Statistical Analysis Plan

Protocol Number: MP-513-C02

A phase 3 randomized, double-blind, placebo-controlled parallel group efficacy and safety monotherapy study of MP-513 in Chinese subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise

Final Version 2.0
Date 11 Dec 2018

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A phase 3 randomized, double-blind, placebo-controlled parallel group efficacy and safety monotherapy study of MP-513 in Chinese subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise

Statistical Analysis Plan

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SIGNATURE PAGE

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded Data Review Meeting
BMI	Body Mass Index
CFDA	China Food and Drug Administration
CI	Confidence Interval
CIP	Clinical Investigational Plan
CRF	Case Report Form
DPP-4	Dipeptidyl Peptidase-4
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GGT	Gamma-Glutamyl Transferase
GIP	Glucose-dependent Insulinotropic Peptide
GLP-1	Glucagon Like Peptide-1
HbA1c	Glycosylated Fraction of Haemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HR	Heart Rate
hr(s)	hour(s)
HOMA-ß	Homeostatic Model Assessment-Beta
HOMA-IR	Homeostatic Model Assessment-Insulin Resistance
IB	Investigator's Brochure
IRB	Institutional Review Board
IWRS	Interactive Web Response System
Kg	Kilograms
LDH	Lactate Dehydrogenase
LDL-C	Low Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
LS-Mean	Least Square Mean
m	Metre
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram

Min	Minimum
MMRM	Mixed Model Repeated Measure
QTc	Q-T interval corrected for heart rate
N	Number of subjects
OR	Odds Ratio
RV	Randomization Visit
PPS	Per-Protocol Set
PT	Preferred Term
PV	Placebo Run-In Visit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SV	Screening Visit
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

2 INTRODUCTION

This Statistical Analyses Plan (SAP) describes the planned analyses to evaluate the efficacy and safety of MP-513 compared with placebo in Chinese subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise.

The general information about the study is detailed in the MP-513-C02 protocol.

3 STUDY OBJECTIVES

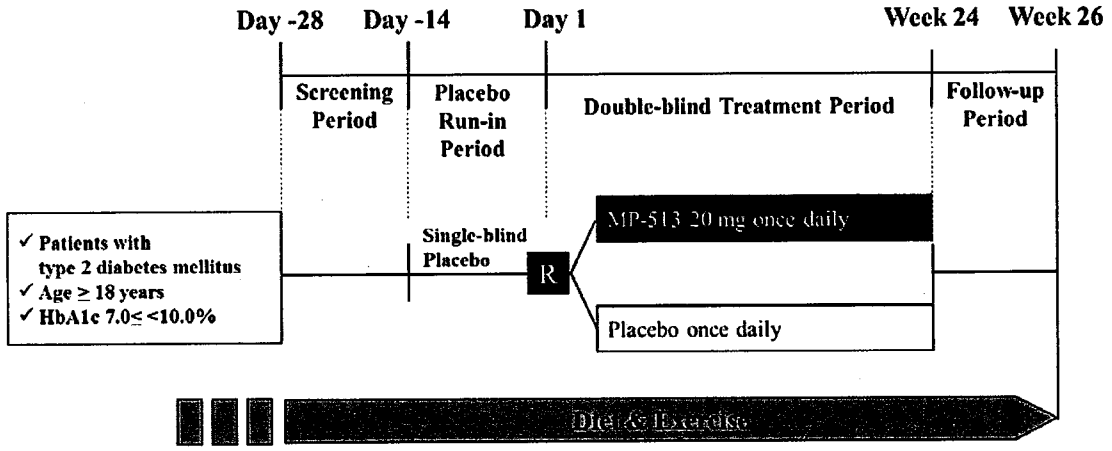
The objective of this study is to evaluate the efficacy and safety of MP-513 compared with placebo in Chinese subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise.

4 STUDY DESIGN

4.1 General Design

This is a multi-centre, randomized, double-blind, placebo-controlled, parallel-group study in subjects with type 2 diabetes mellitus.

The study flowchart is presented below:



4.2 Discussion of Study Design

The main characteristics of this study are:

- **Placebo run-in period:** The intention of the placebo run-in period is to exclude subjects who have poor treatment compliance, to enable a comparison of the effects of different treatments without the influence of placebo effect and to have a relatively stable HbA1c value at baseline.

- **Duration of double-blind treatment period:** HbA1c stabilizes over 24-week period. The double-blind treatment period is planned for 24 weeks to evaluate a stable HbA1c change from baseline compared with placebo and to investigate the safety/tolerability of MP-513 after treatment for this duration.

- **Dosage:** The dose of 20 mg orally administered once daily before breakfast is the established dose for this medication.

- **Safety Follow-up:** The two week safety follow-up period is sufficient to confirm the subjects' safety after the completion/discontinuation of the treatment.

4.3 Method of Assignment of Subjects to Treatment Groups

Treatment assignment will be managed through static blocked randomization and an Interactive Web Response System (IWRS) will be used.

After the Placebo run-in period, the eligible subjects will be randomized to one of the following treatment groups in a 1:1 allocation ratio:

- **Test Product:** One 20 mg tablet of MP-513, once daily before breakfast starting from the randomization visit (Day 1).

- **Placebo:** One placebo tablet, once daily before breakfast starting from the randomization visit (Day 1).

Randomization will be performed according to computer generated randomization scheme where a treatment group designation has been assigned to each subjects' randomization kit number. The treatment designation will remain blinded until the database is closed. An independent unblinded team within [redacted] will hold the randomization codes throughout the study, until authorization is provided by a Mitsubishi Tanabe Pharma Corporation representative to release the randomization schedule.

4.4 Blinding

Study treatments will be packaged for double-blind administration. The placebo is identical to the corresponding active treatments.

During single-blind run-in period, the subjects will not know that they are receiving placebo during the single-blind run-in period.

During the double-blind treatment period the subject, the investigator, the laboratory personnel, and the sponsor other than a designated person would not know the treatment arm to which a subject is assigned.

Unblinding of treatment for a subject may be performed in case investigator considers it necessary for the safety of the subject. The reason for breaking the blind along with date and time must be clearly documented in the source documentation and Case Report Form (CRF), and the subject will be discontinued from the study. The sponsor must be notified immediately upon all unblinding situations.

4.5 Determination of Sample Size

[redacted]

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

This SAP is prepared based on the study protocol version 2.0 dated 29 April, 2016 and there are no planned changes either in the conduct of the study or planned analysis at the time of preparing this SAP.

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

The assessments to be conducted at each scheduled visit are displayed in the below table.

Table 2 Schedule of Visits

Period	Scr. Period	Placebo Run-in Period		Double-Blind Treatment Period						Follow-up Period
Visit	SV	PV	RV	V1	V2	V3	V4	V5	V6	FV
Visiting Windows / Items	Day -28 +/- 3 days	Day -14 +/- 3 days	Day 1	Week 4 +/- 7 days	Week 8 +/- 7 days	Week 12 +/- 7 days	Week 16 +/- 7 days	Week 20 +/- 7 days	Week 24 (5) +/- 7 days	Week 26 (6) + 14 days
Obtain written informed consent	X									
Screening/Inclusion/ Exclusion criteria evaluation	X	X	X							
Demographics and complete medical history	X (7)									
Height	X									
Body Weight	X		X	X	X	X	X	X	X	
Vital signs (1)	X	X	X	X	X	X	X	X	X	
12-lead ECG	X		X			X			X	
Routine laboratory evaluations: hematology, chemistry, urinalysis	X		X	X	X	X	X	X	X	
Serum pregnancy test (2)	X								X	
HbA1c	X	X	X	X	X	X	X	X	X	
Fasting plasma glucose	X	X	X	X	X	X	X	X	X	
Fasting insulin, C-peptide and glucagon			X	X	X	X	X	X	X	
Dispense medication		X	X	X	X	X	X	X		
Return of unused medication			X	X	X	X	X	X	X	
Assessment of adverse events (3) and concomitant medication	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes (4)	X	X	X	X	X	X	X	X	X	X
Dispense subjects diary and glucometer	X									
Subject diary review		X	X	X	X	X	X	X	X	

Scr period: Screening period, SV: Screening visit, PV: Placebo run-in visit, RV: Randomization visit, FV: follow-up visit

(1) Vital signs (sitting blood pressure, pulse rate and body temperature)

(2) The serum pregnancy test will be performed only for female subjects of childbearing potential.

(3) AEs will be collected and reported on the eCRF from the date of informed consent to 14 days after the final dose of the study drug considering the half-life (T1/2) of MP-513.

(4) The occurrence of hypoglycaemic episodes will be recorded continuously throughout the study by a subject diary

(5) These assessments will also be performed at early termination.

(6) Telephone visit

(7) Including physical examination

6.2 Time Point Algorithms

6.2.1 Study Day

The date of first dose of study drug administration during the double blind phase will be considered study day 1, and the day before the first dose of study drug of double blind phase will be study day -1. Study days will be calculated only when the full assessment date is known (i.e., partial dates will have missing study days).

Study Day =
- Date of Assessment – Date of Randomization Visit + 1
  For assessment on or after the day of randomization
- Date of Assessment – Date of Randomization Visit
  For assessment before the day of randomization

6.2.2 Windows

For the purpose of effectiveness and safety analysis, all scheduled and unscheduled clinic visits will be windowed as presented in the below table. The planned protocol visit window will be used for analysis.

Table 3 Schedule of Visits

Visit	Week	Scheduled Study Day	Visit Window in Protocol (Days)
Randomization Visit (RV)	Randomization Visit (RV)	1	1
Visit 1	Week 4	28	21 – 35
Visit 2	Week 8	56	49 – 63
Visit 3	Week 12	84	77 – 91
Visit 4	Week 16	112	105 – 119
Visit 5	Week 20	140	133 – 147
Visit 6	Week 24	168	161 – 175
Follow-up Visit	Week 26	182	182 – 196

If a visit day is outside of these windows, then it is considered as non-windowed, otherwise it is windowed. If a subject has more than one assessment occurring in the same visit window, the data from the visit closest to the scheduled study day will be used. If two visits have the same distance from the scheduled study day, the data of the visit after the scheduled study day will be used.

The unscheduled visits will be chronologically arranged between two scheduled visits. The unscheduled visits will be numbered sequentially with an increment of 0.1 to the visit number corresponding to scheduled visit preceding the unscheduled visit. For example, if two unscheduled visits occur between visit 1 (visit number is 10) and visit 2 (visit number is 20), then these unscheduled visits will be numbered 10.1, 10.2 in the order they occurred.

The assessments made in unscheduled visits will be considered in imputation of missing assessment using Last Observation Carry Forward (LOCF) method for Week 12 or Week 24.

6.3 Baseline Assessments

Baseline assessments will be the most recent assessment prior to the randomization.

6.4 Duration of diabetes

Duration of diabetes will be calculated as:

- Duration of diabetes = (Year of screening visit – Year of Diagnosis) +
  (Month of screening visit – Month of Diagnosis) / 12

Note: If the month of diagnosis is unknown, impute "1 (January)" for the calculation. Duration of diabetes will be displayed to one decimal place.

6.5 Medical History and Prior and Concomitant Medications

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. Prior and Concomitant medications will be coded using the World Health Organisation (WHO) DRUG dictionary version March 2018.

6.6 Extent of Exposure and Compliance to Study Treatment

Study drug exposure during double blind treatment period will be calculated as:

- Exposure duration = (Date of Visit 6 - Date of Randomization Visit)

Note: In case of early withdrawal, the date when unused study treatments are returned will be used to calculate the exposure duration.

Treatment compliance during the double blind treatment period will be calculated as:

- Overall Compliance = 100 X (Number of tablets dispensed – Number of tablets returned)
  / Exposure duration

Note: Overall compliance will be displayed to one decimal place.

6.7 Efficacy Variables

At each scheduled visit, blood sample will be collected from each subject to evaluate HbA1c, fasting plasma glucose (FPG), fasting insulin, C-peptide and glucagon. Blood sample will be analysed in designated central laboratory. Body weight (Kg) will be measured at each scheduled visit.

HOMA-IR and HOMA-ß will be evaluated by FPG and fasting insulin as follows:

- HOMA-IR = Fasting insulin (μU/mL)* FPG (mg/dL)/405
- HOMA-ß = 360 * Fasting insulin (μU/mL)/ (FPG (mg/dL) – 63)

Efficacy variables units for analysis are described in Table 4.

Table 4 Efficacy Variable Units

Variables	Conventional Units	How to Convert	Units for Analysis
HbA1c	%	-	%
FPG	mg/dL	-	mg/dL
Fasting insulin	μU/mL	-	μU/mL
C-peptide	ng/mL	-	ng/mL
Glucagon	pmol/L	Multiply with 0.27241	pg/mL
HOMA-IR	-	-	$\mu U.mg/mL^2$
HOMA-ß	-	-	-
Body Weight	Kg	-	Kg

The efficacy variables will be evaluated for change from baseline. The change from baseline at post-baseline visits will be computed as:

- Change from baseline = Assessed/observed value at post-baseline visit – Value at baseline visit.

6.8 Safety Assessments

6.8.1 Adverse Events

All adverse events (AEs) or hypoglycaemia episodes occurring after signing the informed consent are to be recorded on the AE or the hypoglycaemia episode pages of the CRF. Investigators verbatim term of AE and hypoglycaemia episode will be mapped to system organ class (SOC) and preferred term (PT) using MedDRA version 21.0. All hypoglycaemia episodes will be coded as "Hypoglycaemia" (LLT code=10020993, ver21.0).

Duration of adverse events will be derived as:

- Duration of AE (Days) = End Date - Start Date +1

6.8.1.1 Definitions

Treatment Emergent Adverse Events (TEAEs):
TEAEs are defined as any AEs or hypoglycaemia episodes that occur or worsen (increase in severity) on the same day or after randomized.

The following rules will apply in cases where the start date of an AE is known:

- If the AE onset date is prior to Day 1, then the AE will not be considered a TEAE.
- If the AE onset date or date of AE worsening is equal to or later than Day 1, then the AE will be considered a TEAE.

The same rule will be applied in cases where start date of a hypoglycemic episode is known.

Refer section 7.3.1 to identify TEAE status when start date of an AE or hypoglycaemia episodes is unknown.

Adverse Drug Reactions (ADRs):
ADRs are defined as TEAE whose causal relationship to study drug is "Reasonable possibility". If the causal relationship to study drug is missing, then that TEAE will be treated as ADR.

6.8.1.2 Classifications

Severity:
Severity of AE or hypoglycaemia episode will be graded as "Mild", "Moderate" or "Severe". For AEs or hypoglycaemia episodes with missing severity, the most severe assessment will be imputed for summary analyses.

Causal relationship to study drug:
Causal relationship of AE or hypoglycaemia episode to study drug will be graded as "Reasonable possibility" or "No reasonable possibility". Any missing relationship of an AE or a hypoglycaemia episode to study drug will be considered as "Reasonable possibility", following the worst case principle.

Cardiovascular Events:
AEs will be adjudicated whether the AE is cardiovascular event or not. That information will be recorded in the CRF.

6.8.2 Clinical Laboratory Evaluations

Clinical laboratory parameters to be measured and their units for analysis are shown in the following table.

Table 5 Clinical Laboratory Parameters and Units

Variables		Conventional Units	How to Convert	Units for Analysis
Haematology	Haemoglobin	g/dL	-	g/dL
	Haematocrit	%	-	%
	Red blood cell count	x10^6/μL	Multiply with 10^2	x10^4/μL
	White blood cell count	x10^3/μL	Multiply with 10^2	x10/μL
	Platelet count	x10^3/μL	Divide by 10	x10^4/μL
Blood Chemistry	AST	U/L	-	U/L
	ALT	U/L	-	U/L
	Gamma-glutamyl transferase (GGT)	U/L	-	U/L
	Lactate dehydrogenase (LDH)	U/L	-	U/L
	Alkaline phosphatase	U/L		U/L
	Total bilirubin	mg/dL	-	mg/dL
	Total cholesterol	mg/dL	-	mg/dL

Variables		Conventional Units	How to Convert	Units for Analysis
Blood Chemistry	Triglycerides	mg/dL	-	mg/dL
	Low-density lipoprotein cholesterol (LDL-C)	mg/dL	-	mg/dL
	High-density lipoprotein Cholesterol (HDL-C)	mg/dL	-	mg/dL
	Blood urea nitrogen	mg/dL	-	mg/dL
	Creatinine	mg/dL	-	mg/dL
	Uric acid	mg/dL	-	mg/dL
	Total protein	g/dL	-	g/dL
	Albumin	g/dL	-	g/dL
	Globulin	g/dL	-	g/dL
	Albumin/globulin ratio	-	-	-
	Direct bilirubin	mg/dL	-	mg/dL
	Creatine kinase	U/L		U/L
	Sodium	mEq/L	-	mEq/L
	Potassium	mEq/L	-	mEq/L
	Chloride	mEq/L	-	mEq/L
	Calcium	mg/dL	-	mg/dL
	Magnesium	mg/dL	-	mg/dL
	Phosphate	mg/dL	-	mg/dL
Urinalysis	Glucose	-	-	-
	Protein	-	-	-
	Occult blood	-	-	-
	Urobilinogen	-	-	-
	Ketone bodies	-	-	-
	pH	-	-	-

Any value "Lower Limit of Quantification", e.g. "< x.xx" will be analysed as numerical value "x.xx".

Females of childbearing potential will have serum pregnancy test.

6.8.3 Vital Signs

Vital signs assessment includes measurement of systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), body temperature (celcius) and height (cm).

6.8.4 Electrocardiogram (ECG)

Standard 12- Lead ECG will include recording PR-interval (ms), RR-interval (ms), QRS-interval (ms), QT-interval (ms), QTc (ms) and heart rate (beats/min).

ECGs will be assessed by the Investigators and graded as:

- normal
- abnormal, not clinically significant
- abnormal, clinically significant

6.8.5 Physical Examination

This evaluation will include an examination of general appearance, head, eyes, ears, nose and throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal, neurological and other. These examinations will be categorized as normal or abnormal by the investigator.

7 STATISTICAL METHODS

7.1 General Methodology

All analyses will be performed after the database is locked and access has been removed from the database and the study treatment codes are unblinded.
All statistical tests will be two-sided with a significance level of α=0.05, unless specified otherwise and will be performed using SAS® Version 9.2 or higher.

Statistical tests will be supported by presenting estimates and 95% confidence intervals (CI) for the respective treatment effects and differences between the treatment groups. These estimates, confidence intervals and p-value will be based on the respective statistical models used for the analysis.

Data will be summarized using descriptive statistics (number of non-missing values [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency counts and percentage for discrete variables.

For the purpose of display, the summary results will be rounded as follows:
- Min and Max: same number of decimals as the raw data.
- Mean and Median: one more decimal place than the raw data.
- SD/Standard Error (SE): one more decimal places than the raw data.
- Percentages will be displayed with one decimal precision. A zero count will not have the associated percentage presented on the table (i.e. no 0%).
- All p-values will be displayed with a leading zero except when the value is 1. All p-values will be displayed to four decimal places. If a p-value is less than 0.0001, then the value will be displayed as '<0.0001'. If a p-value is 1, then the value will be displayed as 1.0000. If the p-value cannot be calculated for any reason, the value listed will be 'NA'.
- CI: one more decimal place than the raw data.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Subject listings of all data from the CRFs as well as any derived variables will be presented. Safety listings of clinical laboratory, vital signs and ECG will be presented by planned visit.

7.2 Adjustments for Covariates

The efficacy variable being analysed will be adjusted for its baseline value, as a covariate in the model.

7.3 Handling of Dropouts or Missing Data

Subjects who discontinue the study prior to or after the initiation of the study drug will not be replaced and available data of these subjects until the point of discontinuation will be summarized. The missing baseline assessment will not be imputed.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

The missing HbA1c and FPG value at week 12 or week 24 will be imputed using last observation carried forward (LOCF) approach. Baseline value will not be used to impute missing data. The missing data of Fasting insulin, C-peptide, Glucagon, HOMA-IR, HOMA-ß and Body weight at week 24 will also be imputed using LOCF approach.

The supportive analysis for primary efficacy will be done using observed values.

There will be no imputation of missing values in database of safety data, however missing relationship between AE and study medication will be considered as related to treatment following worst case principle. Missing severity of an AE will be summarized as severe AE.

7.3.1 TEAE status when start date is unknown

The following rules will apply in cases where start date of an AE is unknown:

- If the AE onset date is unknown and the end date is after Day 1 or ongoing, then the AE will be considered a TEAE.
- If the AE onset date is unknown and the end date is before Day 1, then the AE will not be considered a TEAE.
- If both the start and end dates are unknown (or end date is ongoing), then the AE will be considered a TEAE, following the worst case principle.

The same rule will be applied in cases where start date of a hypoglycemic episode is unknown.

7.4 Interim Analyses and Data Monitoring

No interim analysis is planned for this study. However, an independent Event Adjudication Committee (EAC) will be set up to evaluate the cardiovascular events.

7.5 Independent Event Adjudication Committee (EAC)

The study will have an independent EAC to adjudicate the cardiovascular events. The cardiovascular events are defined as:

- Death
- Myocardial Infarction
- Hospitalisation for Unstable Angina
- Stroke & TIA (fatal & non-fatal)
- Urgent Revascularisation Procedures

- Hospitalisation for Heart Failure

The adjudicated cardiovascular events will be used for the safety analyses.

7.6 Multi-center Studies and Pooling of Centers

This study will be conducted at approximately 35 sites in China. Data from all sites will be pooled and pooled data will be used for summary tables and analyses.

7.7 Multiple Comparisons/Multiplicity

Not applicable for this study as there is no multiple comparison and no interim analysis is planned.

7.8 Use of an "Efficacy Subset" of Subjects

Subjects in Full Analysis Set (FAS) who complied with the protocol (i.e. no major protocol violations), who have completed at least 8 weeks of double blinded medication and who have >75% treatment compliance with the investigational product (MP-513 or placebo) during the Double-blind treatment period will form a Per-Protocol set (PPS). Major protocol deviations will be assigned during Blind Data Review Meeting (BDRM) that will be held before database lock.

Analysis based on PPS will serve as a supportive analysis for primary efficacy endpoint.

The FAS and PPS are defined in section 8.3.

7.9 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

7.10 Examination of Subgroups

Exploratory sub-group analysis will be performed for the primary efficacy i.e. change in HbA1c from baseline to Week 24 for following subgroups:

- Gender (male and female)
- Body Mass Index (BMI) (<20 kg/m^2, 20 ≤BMI <25 kg/m^2, 25 ≤ BMI<30 kg/m^2, BMI≥30 kg/m^2)
- Age (<40 years, 40≤ Age<50 years, 50≤ Age <60 years, 60≤ Age <70 years, Age ≥70 years, Age <65 years and Age ≥65 years)
- Alcohol history (Abstainer, >28 units of alcohol per week and ≤28 units of alcohol per week)
- Baseline HbA1c (<7.0%, 7.0% ≤ HbA1c<8.0%, 8.0% ≤ HbA1c<9.0%, HbA1c≥9.0%)
- Baseline FPG (<130 mg/dL, 130 mg/dL≤ FPG<160 mg/dL, 160 mg/dL≤ FPG<200 mg/dL, FPG≥200 mg/dL)
- Duration of diabetes (<1 year, 1≤ Duration<5 years, 5≤ Duration<10 years, Duration≥10 years)

8 STATISTICAL ANALYSIS

8.1 Disposition of Subjects

The number and percentage of subjects randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations, will be summarized by treatment groups. The number of placebo run-in subjects who do not meet randomization criteria will also be presented in the disposition summary table.

A listing of all subjects who discontinued the study after randomization and placebo-run in subjects who do not meet randomization criteria will be provided. This will also include the specific reason for discontinuation.

8.2 Protocol Deviations

Potential deviations will be identified prior to database lock.

All protocol deviations will be reviewed in a blinded fashion during the blind review of the data and will be described in more detail in the minutes of blind data meeting. The sponsor review team will approve all the final protocol deviation assignments. Once all protocol deviation determinations are finalized and approved, the database will be locked and the treatment codes will be unblinded for statistical analysis.

Number and percentage of subjects with at least one major protocol deviations will be summarized by treatment group and overall.

A listing of all major protocol deviations by subjects to determine reasons for exclusion from the FAS and PPS will be presented.

8.3 Analysis Populations

The study will use following analysis populations for data summarization. Number and percentage of subjects in each analysis set will be summarized by treatment group and overall.

Table 6: Analysis Population

Population	Definition	Displays	Note
All Subject Set	The All Subject Set includes all subjects who were screened	Displays on subject disposition	The subjects will be analyzed for disposition
Randomized Set	The Randomized Set includes all subjects who were randomized	Displays on subject population and	The subjects will be analyzed according to the treatment to which they were randomized to, irrespective of treatment received
Full Analysis Set (FAS)	The FAS includes all subjects in the randomized set who have received at least one dose of study medication during the double-blind treatment	Displays related to demography, other baseline characteristics and	The subjects will be analyzed according to the treatment to which they were randomized

Population	Definition	Displays	Note
	period and have at least one post-baseline efficacy observation. Subjects who were not diagnosed with type 2 diabetes mellitus will be excluded.	all efficacy analyses	to, irrespective of treatment received
Per-Protocol Set (PPS)	The PPS includes subjects in the FAS who have no major protocol violations, who have completed at least 8 weeks of double-blinded medication and who have > 75% treatment compliance with the investigational product (MP-513 or placebo) during the Double-blind treatment period.	Demographics and Primary efficacy analysis	All protocol violations will be defined in more detail in the blind review document at a Blind Data Review Meeting that will be held before database lock. The subjects will be analyzed according to the treatment to which they were randomized to, irrespective of treatment received.
Safety Analysis Set	The Safety Analysis Set includes all subjects in the randomized set who have received at least one dose of study medication during the double-blind treatment period.	Displays related to demography, other baseline characteristics and all safety analyses	The subjects will be analyzed as MP-513 if the subjects received MP-513 at least once, irrespective of treatment to which they were randomized to. In other cases, the subjects will be analyzed according to the treatment they were randomized to.

8.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using the FAS, PPS and safety populations. No formal statistical test would be performed to determine statistical significance between treatment groups.

8.4.1 Demographics

Age, height, body weight (at screening) and body mass index (BMI) in kg/m^2 will be summarized as continuous variables by treatment group and overall using descriptive statistics.

Gender and race will be summarized as categorical variables by treatment group and overall using frequency counts and percentages.

Duration of diabetes mentioned in section 6.4 will be summarized descriptively by treatment groups and overall.

Alcohol history will be categorized as:

- Abstainer
- ≤28 units of alcohol per week
- >28 units of alcohol per week

These will be summarized by treatment group and overall using frequency counts and percentages.

All demographic characteristics will be presented in full subject listings.

8.4.2 Medical History

A full subject listing of medical history will be presented.

8.5 Prior and Concomitant Therapy

A full subject listing of prior and concomitant medications will be presented.

8.6 Extent of Exposure and Compliance to Study Treatment

Extent of Exposure and Compliance to Study Treatment will be summarized using the FAS, PPS and safety populations.

Duration of study drug exposure during the double blind treatment period and treatment compliance during the double blind treatment period will be calculated as mentioned in section 6.6 and will be summarized descriptively.

The treatment compliance during double blind period will also be summarized for compliance ≤75% and >75% using frequency counts and percentages.

8.7 Analysis of Efficacy Parameters

All efficacy analysis will be performed on FAS unless otherwise stated.

A full subject listing will be presented for efficacy results (HbA1c, FPG, fasting insulin, C-peptide, glucagon, HOMA-IR, HOMA-ß and body weight).

8.7.1 Analysis of Primary Efficacy Variable

8.7.1.1 Primary Analysis of Primary Efficacy Variable

The primary efficacy endpoint is to evaluate the change in HbA1c from baseline to Week 24 in the group receiving MP-513 compared with the group receiving placebo in Chinese subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. The reduction in HbA1c value indicates improvement.

The primary efficacy will be assessed by testing the null hypothesis that, there is no difference in the change in HbA1c from baseline to Week 24 in the group receiving MP-513 compared to the group receiving Placebo. In statistical notation the hypothesis is defined as follows:

Null Hypothesis $H_0: \mu_{MP\text{-}513} = \mu_{Placebo}$

Alternate Hypothesis $H_A: \mu_{MP\text{-}513} \neq \mu_{Placebo}$

Where $\mu_{MP\text{-}513}$: Mean change in HbA1c from baseline at week 24 for MP-513

$\mu_{Placebo}$: Mean change in HbA1c from baseline at week 24 for placebo

The missing HbA1c values at week 24 will be imputed using LOCF approach prior to analysis. The change in HbA1c from baseline to Week 24 (LOCF) will be analysed using analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline value as a covariate in the model.

For the treatment effects and the difference between the treatment groups, the least square means from ANCOVA will be presented along with the corresponding SE and CI. The treatment difference in mean change from baseline will be computed using the model. The p-values for the test of significance, SE and CI of the mean difference will be presented.

The change in HbA1c from baseline for all the post baseline assessments visits, Week 12 (LOCF) and Week 24 (LOCF) will also be summarized as continuous variable using descriptive statistics.

The line graph for mean change in HbA1c from baseline to Week 24 and Week 24 (LOCF) will be presented. The 95% CIs will also be shown in the graph with error bar. The plots of Week 24 and Week 24 (LOCF) will not be connected.

8.7.1.2 Supportive Analysis of Primary Efficacy Variable

The study will have two supportive analyses to be performed on primary efficacy variable i.e. change in HbA1c from baseline to Week 24, as follows:

- The change in HbA1c from baseline to Week 24 in MP-513 compared to Placebo will be performed on PPS using the same statistical methodology as described for the primary analysis.

The change in HbA1c from baseline to Week 24 in MP-513 compared to Placebo will be analysed using mixed effects model for repeated measure (MMRM), with treatment, visit and interaction of treatment and visit as fixed effects and baseline value as a covariate in the model. An unstructured covariance matrix will be used to model the covariance of within-subject values. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger, 1997). For this analysis, missing data will not be imputed, i.e. only the observed data will be used.

8.7.2 Analysis of Secondary Efficacy Variables

All analysis on secondary efficacy variables will be performed using FAS.
The secondary efficacy endpoint is to evaluate the change in FPG from baseline to week 24 of MP-513 compared to Placebo. The same statistical methodology as described for primary analysis on primary efficacy endpoint will be used.

The line graph for mean change in FPG from baseline to Week 24 and Week 24 (LOCF) will be presented. The 95% CIs will also be shown in the graph with error bar. The plots of Week 24 and Week 24 (LOCF) will not be connected.

8.7.3 Analysis of Other Efficacy Variables

All other efficacy endpoint will be analysed using FAS. The other efficacy endpoints are as follows:

- Proportion of subjects who achieved HbA1c < 7.0% at Week 24
- Change in fasting insulin, C-peptide, and glucagon from baseline to Week 24
- Change in HOMA-IR and HOMA-ß from baseline to Week 24
- Change in body weight from baseline to Week 24
- Change in HbA1c and FPG from baseline to Week 12

Proportion of subjects who achieved HbA1c < 7.0% at Week 24 (LOCF):
For the proportion of subjects who achieved HbA1c < 7.0% at Week 24 (LOCF), the comparison between treatments will be performed using logistic regression with treatment as fixed effect and baseline HbA1c value as a covariate. The subjects who have HbA1c < 7.0% at baseline will be excluded from the analysis.

The odds ratio (OR) with 95% Wald CIs will be presented for between treatment groups comparison of responder rate (i.e. proportion of subjects who achieved HbA1c < 7.0% at Week 24). The Wald Chi-Square p-value for significance of treatment effect after controlling for baseline HbA1c will also be displayed.

For logistic regression analysis, the dichotomous response variable will be coded as '1' (for subjects who achieved HbA1c < 7.0% at Week 24) and '0' for subjects for whom HbA1c ≥ 7.0% at week 24.

The frequency count and percentage of subjects who achieved HbA1c < 7.0% at week 24 will also be summarized by treatment groups.

Other efficacy endpoints:
For the remaining other efficacy endpoints, namely;
- Change in fasting insulin, C-peptide, and glucagon from baseline to Week 24
- Change in HOMA-IR and HOMA-ß from baseline to Week 24
- Change in body weight from baseline to Week 24
- Change in HbA1c and FPG from baseline to Week 12

The line graph for mean change in other efficacy endpoints from baseline to Week 24 and Week 24 (LOCF) will be presented. The 95% CIs will also be shown in the graph with error bar. The plots of Week 24 and Week 24 (LOCF) will not be connected.

The same statistical methodology as described for primary analysis on primary efficacy endpoint will be used.

8.7.4 Subgroup Analyses

The sub-group analysis will be performed for the primary efficacy endpoint i.e. Change in HbA1c from baseline to Week 24 for the subgroups mentioned in section 7.10.

Analyses of these subgroups will be performed using FAS. The analysis will be based on the same methods described for the primary analysis of primary efficacy endpoint.

8.8 Analysis of Safety

All safety data will be summarized by treatment groups using the Safety Analysis Set. No formal statistical test would be performed to determine statistical significance between treatment groups.

8.8.1 Adverse Events

All AE summary tables will include only TEAEs, unless otherwise specified.

Adverse events will be summarized by SOC and PT. A subject will only be counted once per SOC and PT within a treatment.

For AEs by severity grade (mild, moderate, severe), if a subject has multiple events occurring in the same SOC or same PT, then the event with the maximum intensity (i.e. severe) will be counted.

For AEs by relationship to study drug, if a subject has multiple events occurring in the same SOC or same PT, the event with the highest association (i.e. related) to study drug will be summarized.

Adverse events will be presented in Internationally Agreed Order at SOC level and within each SOC, in decreasing order of the incidences (in MP-513, then in Placebo) at the PT level.

An overall summary of adverse events will be presented and will include:

- Subjects with at least one TEAE
- Subjects with any severe TEAE
- Subjects with any serious TEAE
- Subjects with any ADRs
- Subjects with any serious ADRs
- Subjects with any treatment emergent cardiovascular events
- Subjects with any study drug related treatment emergent cardiovascular events
- Subjects with any TEAE resulting in death
- Subjects with any ADR resulting in death
- Subjects with any TEAE leading to drug discontinuation
- Subjects with any ADR leading to drug discontinuation
- Subjects with Hypoglycaemia
- Subjects with study drug related Hypoglycaemia

The following summary tables will be presented by SOC and PT:

- All TEAEs
- TEAEs by relationship to study drug
- TEAEs by severity grade
- Serious TEAEs
- Treatment emergent cardiovascular events

- Study drug related treatment emergent cardiovascular events
- All ADRs
- Serious ADRs
- TEAEs leading to drug discontinuation,
- ADRs leading to drug discontinuation

The following listings will be presented by subject:

- All AEs
- TEAEs
- Serious TEAEs
- TEAEs leading to drug discontinuation
- Treatment emergent cardiovascular events
- All ADRs
- All hypoglycaemic episodes

8.8.2 Clinical Laboratory Evaluations

Laboratory results (hematology and blood chemistry) will be summarized by treatment groups using descriptive statistics for observed and change from baseline values for all the post baseline assessments visits. The categorical parameters from urinalysis will be summarized by frequency counts and percentages.

Additionally, shift tables will be produced. The shift tables will be based on the classification of laboratory results i.e. Low/Normal/High of post baseline visits compared to the grading of baseline results.

A full subject listing will be presented for laboratory results.

Serum pregnancy test results for female subjects will be listed.

8.8.3 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure, and body temperature) will be summarized by treatment groups using descriptive statistics for observed and change from baseline values for all the post baseline assessments visits.

A full subject listing will be presented for vital signs results.

8.8.4 Electrocardiogram (ECG)

ECG measurements (PR-interval (ms), RR-interval (ms), QRS-interval (ms), QT-interval (ms), QTc (ms) and heart rate (beats/min)) will be summarized by treatment groups using descriptive statistics for observed and change from baseline values for all the post baseline assessments visits.

The investigator interpretation of ECG results (normal, abnormal not clinically significant and abnormal clinically significant) will be summarized by treatment groups using frequency counts and percentages.

A full subject listing will be presented for the ECG result and investigator interpretation.

8.8.5 Physical Findings

A full subject listing will be presented for the physical examination screening result.

9 COMPUTER SOFTWARE

All analyses will be performed by [redacted] using version 9.2 or later of SAS® software. All summary tables and data listings will be prepared by utilizing SAS® software. The standard operating procedures (SOPs) of [redacted] will be followed in the creation and quality control of all data displays and analyses.

10 REFERENCES

1. Kenward, M. G. and Roger, J. H. (1997), "Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood," *Biometrics*, 53, 983–997.

11 APPENDICES

11.1 APPENDIX 1: STATISTICAL ANALYSIS AND PROGRAMMING DETAILS

11.1.1 Analysis of Covariance

This test will be used for testing whether population means of response variable (e.g. change in HbA1c from baseline to week 24) are equal across levels of treatment (MP-513 and Placebo) after controlling for the effect of continuous covariate i.e. baseline value and fixed effects i.e. treatment. Following code can be used for fitting ANCOVA model:

```
proc mixed data=mydata(where=(visit='Week 24'));
   class trt;
   model change = base trt/solution ddfm=kr;
   lsmeans trt/diff=CONTROL('placebo') cl;
   Ods output LSMeans = lsm (keep=trt estimate);
   Ods output Diffs = difflsm;
run;
```

Where,

- *Response variable 'change' is the change from baseline to an endpoint visit*
- *trt is a categorical variable for treatment group (MP-513 or placebo)*
- *base is continuous baseline covariate*
- *Class statement specifies the classification variables.*

- *diff=CONTROL requests the differences with a control that, by default, is the first level of the specified LS-mean effect. Thus to specify which level is to be considered as control specify that in parentheses i.e. ('placebo'),*
- *Dataset **'lsm'** will contain the estimate for least square means (LS-means) for treatment groups under the variable 'estimate'.*
- *Dataset **'difflsm'** will contain estimate of difference of LS- means under variable 'estimate', standard error of LS -means difference under variable 'stderr', p value (using t test) for testing the significance of the difference between LS-means under variable 'probt' and the confidence limits for difference of LS-means under variable 'lower' and 'upper'.*

11.1.2 Mixed Effects Model for Repeated Measure Analysis

This test will be used for testing whether population means of response variable (e.g. change in HbA1c from baseline to week 24) are equal across levels of treatment (MP-513 and Placebo) after controlling for the effect of continuous covariate i.e. baseline value and fixed effects i.e. treatment, visit and interaction of treatment and visit. Following code can be used for MMRM analysis:

```
proc mixed data=mydata;
   class subid trt visit;
   model change = base trt visit trt*visit / solution ddfm=kr;
   repeated visit/ subject=subid type=un;
   lsmeans trt*visit/cl diff;
   ods output LSMeans = lsm(keep=trt visit estimate where=(trt='MP-513' and
                        visit='Week 24'));
   ods output Diffs = difflsm(keep=trt visit _trt _visit estimate stderr
                      probt lower upper where=(trt='MP-513' & _trt='Placebo'
                      & visit='Week 24' & _visit='Week 24'));
run;
```

Where,

- *Response variable 'change' is the change from baseline to different visits.*
- *Class statement specifies the classification variables.*
- *trt is a categorical variable for treatment group (MP-513 or placebo)*
- *base is continuous baseline covariate*
- *Ddfm=kr specifies 'Kenwardroger' method of computing denominator degree of freedom for the tests of fixed effects.*
- *Type= un specifies the within- subject variance covariance matrix as 'unstructured variance covariance matrix'.*
- *Dataset **'lsm'** will contain the estimate for least square means (LS-means) for treatment groups at week 24 under the variable 'estimate'.*
- *Dataset **'difflsm'** will contain estimate of difference of LS- means under variable 'estimate', standard error of LS-means difference under variable 'stderr', p value (using t test) for testing the significance of the difference between LS-means under variable 'probt' and the confidence limits for difference of LS-means under variables 'lower' and 'upper'.*

11.1.3 Logistic Regression

The response variable will be dichotomous with values 'Y' (representing the event of interest, ex. subjects achieving HbA1c<7.0%) and 'N'. For the categorical fixed effect, i.e. variable 'treatment', the lower value of the coded variable will be used as the denominator of the ratio. So if treatment is coded as: 1='MP-513', 2='Placebo' then option ref=last in the 'class' statement will specify the reference level as 2 i.e. 1 vs 2.

The following code can be used for logistic regression model:

```
proc logistic data=mydata;
   class treatment/ref=last;
   model response (event='Y')=base treatment;
   ods output
      ParameterEstimates= pval (where= (variable='Treatment'))
      OddsRatios=oddr;
run;
```

Where,

- *Class statement specifies the classification variables.*
- *base is continuous baseline covariate.*
- *Dataset **pval** will contain the p value for wald chi square test (under variable 'ProbChiSq') for testing the significance of treatment effect.*
- *Data **oddr** will contain odds ratio (under variable 'OddsRatioEst') and 95% Wald confidence limits for odds ratio (under variables 'LowerCL' and 'UpperCL') for between treatment comparison of responder rate*