the change will be handled as 8.5 for analysis.

- The measured glucose values will be analyzed separately before and after the change, as well as overall.

6.5.3 Vital Signs

For systolic and diastolic blood pressure (mmHg) at rest in a sitting position, pulse rate (beats/minute), and body temperature, the following analyses will be performed:

- Summary statistics of measured values and changes from baseline will be calculated at each assessment time point.
- A box plot of measured values will be created at each assessment time point.

6.6 Pharmacokinetic Analysis

Not applicable.

6.7 Pharmacodynamic Analysis

Not applicable.

6.8 Subgroup Analyses

Subgroup analyses will be performed for the parameters listed in Table 7. In the subgroup analysis by BMI level ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), BMI level ($<25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$) will be excluded from the explanatory variables of the MMRM and logistic regression model. If less than five participants receive assessment and intervention related to the study in the DCT, no subgroup analysis by DCT will be performed.

Table 7 Summary of Subgroup Analyses

Type of Summary	Subgroups
Efficacy: Primary endpoint	• HbA1c level at screening (central lab measurement: <8.5%, ≥8.5%) • BMI level (<25 kg/m², ≥25 kg/m²) • HLS-14 (total score ≥ median, total score < median) • DCT (group of participants who received assessment and intervention related to the study in the DCT, group of participants who received assessment and intervention at usual study sites)
Efficacy: Secondary endpoints	• HbA1c level at screening (central lab measurement: <8.5%, ≥8.5%) • BMI level (<25 kg/m², ≥25 kg/m²) • DCT (group of participants who received assessment and intervention related to the study in the DCT, group of participants who received assessment and intervention at usual study sites)
Safety: TEAEs by SOC and PT	• HbA1c level at screening (central lab measurement: <8.5%, ≥8.5%) • BMI level (<25 kg/m², ≥25 kg/m²) • DCT (group of participants who received assessment and intervention related to the study in the DCT, group of participants who received assessment and intervention at usual study sites) • Diet and exercise restrictions (group of participants who have complications requiring diet and exercise restrictions, group of participants who do not have complications requiring diet and exercise restrictions)

6.9 Others

The following analyses will be performed on the Randomized analysis set:

- For body weight, summary statistics of measured values and changes from baseline will be calculated at each assessment time point in each treatment group.
- The percentage of participants who are or are not directed about the use of sphygmomanometers and scales for weight measurement will be calculated at each assessment time point in each treatment group.
- The number and percentage of participants at each study site will be calculated in each treatment group.

6.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

There will be no interim analysis.

6.11 Handling of Missing Data, Outliers, Analysis Windows, and Other Information

6.11.1 Imputation Rules for Missing Data

6.11.1.1 Imputation of Start and Stop Dates for Concomitant Medications and Concomitant Therapies

In the case of missing or partial start or stop dates for previous or concomitant medications or previous or concomitant therapies, the following rules will be used for imputation:

If the start date is missing or partial:

- if the month is missing, use January
- if the day is missing, use the first day of the month under consideration
- if the year is missing, use the year of the informed consent date
- if the entire date is missing, use the informed consent date

If the stop date is missing or partial:

- if the month is missing, use December
- if the day is missing, use the last day of the month under consideration
- if the year is missing, or if the entire date is missing in participants who are not on (ongoing) treatment, set the stop date to December 31, 2099
- in participants who are on (ongoing) treatment, the stop date will remain missing.

If the imputed start date is after the stop date, then the imputed start date will be 1 day prior to the stop date.

6.11.1.2 Imputation of HbA1c levels

If the HbA1c level is missing to assess the percentage of participants who have achieved the target HbA1c level, the HbA1c level imputed using the MI under the assumption of MAR will be used. Missing data imputation will be implemented using the common three processes of MI:

1. In the imputation phase, missing data sets will be imputed to create M imputation data sets (M=30).
2. In the analysis phase, each of the M data sets with imputed missing data will be analyzed.
3. The analysis results based on the M substitution data sets will be pooled using Rubin's rule.

6.11.1.3 Imputation of Onset Dates of Adverse Events/Deficiencies

For AEs/deficiencies, a missing or incomplete onset date will be imputed according to the following conventions.

If the onset date of AEs/deficiencies is missing, the imputed onset date will be the date of visit 2.

If only the year is known for the AE/deficiency onset date and it is in or after the year of visit 2, the imputed onset date will be the latest of the following non-missing dates:

- Date of visit 2
- January 1 of the year of AE/deficiency onset date

If only the year is known for the AE onset date and it is earlier than the year of visit 2, the AE will be considered to have occurred before randomization and will not be handled as a TEAE.

If only the month and year are known for the AE/deficiency onset date, set the surrogate onset date to the first day of that month and then apply the following rules.

- If the month and year of the onset date are prior to the month and year of visit 2, then the surrogate onset date will be the imputed onset date.
- If the month and year of the onset date are in or after the month and year of visit 2, then the imputed onset date will be the latest of the following non-missing dates:
 - Date of visit 2
 - Surrogate onset date

If the imputed onset date is after the AE/deficiency end date, the imputed onset date will be the same as the AE/deficiency end date. If only the month and year are known for the AE onset date, and the month and year are prior to the month and year of visit 2, the AE will be considered to have occurred before randomization and will not be handled as a TEAE. If the onset date is imputed using the date of visit 2, the AE will be considered to have occurred after randomization and will be handled as a TEAE.

If the deficiency onset time is missing, use 0:00.

6.11.2 Outliers

No special processing will be performed for outliers.

6.11.3 Analysis Windows

6.11.3.1 Efficacy Analysis Windows

The analysis visit windows for efficacy assessment are specified in Table 8. If more than one observation exists within the analysis window, the observation closest to the scheduled visit day will be selected for that visit. If there are two observations that have the same distance from the scheduled day, the value that is after the scheduled day will be selected in the analysis. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

Table 8 Analysis Visit Windows

Analysis Visit	Target Day	Analysis Window
Screening	Day -28 to Day -1	Day -28 to Day -1
Baseline	Day 1	-
Week 2 ^a	Day 15	Day 12 to Day 18
Week 4	Day 29	Day 22 to Day 36
Week 8	Day 57	Day 50 to Day 64
Week 12	Day 85	Day 78 to Day 92
Week 16	Day 113	Day 106 to Day 120
Week 20	Day 141	Day 134 to Day 148
Week 24	Day 169	Day 162 to Day 176
Week 28	Day 197	Day 190 to Day 204
Week 32	Day 225	Day 218 to Day 232
Week 36	Day 253	Day 246 to Day 260

^a Week 2 will not be used for the analysis visits for HbA1c levels, fasting blood glucose, fasting insulin, laboratory tests, EQ-5D-5L, or DTSQ.

6.11.3.2 Safety Analysis Windows

The analysis visit windows for safety tests will be the same as those specified in Table 8. If more than one observation exists within the analysis window, the observation closest to the scheduled visit day will be selected for that visit. If there are two observations that have the same distance from the scheduled day, the value that is after the scheduled day will be selected in the analysis. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

7 DOCUMENT HISTORY

Version	Date	Description
1.0	January 30, 2024	Final version
2.0	November 29, 2024	I. Added the definition of baseline.
		4.2, 4.5 Revised the description of analysis sets.
		5.1.3 Updated the data sets used for the access rate and access count
		5.1.3, 5.5, 6.2.3, 6.3.1, 6.4.4, 6.5.1, 6.8, 6.9, 6.11.3 Made minor revisions to the description.
		6.1 Added the description of handling of laboratory test values used as reference data.
		6.2.1 Modified the analysis sets used to present the participant disposition and added the table number.
		6.2.3 Changed the age categories and added the characteristic categories (DCT, diet and exercise restrictions).
		6.2.4 Modified the definitions of previous and concomitant treatments and previous and concomitant therapies and revised the description.
		6.4.1.2.2 Added the criteria for analysis using the multiple imputation method based on the reason for discontinuation.
		6.4.3 Revised the description of the analysis to assess the relationship between the BAP0527 access rate or blood glucose level data input rate and HbA1c levels.
		6.5.2 Modified the description of baseline, added the description of handling of measured values, and deleted the summary of changes over time in categorical data.
		6.8 Deleted subgroups (hypoglycemics, access rate, blood glucose level data input rate) and added a subgroup (diet and exercise restrictions), as well as added the criteria for subgroup analysis by the DCT.
		6.9 Added the analysis of participants at each study site.
		6.11.1.3 Added the description of handling of TEAEs.

Version	Date	Description
3.0	April 25, 2025	6.11.3 Modified the criteria for data selection in case of more than one observation and modified the table.
		9.1 Changed the person who approved the document.
		5.1.3 Added the description of handling app input data observed simultaneously.
		6.3.1 Modified the categories of the duration of product use, treatment duration, and follow-up duration.
		6.4.3 Changed the categories of access rate and blood glucose level data input rate.
		6.4.4 Added the description of missing data imputation.
		6.5.2, 6.11.3.1 Revised the description and modified the table.
		9.1 Updated the affiliation name.
		5.1.4, 5.5, 6.2.4, 6.4.3, 6.4.4 Added endpoints and analyses for investigating cost-effectiveness.
		6.1, 6.2.1, 6.4.3, 6.4.4, 6.5.2 Revised the description.
4.0	July 23, 2025	6.5.2 Added the description of handling of measured values.
		5.1.4, 6.4.4, 6.5.2, 6.11.1.1 Revised the description.
5.0	October 21, 2025	5.5 Modified the definition of the number of days of the follow-up period.
		6.2.3 Modified the time of obtaining age information.
		9.1 Updated the affiliation name.

8 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; “Efficacy” Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; “Efficacy” Topics)

O’Kelly M & Ratitch B. Clinical Trials with Missing Data: A Guide for Practitioners. Statistics in Practice (2014):189 – 190.

9 APPENDICES

9.1 Appendix 1. Author and Approvers

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