Study Protocol

Protocol Number: MP-513-C03

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

Version: 2.0
Date: 29 Apr 2016

NCT number: NCT02924064

Study Protocol

Version 2.0 – 29 Apr 2016

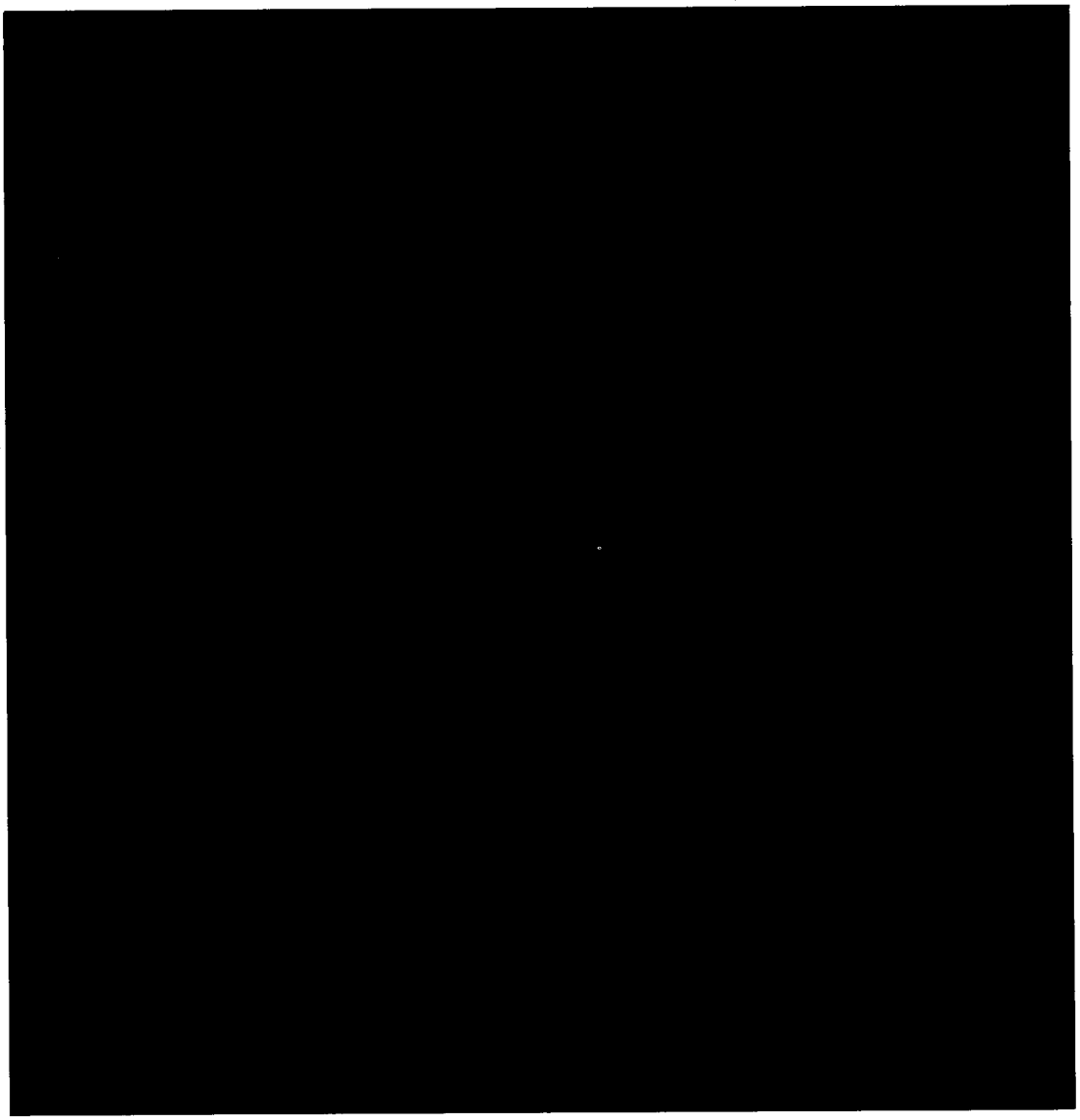
A phase 3 randomized, double-blind, placebo-controlled parallel group efficacy and safety metformin combination study of MP-513 in Chinese subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise

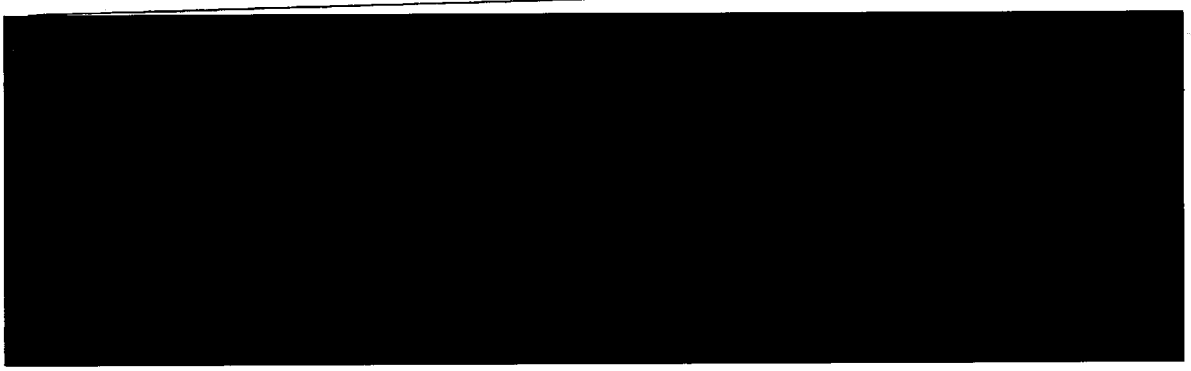
Development Phase:	Phase 3
Investigational Product:	MP-513
Indications:	Type 2 diabetes mellitus
Sponsor:	Mitsubishi Tanabe Pharma Corporation 17-10, Nihonbashi-Koamicho, Chuo-ku Tokyo 103-8405 Japan
Protocol Code:	MP-513-C03

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation guidelines on Good Clinical Practice and regulatory requirements as applicable.

1.1 Protocol Approval Signature Page

I have carefully read this protocol and agree to conduct the study according to the protocol specifications and in compliance with the International Conference on Harmonisation guidelines on Good Clinical Practice (ICH GCP) Guidelines and the Declaration of Helsinki and after having obtained approval from the Ethics Committee and consent in writing from the subjects. Signing this form constitutes a written agreement between the Investigator, Mitsubishi Tanabe Pharma Corporation, and their representative(s).





1.2. Protocol Synopsis

Sponsor: Mitsubishi Tanabe Pharma Corporation	**Name of Medical Product:** MP-513	**Active Ingredient(s):** Teneligliptin
Study Centre(s): Multi-centre study that will be conducted in approximately 35 sites in China		
Study Duration: 30 weeks (2 weeks screening, 2 weeks placebo run-in, 24 weeks treatment, 2 weeks follow-up) The study period is estimated to start from [redacted] to [redacted].		**Study Phase:** 3
Study Title: A phase 3 randomized, double-blind, placebo-controlled parallel group efficacy and safety metformin combination study of MP-513 in Chinese subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise		
Study objectives: To evaluate the efficacy and safety of MP-513 compared with placebo in Chinese subjects with type 2 diabetes mellitus inadequately controlled with metformin monotherapy		
Methodology: Multi-centre, randomized, double-blind, placebo-controlled, parallel-group study		
Number of Subjects (Planned): 240 subjects (120 subjects to MP-513 and 120 subjects to placebo)		
Diagnosis and Inclusion Criteria: The subjects have to meet all of the following inclusion criteria: 1. A signed and dated informed consent form has been obtained from the subject, in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice (ICH GCP), before any screening or study related procedures take place. 2. The subject is aged ≥18 years at signature of the informed consent form 3. Hospitalization status: outpatient 4. The subject has had a documented diagnosis of type 2 diabetes mellitus for at least 3 months at the screening visit (Day –28) 5. The subject's type 2 diabetes mellitus is managed by metformin monotherapy ≥ 1000 mg/day plus diet and exercise therapy, and the dosage or dose regimen of metformin and diet and exercise regimen has not been changed for at least 8 consecutive weeks at the screening visit (Day –28). Subjects who cannot do exercise due to complication are not limited to this criteria. 6. The subject's glycosylated fraction of haemoglobin (HbA1c) is ≥ 7.0% and < 10.0% at the screening visit (Day –28) and on Day –14. 7. The subject's fasting plasma glucose (FPG) is < 270 mg/dL (15 mmol/L) at the screening visit (Day –28) and on Day –14. 8. The subject is capable of giving informed consent, complying with the restrictions and requirements of the protocol and, in the opinion of the investigator, will be able to complete the study.		

Sponsor: Mitsubishi Tanabe Pharma Corporation	**Name of Medical Product:** MP-513	**Active Ingredient(s):** Teneligliptin

Exclusion Criteria:

Potential study subjects will be excluded if one of the following exclusion criteria is present:

1. The subject has a history of type 1 diabetes mellitus or a secondary form of diabetes.
2. The subject has received insulin within 1 year prior to the screening visit (Day –28), with the exception of insulin therapy during hospitalization or insulin therapy for medical conditions not requiring hospitalization (< 2 weeks' duration).
3. The subject has received an anti-diabetic drug (described in "6.5.1 Prohibited Concomitant Medications (1)Anti-diabetic drugs") within 8 weeks prior to the screening visit (Day –28).
4. The subject has a medical history of heart failure (New York Heart Association class III-IV), ventricular tachycardia or ventricular fibrillation.
5. The subject has a history of acute myocardial infarction, congestive heart failure or unstable angina within 6 months prior to the screening visit (Day –28).
6. The subject has any clinically significant electrocardiogram (ECG) abnormalities such as QTc prolongation of ≥ 500 ms at either or both of the screening visit (Day –28) and at the randomization visit (Day 1).
7. The subject has a serious diabetic complication (Proliferative retinopathy, Grade IV or more severe renal impairment or serious diabetic neuropathy).
8. The subject has a history of drug abuse.
9. The subject drinks on average more than 28 units of alcohol per week. (One unit of alcohol equals approximately 250 mL of beer, 125 mL of wine or 20 mL of spirits)
10. The subject is suffering from serious concurrent renal disease or has serum creatinine > 2.0 mg/dL at the screening visit (Day –28).
11. The subject has a clinically significant liver disease with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times the upper limit of normal at the screening visit (Day –28).
12. The subject is suffering from concurrent malignancy or has a history of malignancy, except those with no recurrent malignancy over the last 5 years.
13. The subject has systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg at the screening visit (Day –28) or on Day –14.
14. The subject has participated in any other clinical study involving blood draws or administration of an unlicensed medicinal product within 3 months prior to the screening visit (Day –28).
15. The subject has donated blood within 3 months prior to the screening visit (Day –28).
16. Male subject and female subject of childbearing potential, who do not agree to prevent conception during the study. Females of childbearing potential (including those less than 2 years postmenopausal) must agree to maintain reliable birth control throughout the study. Reliable contraception is defined as hormonal contraception (eg, oral contraceptives consisting of an estrogen-progestin combination or progestin alone, transdermally delivered contraceptives, depot injections, NuvaRing, Implanon), an intrauterine device, or double-barrier methods (diaphragm plus condom).
17. Female subject who is pregnant, lactating or are planning to become pregnant during the study.
18. The subject with < 75% treatment compliance with the investigational product (placebo) during the placebo run-in period.
19. The subject has a history of joint pain with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors

Test and Reference Product, Dose, and Mode of Administration:

Sponsor: Mitsubishi Tanabe Pharma Corporation	**Name of Medical Product:** MP-513	**Active Ingredient(s):** Teneligliptin
MP-513 Form: Film-coated tablet for oral administration Strength: 20 mg and matching placebo during the placebo run-in period of 2 weeks, 1 tablet of single-blinded study treatment (placebo tablet) will be orally administered once daily before breakfast. During the double-blind treatment period of 24 weeks, 1 tablet of double-blinded study treatment (20 mg tablet or placebo tablet) will be orally administered once daily before breakfast. The underlying metformin treatment with a fixed dose of ≥1000 mg/day and the accompanying diet and exercise regimen must have been stable for at least 8 weeks prior to study start and must be continued without changes during the study. The metformin prescribed in the sites will continue to be prescribed and dispensed during the study.		

Sponsor: Mitsubishi Tanabe Pharma Corporation	**Name of Medical Product:** MP-513	**Active Ingredient(s):** Teneligliptin

Criteria for Evaluation:

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

Primary efficacy endpoint:

- Change in HbA1c from baseline to Week 24

Secondary efficacy endpoint:

- Change in FPG from baseline to Week 24

Other efficacy endpoints:

- 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 Homeostatic Model Assessment- Insulin resistance (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

Safety Endpoints

- Adverse Events (AEs)
- Adverse drug reactions (ADRs)
- Hypoglycaemic episodes
- Cardiovascular events
- Vital signs (blood pressure, pulse rate and body temperature)
- Laboratory measurements
- 12-lead ECG

Statistical Methods:

Sponsor: Mitsubishi Tanabe Pharma Corporation	**Name of Medical Product:** MP-513	**Active Ingredient(s):** Teneligliptin

All significance tests will be carried out at a 5%, 2-sided significance level. Statistical tests will be supported by presenting estimates and 95% confidence intervals 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.
For the primary efficacy endpoint, the change in HbA1c from baseline to Week 24, analysis of covariance will be performed, with treatment as fixed effect and baseline as a covariate. As a supportive analysis, mixed-effects model for repeated measures will be performed, with treatment, visit and interaction of treatment and visit as fixed effects and baseline as a covariate.

For the secondary efficacy endpoints, the change in FPG from baseline to Week 24, the same statistical methodology as described for primary analysis on primary efficacy endpoint will be used..

For the other efficacy endpoints:
The same statistical methodology as described for primary analysis on primary efficacy endpoint will be used for the following other efficacy endpoints.

- 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

For the other efficacy endpoint, proportion of subjects who achieved HbA1c < 7.0% at Week 24, a logistic regression will be performed with treatment as fixed effects and baseline HbA1c value as a covariate.

1.3. Table of Contents

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1.4 Glossary of Abbreviations

Abbreviation	Definition
ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under The Curve
C	Celsius Degree
Cmax	Maximum Concentration
CRO	Contract Research Organisation
DPP-4	Dipeptidyl Peptidase-4
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GIP	Glucose-Dependent Insulinotropic Peptide
GLP-1	Glucagon-Like Peptide-1
GMP	Good Manufacturing Practice
HbA1c	Glycosylated Fraction Of Haemoglobin
HDL-C	High-Density Lipoprotein-Cholesterol
HOMA-ß	Homeostatic Model Assessment-Beta
HOMA-IR	Homeostatic Model Assessment-Insulin Resistance
ICH	International Conference On Harmonisation
IEC	Independent Ethics Committee
IUD	Intrauterine Device
IWRS	Interactive Web Randomization System
LDH	Lactate Dehydrogenase
LDL-C	Low Density Lipoprotein-Cholesterol
LOCF	Last Observation Carried Forward
LS	Least Squares
MedDRA	Medical Dictionary For Regulatory Activities
PPG	Postprandial Glucose
PPS	Per-Protocol Set
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
TIA	Transient Ischaemic Attack
WHO	World Health Organisation

2. Ethics

2.1 Independent Ethics Committee

Before initiation of the study at each study site, the protocol, informed consent and subject information sheet, Investigator's Brochure, and the electronic case report form (eCRF) and all other required information will be submitted to the independent ethics committee (IEC) for review and approval, in accordance with applicable regulatory and local requirements. The IEC's approval will be documented in writing and forwarded to the contract research organisation (CRO) with responsibility for conducting the study.

The investigator will not begin the study until he/she has received written confirmation of approval by the IEC and the sponsor (Mitsubishi Tanabe Pharma Corporation) has authorised release of study treatments.

Any substantive amendments to the protocol must be approved in writing by the IEC prior to implementation by the investigator.

In accordance with local legislation, the reports for serious and unexpected adverse reactions (i.e. adverse reactions not expected from Investigator's Brochure) are to be submitted to the IEC according to the local rules regulation. As necessary, the sponsor will report serious and unexpected adverse reactions to the authority concerned. All information sent to the investigator will be in a blinded format.

After completion or termination of the study, the results will be submitted to the IEC.

2.2 Ethical Conduct of the Study

The study will be conducted in compliance with

- the study protocol,
- ethical principles of the Declaration of Helsinki and its amendments,
- the principles of the Good Clinical Practice (GCP) provided in the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for GCP 1996, and
- all applicable national laws and regulations including country-specific GCP.

2.3 Subject Information and Informed Consent

The informed consent document will be used to explain to the subject or legally authorised representative (in simple terms) the risks and benefits of study participation.

The consent form will comply with all applicable regulations governing the protection of human subjects, including ICH GCP guidelines, the Declaration of Helsinki, subject confidentiality and data protection. The IEC's written approval of the informed consent form and subject information sheet will be obtained.

Prior to screening, subjects will be provided with a copy of the approved subject informed consent and subject information sheet. The investigator or an authorised member of the study team will discuss with the subject the nature of the study and the treatments to be administered (including the risks and discomforts to be expected). Subjects will have sufficient opportunity to inquire about details of the study and to decide whether or not to participate. They will be instructed that they are free to withdraw their participation in the study at any time and for any reason without prejudice.

The investigator will ensure that appropriate signatures and dates on the informed consent document are obtained prior to the performance of any protocol procedures and prior to the administration of study treatments. The investigator will provide each subject with a copy of the signed and dated consent and document the provision of consent in the subject's source notes.

The investigator will inform subjects of new information that may be relevant to the subjects' willingness to continue participation in the study and is also obligated to protect the subjects' confidentiality. Any revision of the informed consent form and subject information sheet must be approved by the IEC prior to use.

2.4 Protocol Amendments

The implementation of any change in the protocol's assessments/requirements will not be permitted until the principal investigator, the sponsor, and the IEC have provided written approval of the change. Other administrative changes (not affecting the scope of the investigation or the scientific quality of the study) can be made following approval by the sponsor and the principal investigator; however the IEC must be put on records of these protocol changes (as appropriate).

The CRO designee will be responsible for the distribution of all amendments to the investigator. The investigator will be responsible for implementing any amendments at the study site (including the distribution of amendments to all staff concerned).

2.5 Subject Insurance Coverage and Investigator Indemnity

The sponsor will provide appropriate insurance coverage and compensation for the subjects, in accordance with legal requirements and local law, unless the relationship between trial and accidence is verified to be irrelevant a copy of the insurance certificate will be provided for the investigator's site file.

2.6 Confidentiality

The investigators, the CRO, and the sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with ICH GCP and local regulations. The confidentiality of all subject identities will be maintained except during source data verification, when monitors, auditors, and other authorised agents of the sponsor or its designee, the ethics committees approving this research, as well as any other applicable regulatory authorities, will be granted direct access to the study subjects' original medical records. No material bearing a subject's name will be kept on file by the CRO or the sponsor. The data retained from this study will be protected in accordance with all applicable legal requirements.

2.7 Notification of Regulatory Authorities (if applicable)

The study, and any amendments, will only be implemented following compliance with all legally required regulatory requirements.

3. Study Personnel and Study Administration

The study is sponsored and planned by Mitsubishi Tanabe Pharma Corporation as a prospective, multi-centre, parallel-group, randomised, double-blind, Phase 3 clinical study.

Sponsor:	Mitsubishi Tanabe Pharma Corporation 17-10, Nihonbashi-Koamicho, Chuo-ku Tokyo 103-8405 Japan
Sponsor's Subsidiaries:	Mitsubishi Tanabe Pharma Development (Beijing) Co.,Ltd. Room 1606, Floor 16th, Office Building F, Phoenix Place, Tower 21, No. A5, Shuguangxili, Chaoyang District, Beijing 100028, China
CRO:	[redacted]

[redacted] will be responsible for project management, monitoring, evaluation of data and quality assurance.

4. Introduction and Study Rationale

Background of the trial

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. The chronic hyperglycaemia of diabetes mellitus is associated with significant long term sequelae, particularly damage, dysfunction and failure of various organs – especially the kidneys, eyes, nerves, heart and blood vessels [EMA 2012, ADA 2014].

Type 2 diabetes is a complex disorder which involves various degrees of decreased beta-cell function, peripheral insulin resistance and abnormal hepatic glucose metabolism. Glucose control in type 2 diabetes deteriorates progressively over time, and, after failure of diet and exercise alone, needs on average a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good control. Despite combination therapy and/or insulin treatment, a sizeable proportion of subjects remain poorly controlled [EMA 2012, ADA 2014].

Type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease. Overweight, hypertension and dyslipidaemia are often associated with diabetes mellitus and multiple cardiovascular risk factor intervention is a key issue in type 2 diabetes. Therefore, global treatment aims in management of diabetes mellitus cover both lowering of blood glucose to near normal levels and correcting metabolic abnormalities and cardiovascular risk factors including weight management. Indeed, it has been shown that normalisation or near normalisation of glucose levels (assessed by changes in glycosylated fraction of haemoglobin [HbA1c]) in subjects with type 1 and type 2 diabetes significantly reduces the risk of microvascular complications (retinopathy, nephropathy and neuropathy); the macrovascular risk reduction is less certain.

An important class of antidiabetic medications used for diabetes mellitus type 2 are secretagogues, i.e. substances that stimulate insulin secretion. Incretins are insulin secretagogues. The two main candidate molecules that fulfil criteria for being an incretin are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitors or gliptins, are a class of oral hypoglycaemics that block DPP-4.

Glucagon increases blood glucose levels, and DPP-4 inhibitors reduce glucagon and blood glucose levels. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which increases insulin secretion, inhibits glucagon release, decreases gastric emptying, and decreases blood glucose levels.

Pre-Clinical Findings

Pre-clinical data in full can be found in the Investigator's Brochure.

Clinical Experience

Clinical Studies in Japan

A phase 3, confirmatory study (3000-A5) was conducted in subjects with type 2 diabetes mellitus to evaluate efficacy and safety of MP-513 20 mg versus placebo for 12 weeks.

The placebo-subtracted change in HbA1c from baseline at Week 12 was -0.79 ± 0.07% (Least squares mean ± standard error [LS mean ± SE]). There were no serious adverse events (SAEs) in the MP-513 group but 4 SAEs observed in 4 subjects in the placebo group. There were no significant differences in the incidences of adverse events (AEs) and adverse drug reactions (ADRs) between the placebo and MP-513 groups.

A phase 3, combination therapy study with sulfonylurea (3000-A6) was conducted in subjects with type 2 diabetes mellitus to evaluate efficacy and safety of MP-513 20 mg versus placebo for 12 weeks (double-blind period). The safety and efficacy of MP-513 20 mg for following 40 weeks are also evaluated (open-label period).

In the double-blind period, the placebo-subtracted change in HbA1c from baseline at Week 12 was -1.00 ± 0.08% (LS mean ± SE). There was no significant difference in the incidences of AEs and ADRs between the placebo and MP-513 groups.

In open-label period, although all subjects received MP-513 for another 40 weeks following the double-blind period, the incidence of AEs was not demonstrated increasing tendency in association with the prolonged treatment period. There were 10 SAEs in 7 of 96 subjects (7.3%) in the MP-513 group (weeks 0 to 52) and 5 SAEs in 4 of 98 subjects (4.1%) in the placebo group (weeks 0 to 52). The result also suggested that the HbA1c lowering effect of MP-513 was maintained throughout the study.

A phase 3, combination therapy study with thiazolidinedione (3000-A7) was conducted in subjects with type 2 diabetes mellitus to evaluate efficacy and safety of MP-513 20 mg versus placebo for 12 weeks (double-blind period). The safety and efficacy of MP-513 20 mg for following 40 weeks are also evaluated (open-label period).

In the double-blind period, the placebo-subtracted change in HbA1c from baseline at Week 12 was -0.74 ± 0.06% (LS mean ± SE). The incidences of AEs and ADRs were significantly higher in the MP-513 group (61.2% and 11.7%, respectively) than in the placebo group (46.5% and 2.0%, respectively).

In the open-label period, although all subjects received MP-513 for another 40 weeks following the double-blind period, an increasing incidence of AEs was not demonstrated in association with the prolonged treatment period. There were 12 SAEs in 11 of 103 subjects (10.7%) in the MP-513 group (weeks 0 to 52) and 6 SAEs in 4 of 101 subjects

(4.0%) in the placebo group (weeks 0 to 52). The result also suggested that the HbA1c lowering effect of MP-513 was maintained throughout the study.

A phase 3, long-term treatment study of monotherapy and combination therapy study with sulfonylurea (3000-A8) was conducted in subjects with type 2 diabetes mellitus to evaluate safety and efficacy of MP-513 20 mg for 52 weeks.

An increasing incidence of AEs was not demonstrated in association with the duration of treatment period, in neither monotherapy with MP-513 nor in combination with glimepiride. There were 6 SAEs in 6 of 151 subjects (4.0%) in the MP-513 monotherapy group and 9 SAEs in 7 of 89 subjects (7.9%) in the glimepiride combination group. The change in HbA1c from baseline to Week 52 in the MP-513 monotherapy group was -0.63 ± 0.67% (mean ± standard deviation [SD]) and in the glimepiride combination group was -0.81 ± 0.76% (mean ± SD).

An increasing incidence of AEs was not demonstrated in association with the duration of the treatment period, in neither monotherapy with MP-513 nor in combination therapy with glinide, biguanide nor alpha-glucosidase inhibitor (3000-A14). There were 15 SAEs in 14 of 212 subjects (6.6%) in the MP-513 monotherapy group, 3 SAEs in 3 of 80 subjects (3.8%) in the glinide group, 6 SAEs in 6 of 95 subjects (6.3%) in the biguanide group and 7 SAEs in 6 of 75 subjects (8.0%) in the alpha-glucosidase inhibitor group. The change in HbA1c from baseline to Week 52 were -0.63 ± 0.64%, -0.76 ± 0.70%, -0.78 ± 0.75% and -0.89 ± 0.64% (mean ± SD) in the MP-513 monotherapy group, the glinide group, the biguanide group and the alpha-glucosidase inhibitor group, respectively.

[redacted]

A phase 3, pharmacokinetic and pharmacodynamic study (3000-A12) was conducted in subjects with type 2 diabetes mellitus to assess the blood glucose control over 24 hours and safety of MP-513 10, 20 mg versus placebo for 4 weeks.

The postprandial glucose lowering effects of MP-513 administrated before breakfast were sustained over 24 hours. In addition, there were no SAEs and no significant differences in the incidences of AEs and ADRs between the placebo and MP-513 groups.

Clinical Studies in the EU and US

A phase 2b, combination study with metformin (MP-513-E07) was conducted in subjects with type 2 diabetes mellitus to evaluate efficacy and safety of multiple doses of MP-513 5, 10, 20 and 40 mg versus placebo for 24 weeks (double-blind period). The safety and

efficacy of MP-513 20 mg administered once daily for the following 28 weeks were also evaluated (open-label period).

In the double-blind period, the placebo-subtracted change in HbA1c from baseline at Week 24 was -0.30%, -0.40%, -0.48% and -0.63% (LS mean) for the 5, 10, 20 and 40 mg groups, respectively. There were no significant differences in the incidences of AEs and ADRs between the placebo and each of the four MP-513 groups (5, 10, 20 and 40 mg).

In the open-label period, all of the subjects in each group received MP-513 20 mg for 28 weeks. There were no major differences in the incidence of AEs between the double-blind period and open-label period. An increasing incidence of AEs was not demonstrated in association with the prolonged treatment period. There were 4 SAEs in 4 of 87 subjects (4.6%) in the 5 mg groups (weeks 0 to 52), 7 SAEs in 6 of 93 subjects (6.5%) in the 10 mg group (weeks 0 to 52), 6 SAEs in 4 of 91 subjects (4.4%) in the 20 mg group (weeks 0 to 52), 8 SAEs in 7 of 88 subjects (8.0%) in the 40 mg group (weeks 0 to 52). In the placebo group, there were 8 SAEs in 6 of 88 subjects (6.8%) in double-blind period and 1 SAEs in 1 of 70 subjects (1.4%) in open-label period. The HbA1c lowering effect of MP-513 was maintained until Week 52.

[redacted]

Ethnic differences in pharmacokinetics and pharmacodynamics

The ethnic differences of teneligliptin in pharmacokinetics and pharmacodynamics were evaluated based on the study result of phase I studies in healthy volunteers and pharmacokinetic and pharmacodynamic studies in subjects with type 2 diabetes mellitus conducted in Japan and the EU.

The result indicated that AUC and Cmax of plasma teneligliptin were almost similar between Japanese and Caucasians, and also between healthy volunteers and type 2 diabetic subjects. Also, the plasma DPP-4 activity and the plasma active GLP-1 concentration were almost similar between Japanese and Caucasians, and also between healthy volunteers and type 2 diabetic subjects.

Therefore, it is considered that there was no ethnic difference in pharmacokinetic and pharmacodynamic profiles of teneligliptin.

Possible risks and benefits for human subjects known to date

MP-513 (teneligliptin) is a new DDP-4 inhibitor that is expected to be safely used as a treatment for type 2 diabetes because it has no risk of hypoglycaemia and/or weight gain (which are reported in pre-existing diabetes therapies), no inconvenience related to dose adjustment depending on the subject's condition, and no cases of fatal side effects. For further details refer to the Investigator's Brochure.

In many countries, the most commonly prescribed primary oral diabetes drug that does not cause hypoglycaemia or weight gain, is metformin.

Taking that into consideration, MP-513 could serve as a new add on treatment which is considered to be safe and can also be expected to increase efficacy of antidiabetic treatment, i.e. this combination has a clearly positive risk-benefit ratio.

The purpose and objective of the trial

Thus, the aim 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 metformin monotherapy.

5. Study Objectives

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

6. Investigational Plan

6.1 Overall Design and Plan of the Study

This is a multi-centre, randomized, double-blind, placebo-controlled, parallel-group study in subjects with type 2 diabetes mellitus, age > 18 years and a HbA1c ranging from 7.0% to below 10.0%.

The study consists of 2 week screening period and 2 week single-blind placebo run-in period, 24 week double-blind treatment period and a 2 week follow-up period.

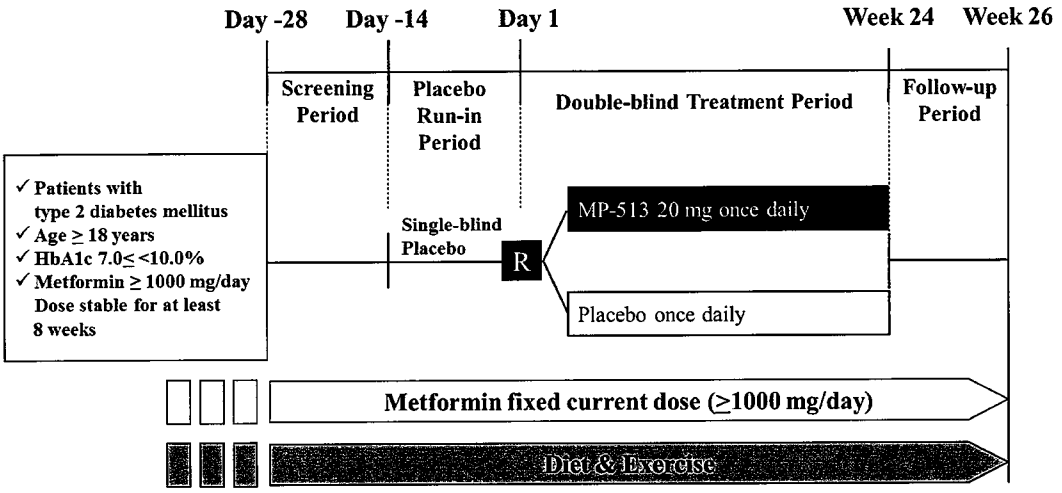
At the end of the placebo run-in period, subjects will attend the site for the randomization visit (RV). Subjects with 75% or higher treatment compliance with the investigational product (placebo) during the placebo run-in period will be r randomized to either treatment groups 20 mg MP-513 (teneligliptin) or placebo once daily in a 1:1 ratio.

The underlying metformin treatment with a fixed dose of ≥1000 mg/day accompanying diet and exercise regimen must have been stable for at least 8 weeks prior to study start and must be continued without changes during the study.

Subjects will have 6 additional visits (at Week 4, 8, 12, 16, 20 and 24) with treatment and will have a follow-up telephone visit at Week 26. The study duration for a subject who completes the study is 30 weeks (2 weeks screening, 2 weeks placebo run-in, 24 weeks treatment, 2 weeks follow-up).

The study period is from [redacted] to [redacted].

Table 1 Flow Chart



Enrolled subjects will meet all of the inclusion criteria and none of the exclusion criteria.

6.2 Discussion of Study Design

This study is designed as a prospective, multi-centre, parallel group, double-blind randomised, placebo-controlled, phase 3 clinical study to evaluate the efficacy and safety of MP-513.

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. 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. The dose of 20 mg orally administered once daily before breakfast is the established dose for this medication. Placebo subjects are also treated with metformin and are thus protected against their diabetes with a well-established standard regimen. The follow-up period is to confirm the subjects' safety after the completion/discontinuation of the treatment.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

The subjects have to meet all of the following inclusion criteria:

1. A signed and dated informed consent form obtained from the subject, in accordance with ICH GCP, before any screening or study related procedures take place.

2. The subject is aged ≥18 years at signature of the informed consent form
3. Hospitalization status: outpatient
4. The subject has a documented diagnosis of type 2 diabetes mellitus for at least 3 months at the screening visit (Day –28)
5. The subject's type 2 diabetes mellitus is managed by metformin monotherapy ≥1000 mg/day plus diet and exercise therapy, and the dosage or dose regimen of metformin and diet and exercise regimen has not been changed for at least 8 consecutive weeks at the screening visit (Day –28). Subjects who cannot do exercise due to complication are not limited to this criteria.
6. The subject's HbA1c is ≥ 7.0% and < 10.0% at the screening visit (Day –28) and on Day –14.
7. The subject's fasting plasma glucose (FPG) is < 270 mg/dL (15 mmol/L) at the screening visit (Day –28) and on Day –14.
8. The subject is capable of giving informed consent, complying with the restrictions and requirements of the protocol and, in the opinion of the investigator, will be able to complete the study.

6.3.2 Exclusion Criteria

Potential study subjects will be excluded if one of the following exclusion criteria is present:

1. The subject has a history of type 1 diabetes mellitus or a secondary form of diabetes.
2. The subject has received insulin within 1 year prior to the screening visit (Day –28), with the exception of insulin therapy during hospitalization or insulin therapy for medical conditions not requiring hospitalization (< 2 weeks' duration).
3. The subject has received an anti-diabetic drug (described in "6.5.1 Prohibited Concomitant Medications (1)Anti-diabetic drugs") within 8 weeks prior to the screening visit (Day –28).
4. The subject has a medical history of heart failure (New York Heart Association class III-IV), ventricular tachycardia or ventricular fibrillation.
5. The subject has a history of acute myocardial infarction, congestive heart failure or unstable angina within 6 months prior to the screening visit (Day –28).
6. The subject has any clinically significant electrocardiogram (ECG) abnormalities such as QTc prolongation of ≥ 500 ms at either or both of the screening visit (Day –28) and at the randomization visit (Day 1).

7. The subject has a serious diabetic complication (proliferative retinopathy, Grade IV or more severe renal impairment or serious diabetic neuropathy).
8. The subject has a history of drug abuse.
9. The subject drinks on average more than 28 units of alcohol per week. (One unit of alcohol equals approximately 250 mL of beer, 125 mL of wine or 20 mL of spirits)
10. The subject is suffering from serious concurrent renal disease or has serum creatinine > 2.0 mg/dL at the screening visit (Day –28).
11. The subject has a clinically significant liver disease with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times the upper limit of normal at the screening visit (Day –28).
12. The subject is suffering from concurrent malignancy or has a history of malignancy, except those with no recurrent malignancy over the last 5 years.
13. The subject has systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg at the screening visit (Day –28) or on Day –14.
14. The subject has participated in any other clinical study involving blood draws or administration of an unlicensed medicinal product within 3 months prior to the screening visit (Day –28).
15. The subject has donated blood within 3 months prior to the screening visit (Day –28).
16. Male subject and female subject of childbearing potential, who do not agree to prevent conception during the study. Females of childbearing potential (including those less than 2 years postmenopausal) must agree to maintain reliable birth control throughout the study. Reliable contraception is defined as hormonal contraception (eg, oral contraceptives consist-ing of an estrogen-progestin combination or progestin alone, transdermally delivered contra-ceptives, depot injections, NuvaRing, Implanon), an intrauterine device, or double-barrier methods (diaphragm plus condom).
17. Female subject who is pregnant, lactating or are planning to become pregnant during the study.
18. The subject with < 75% treatment compliance with the investigational product (placebo) during the placebo run-in period.
19. The subject has a history of joint pain with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors

6.3.3 Withdrawals and Replacement of Subjects

Subjects may be discontinued from study at any time. Subjects are also free to discontinue their participation in the study at any time without prejudice to further treatment.

In the eCRF, study completion or discontinuation will be documented with the reason for any discontinuation. Possible reasons for a subject discontinuing participation in the study are:

- AE(s) that endanger the health of subjects, making it ethically unacceptable to continue
- Deterioration of the subject's clinical condition(s) that requires appropriate therapy/treatment during the study period
- Withdrawal of consent
- Other cases where the investigator decides the study for the relevant subject should be discontinued.

Subjects' condition are clearly no longer suitable to continue in the study The subjects with a lack of glycaemic control during the double-blind treatment period will be discontinued from the study and referred to appropriate anti-hyperglycaemic therapy. Inadequate FPG measured in the central laboratory is defined as follows:

(1) FPG > 270 mg/dL (15 mmol/L) from baseline to Week 8 (inclusive).

(2) FPG > 240 mg/dL (13.3 mmol/L) from Week 8 to Week 12 (inclusive).

(3) FPG > 200 mg/dL (11.1 mmol/L) from Week 12 to Week 24 (exclusive).

In case of an AE, the subject should be followed up, whenever possible, until the subject recovers or until the investigator considers the situation to be no longer clinically significant. Subjects who discontinue prematurely from the study will not be replaced.

6.3.4 Study Discontinuation by the Sponsor or the Investigator

The Sponsor reserves the right to terminate this study prematurely, either in its entirety or at a specific site, for reasonable cause provided that written notice is submitted at a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to the Sponsor at a reasonable time in advance of the intended termination. Neither party requires advance notice if the study is stopped due to safety concerns. If the Sponsor chooses to terminate the study for safety reasons, it will immediately notify the Investigator and subsequently provide written instructions for study termination. Subjects who have not completed treatment in the study at the time of termination will be advised and offered alternative treatment, as medically indicated.

6.3.5 Study Discontinuation at the Relevant Site Based on the Decision of the IEC

If the IEC decides termination or suspension of the study at its own discretion, the IEC will immediately notify the investigator and the sponsor of the decision on and detailed reason for termination or suspension in writing.

6.3.6 Study Discontinuation Based on Cancellation of the Contract with the Site

If the sponsor terminates the study due to significant or persistent violation of the GCP, the protocol, or the study contract by the site during the study period, the sponsor will immediately report the matter to regulatory authorities.

6.4 Study Medication

6.4.1 Description of Study Medication

The characteristics of the Investigational Product are provided below:

Name:	MP-513 20 mg
Active Ingredient:	Teneligliptin (Teneligliptin Hydrobromide Hydrate)Pharmaceutical form: Film coated-tablet
Source:	Mitsubishi Tanabe Pharma Corporation 3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan
Unit Strength:	20 mg
Route of administration:	per os (orally)

Name:	Placebo matching with MP-513 20 mg
Active Ingredient:	NA
Pharmaceutical form:	Film coated tablet
Source:	Mitsubishi Tanabe Pharma Corporation 3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan
Route of administration:	per os (orally)

In addition, subjects continue to take their prescribed metformin treatment.

6.4.2 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized to MP-513 or placebo in a 1:1 ratio according to a computer-generated randomization code.

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

The randomization scheme will be reproducible and will be prepared by the CRO via a computerized system prior to start of the study. Separate lists will be prepared for subjects' randomization (randomization code list) and study medication packaging (kit code list). The IWRS provider will retain master copies of the randomization and kit code list (in a secure fashion in order to maintain the blind).

At the randomization visit (Day 1), after confirmation of subject eligibility, the Investigator will connect to the randomization system in order to receive kit number containing the study treatment, then subjects will receive the double-blinded study treatment which is assigned to them.

6.4.3 Dosage and Administration of Study Medication

Subjects should understand that they may receive either active treatment or placebo randomly at any time during the study.

Placebo Run-in Period

All subjects will take orally 1 tablet of single-blinded study treatment (placebo), once daily before breakfast during the placebo run-in period. Subjects are not to be informed of the contents of single-blind medication. Placebo run-in period will be 2 weeks for each enrolled subjects.

Double-blind Treatment Period

All subjects randomised will take the first dose of double-blinded study treatment from the randomization visit (Day 1). All subjects will take orally 1 tablet of double-blinded study treatment (20 mg tablet or placebo tablet), once daily before breakfast during the double-blind treatment period. Double-blind treatment period will be 24 weeks for each enrolled subjects.

6.4.4 Blinding

Study treatments will be packaged for double-blind administration. The placebo is identical to the corresponding active treatments. During the single-blind run-in period, the subject will not know that they are receiving placebo. 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.

Only the IWRS provider will know the treatment arm that each individual subject is randomised to.

The investigators are strongly discouraged from requesting the blind be broken for an individual subject, unless there is a subject safety issue that requires unblinding and

knowledge of the treatment group would change subject management. If the blind is broken by the Investigator, the date, time and reason must be recorded in source document and subject's eCRF and the relevant subject will discontinue the study. The unblinding procedure is described in detail in the IWRS instruction manual that will be provided separately to the Investigator.

6.4.5 Packaging and Labelling of Study Medication

Packaging and labelling will be carried out in accordance with the requirements of the Good Manufacturing Practice (GMP) guidelines, ICH GCP requirements, sponsor approved standard operating procedures and all applicable local laws.

Product storage and dispensation

All study material, together with relative documentation, will be supplied to the centre before starting the trial. Sealed cartons (kits) containing the study medications will be prepared according to the kit code list. An appropriate amount of treatment kits will be supplied to the designated person at the investigational sites (with further re-supplies scheduled once the site's pre-set threshold is reached). The centre will acknowledge receipt of all study material via fax.

All supplies will be maintained under adequate security by the clinical investigator or designated pharmacist, who will be responsible for all supplies.

The centre has to store the drug as indicated in the original packaging between 1°C - 30°C, but not frozen.

The study drugs are to be dispensed only under the restricted conditions defined in the present protocol.

Any test materials remaining at the end of the study will be returned to the sponsor or destroyed in accordance with the guidelines provided by the sponsor. Before destruction, detailed product accountability has to be performed. An official document on what has been destroyed has to be issued and sent to the Sponsor.

Product accountability

Each centre will be responsible for maintaining an accurate log and inventory of study material received and returned to the CRO.

6.4.6 Drug Storage and Accountability

The centre will store the drug as indicated in the original packaging between 1°C - 30°C, but not frozen, kept in an appropriate secure area (e.g., a locked cabinet). Certificates of deliveries and returns have to be signed by the responsible person(s).

At the end of the study, it must be possible to reconcile delivery records with records of used and returned study treatments. An account of any discrepancies has to be provided.

The CRO will provide the framework for documenting study treatment accountability throughout the study. The investigator has to maintain an accurate written record of the shipment, dispensing, and return of study treatments on the drug accountability form. An accurate record of the date and amount of study drug dispensed to each subject has to be available for inspection at any time. The CRO representatives will verify drug accountability during routine site monitoring visits and at the completion of the trial.

At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused drug containers, drug labels, and a copy of the completed drug accountability form to the sponsor. Some sites may destroy medications locally at an appropriate time point and record the process, if previously agreed with the sponsor.

6.4.7 Treatment Compliance

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

> 100 × (Number of tablets dispensed - Number of tablets returned) / (Date of Treatment Visit 6 - Date of Randomization Visit)

Treatment compliance during the placebo run-in period will also be calculated as follows. Subjects with < 75% drug compliance during the placebo run-in period have to be excluded.

> 100 × (Number of tablets dispensed - Number of tablets returned) / (Date of Randomization Visit - Date of Placebo Run-in Visit)

6.5 Prior and Concomitant Therapy

6.5.1 Prohibited Concomitant Medications

(1) Anti-diabetic drugs

Concomitant use of the following medications is not permitted within at least 8 weeks before the screening visit until 2 weeks after the final dose of the study drug. Subjects may use the following medications after 2 weeks after the final dose of the study drug including the early termination if required when judged by the investigator: Insulin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, Repaglinide, DPP-4 inhibitors, GLP-1 receptor agonists, herbal medicines that lower blood glucose levels, new drugs intended for diabetes, fixed dose combination tablets including above active ingredients.

Subjects can use the anti-diabetic treatment after Early termination visit when the subject discontinue the study due to a lack of glycaemic control.

(2) Others

The following medications are not permitted in the period from the screening visit to 2 weeks after the final dose of the study drug out of a concern for the influence on the efficacy and safety assessment. Subjects may use the following medications after 2 weeks after the final dose of the study drug including the early termination if required when judged by the investigator: Adrenocorticosteroids (excluding for external use) for more than 2 consecutive weeks and other investigational products (including placebo)

Subjects can use the adrenocorticosteroids after Early termination visit when the investigator consider that the treatment is necessary.

6.5.2 Permitted Concomitant Medication

Medications not mentioned above may be concomitantly used for treatment of complications and AEs. In principle, medications already in use at the screening visit should be used until the 2 weeks after final dose of the study drug without any change in prescription.

Concomitant therapy, ongoing diet or exercise therapy or both will be continued without any changes from at least 8 weeks before the screening visit to 2 weeks after the final dose of the study drug.

Subjects may change the dosage and/or the dose regimen and/or the concomitant therapy after 2 weeks after the final dose of the study drug including the early termination if required when judged by the investigator.

6.5.3 Treatment with Metformin

Treatment with metformin (≥1000 mg/day) will be continued without any changes to the dosage and/or the dose regimen from at least 8 weeks before the screening visit to the final dose of the study drug. The metformin prescribed in the sites will continue to be prescribed and dispensed during the study.

Subjects may change the dosage and/or the dose regimen after the final dose of the study drug including the early termination if required when judged by the investigator.

6.6 Study Procedures

6.6.1 Schedule of Investigations and Data Collection

A schedule of study procedures and events is provided in Table 2.

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] + 7 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 subject 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

A description of the subject assessments at each visit is presented below. All the blood and urine sample collected will be sent to central lab [redacted] for measurement.

Screening Visit (28 days plus/minus 3 days prior to treatment)

Once a suitable candidate is identified from among the outpatients coming to the site for the scheduled visit, the investigator or designated healthcare professional will ask the subject about their willingness to be included in the clinical trial. The subject is to be informed verbally and in writing about the nature, risks, benefits, and expectations of participating in the clinical trial and a copy of the subject informed consent form is to be given to the subject in the appropriate language. The subject informed consent form is to be signed by the subject and countersigned by the attending investigator prior to proceeding with the visit. At this point, a subject screening number is to be assigned.

The investigator will provide subjects with a subject diary and glucometer, and will instruct them when and how to write in the subject diary and also when and how to monitor their own blood glucose by glucometer. The subjects should write in the subject diary and should monitor their blood glucose by glucometer as much as possible when hypoglycaemia occurs. The subjects should visit the investigator promptly when the hypoglycaemia is not recovered by the treatment such as taking glucose.

The following observations/procedures are to be performed and checked:

- Check inclusion/exclusion criteria
- Obtain written informed consent
- Complete physical examination including body weight, height, vital signs and ECG
- Complete demographic data and medical history
- Review use of previous/concomitant treatments and of the regular metformin therapy
- Conduct a pregnancy test for female subjects of childbearing potential at the screening visit. Female subjects of childbearing potential have to confirm that they are using approved means of contraception. Menopause and hysterectomy and/or oophorectomy are to be documented.
- Blood and urine is to be drawn and sent to the central laboratory according to the local procedure for evaluation of haematology, clinical chemistry, urinalysis, HbA1c, and FPG.
- Subjects will be instructed to return for the placebo run-in visit 2 weeks later.
- Dispense of subject diary and glucometer.

Placebo Run-in Visit (14 days plus/minus 3 days prior to treatment)

The following observations/procedures are to be performed and checked:

- Check inclusion/exclusion criteria
- Review of subject's clinical charts, results of laboratory examination and blood pressure to confirm entry criteria
- Vital signs
- Blood is to be drawn and sent to the central laboratory* according to the local procedure for evaluation of HbA1c, and FPG.
- Evaluation for any AEs including hypoglycaemic episodes experienced by the subjects since last visit
- Subjects receive single-blinded placebo to take once daily. This will be dispensed to the subjects. Subjects should start administration of placebo from the placebo run-in visit.
- Review of subject diary
- Subjects are to be instructed that they have to return for the next scheduled visit day.

* When the investigator considers there are proper reasons, it is allowed to evaluate HbA1c and FPG at each study site.

Randomization Visit (1 day of treatment)

The following observations/procedures are to be performed and checked:

- Check inclusion/exclusion criteria
- Review of subject's clinical charts, results of laboratory examination and blood pressure to confirm entry criteria
- Vital signs, body weight and ECG
- Review use of concomitant treatments and of the regular metformin therapy
- Blood and urine is to be drawn and sent to the central laboratory according to the local procedure for evaluation of haematology, clinical chemistry, urinalysis, HbA1c, FPG, fasting insulin, C-peptide and glucagon
- Evaluation for any AEs including hypoglycaemic episodes experienced by the subjects since last visit
- Review subject diary

- Randomization to MP-513 or placebo. This will be dispensed to the subjects. Unused placebo from the placebo run-in period has to be returned to the site. Investigator calculates the drug compliance of the placebo run-in period and confirms whether the subject doesn't meet the exclusion criteria #18. Subjects should start administration of MP-513 or placebo from the randomization visit.
- Subjects are to be instructed that they have to return for the next scheduled visit day.

Treatment Visit 1 (Week 4 plus/minus 7 days of treatment)

The following observations/procedures are to be performed and checked:

- Vital signs, body weight
- Review use of concomitant treatments and of the regular metformin therapy
- Blood and urine is to be drawn and sent to the central laboratory according to the local procedure for evaluation of haematology, clinical chemistry, urinalysis, HbA1c, FPG, fasting insulin, C-peptide and glucagon
- Evaluation for any AEs including hypoglycaemic episodes experienced by the subjects since last visit
- Review subject diary
- MP-513 or placebo will be dispensed to the subjects. Unused medication has to be returned to the site.
- Subjects are to be instructed that they have to return for the next scheduled visit day.

Treatment Visit 2 (Week 8 plus/minus 7 days of treatment)

The following observations/procedures are to be performed and checked:

- Vital signs, body weight
- Review use of concomitant treatments and of the regular metformin therapy
- Blood and urine is to be drawn and sent to the central laboratory according to the local procedure for evaluation of haematology, clinical chemistry, urinalysis, HbA1c, FPG, fasting insulin, C-peptide and glucagon
- Evaluation for any AEs including hypoglycaemic episodes experienced by the subjects since last visit
- Review subject diary
- MP-513 or placebo will be dispensed to the subjects. Unused medication has to be returned to the site.

- Subjects are to be instructed that they have to return for the next scheduled visit day.

Treatment Visit 3 (Week 12 plus/minus 7 days of treatment)

The following observations/procedures are to be performed and checked:

- Vital signs, body weight and ECG
- Review use of concomitant treatments and of the regular metformin therapy
- Blood and urine is to be drawn and sent to the central laboratory according to the local procedure for evaluation of haematology, clinical chemistry, urinalysis, HbA1c, FPG, fasting insulin, C-peptide and glucagon
- Review subject diary
- Evaluation for any AEs including hypoglycaemic episodes experienced by the subjects since last visit
- MP-513 or placebo will be dispensed to the subjects. Unused medication has to be returned to the site
- Subjects are to be instructed that they have to return for the next scheduled visit day.

Treatment Visit 4 (Week 16 plus/minus 7 days of treatment)

The following observations/procedures are to be performed and checked:

- Vital signs, body weight
- Review use of concomitant treatments and of the regular metformin therapy
- Blood and urine is to be drawn and sent to the central laboratory according to the local procedure for evaluation of haematology, clinical chemistry, urinalysis, HbA1c, FPG, fasting insulin, C-peptide and glucagon
- Evaluation for any AEs including hypoglycaemic episodes experienced by the subjects since last visit
- Review subject diary
- MP-513 or placebo will be dispensed to the subjects. Unused medication has to be returned to the site
- Subjects are to be instructed that they have to return for the next scheduled visit day.

Treatment Visit 5 (Week 20 plus/minus 7 days of treatment)

The following observations/procedures are to be performed and checked:

- Vital signs, body weight
- Review use of concomitant treatments and of the regular metformin therapy
- Blood and urine is to be drawn and sent to the central laboratory according to the local procedure for evaluation of haematology, clinical chemistry, urinalysis, HbA1c, FPG, fasting insulin, C-peptide and glucagon
- Evaluation for any AEs including hypoglycaemic episodes experienced by the subjects since last visit
- Review subject diary
- MP-513 or placebo will be dispensed to the subjects. Unused medication has to be returned to the site
- Subjects are to be instructed that they have to return for the next scheduled visit day.

Treatment Visit 6 (Week 24plus/minus 7 days of treatment /Early termination visit: date of discontinuation* plus 7 days)

*Date of discontinuation is defined as the date of decision of discontinuation for subjects by the investigator.

This visit is the regular **end of treatment visit**. In case of premature termination, the same evaluations have to be performed as **the early termination visit**.

The following observations/procedures are to be performed and checked:

- Vital signs, body weight and ECG
- Review use of concomitant treatments and of the regular metformin therapy
- Blood and urine is to be drawn and sent to the central laboratory according to the local procedure for evaluation of haematology, clinical chemistry, urinalysis and HbA1c, FPG, fasting insulin, C-peptide and glucagon.
- A serum pregnancy test is to be performed in females with childbearing potential.
- Evaluation for any AEs including hypoglycaemic episodes experienced by the subjects since last visit
- Review and final collection of subject diary
- Unused MP-513 or placebo has to be returned to the site.

Follow-up Visit (Week 26 plus 14 days following completion / Early termination of double-blind treatment period)

Two weeks after end of treatment, a telephone follow-up visit will take place to ask the subjects about any AEs including hypoglycaemic episodes experienced by the subjects since the last visit and use of concomitant treatments.

- Review of the use of the regular metformin therapy.

6.6.2 Methods of Assessment

6.6.2.1 Primary Efficacy Parameter

HbA1c

This parameter will be measured by taking a blood sample. Blood samples will be collected at the sites and HbA1c will be measured at a central laboratory.

6.6.2.2 Secondary Efficacy Parameters

Glucose (FPG)

This parameter will be measured by taking a blood sample. Blood samples will be collected at the sites and FPG will be measured at a central laboratory.

6.6.2.3 Other Efficacy Parameters

Insulin, C-peptide and glucagon will be taken in a fasting state. Blood samples will be collected at the sites and parameters will be measured at a central laboratory.

Homeostatic model assessment (HOMA)

Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) and HOMA-ß will be evaluated by fasting glucose and fasting insulin as follows:

HOMA-IR = fasting insulin (mU/L)* fasting glucose (mg/dL)/405

HOMA-ß = 360 * fasting insulin (mU/L)/(fasting glucose (mg/dL) – 63)

Body weight

Body weight will be measured at the beginning of the respective visits.

6.6.2.4 Safety Parameters

Laboratory Monitoring

In addition to the above mentioned special diabetes-related measurements, blood samples will collected and sent to the central laboratory according to the local procedure for evaluation.

Clinical laboratory parameters to be measured include:

- haematology: haemoglobin, haematocrit, red blood cell count, white blood cell count (with differential in %), platelet count
- blood chemistry: AST, ALT, gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen, creatinine, uric acid, total protein, albumin, albumin/globulin ratio, direct bilirubin, creatine kinase, sodium, potassium, chloride, calcium, phosphate, and magnesium
- Pregnancy tests will also be done as serum test at the beginning and the end of study in women with childbearing potential
- Urinalysis will be done via dipstick test and includes sugar, protein, occult blood, urobilinogen, ketone bodies, and pH.

Any clinically significant change observed at each visit in comparison with baseline has to be evaluated carefully and a relationship with a possible cause is to be given (test medication or other treatment received or concomitant pathology).

Vital Signs

Vital signs (sitting systolic/diastolic blood pressure, pulse rate and body temperature) will be evaluated by comparison of the results obtained pre- and post-treatment and record in the eCRF.

Any clinically significant change observed at each visit in comparison with baseline has to be evaluated carefully and a relationship with a possible cause is to be given (test medication or other treatment received or concomitant pathology).

Electrocardiogram (ECG)

Standard 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be evaluated by comparison of the results obtained pre- and post-treatment. PR-interval, RR-interval, QRS-interval, QT-interval, QTc and heart rate will be recorded in the eCRF.

The results of ECG are to be classified as follows:

1. normal

2. abnormal, but not a clinically significant change

3. abnormal, clinically significant change

Any clinically significant change observed at each visit in comparison with baseline has to be evaluated carefully and a relationship with a possible cause is to be given (test medication or other treatment received or concomitant pathology).

Hypoglycaemic episode

The investigator will instruct the subjects to write the subject diary and monitor the blood glucose by glucometer as much as possible when hypoglycaemia occurred. Subjects should visit hospital if hypoglycaemia symptom is not resolved after taking sugar.

Subjects should carry their diary on each visit, the investigator will check the subject diary until last dose and check if hypoglycaemia occurred.

If a suspicious symptom of hypoglycaemia occurred, Investigators should diagnose and record on eCRF as the following criteria:

Patient's hypoglycaemia symptom after taking sugar	
Resolved	Unresolved
Hypoglycaemia	AE

Investigators will classify the event in accordance with the following categories:

- Severe hypoglycaemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- Documented symptomatic hypoglycaemia: An event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).
- Asymptomatic hypoglycaemia: An event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).
- Probable symptomatic hypoglycaemia: An event during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).
- Relative hypoglycaemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets the symptoms as indicative of hypoglycaemia, but with a measured plasma glucose concentration > 70 mg/dL (3.9 mmol/L).

The investigator will collect the following items and record them on the eCRF. The definitions of the items are equivalent to those for AEs.

- Symptom of hypoglycaemia
- Duration (start and end dates and times)
- Severity grade (mild, moderate, severe)
- Investigator causality (relationship to the study product)
- Action taken (change of study medication)
- Action(s) taken other than change of study medication
- Outcome
- Seriousness
- Value of glucose levels measured by glucometer (when hypoglycaemia occurred)
- Time of glucose levels measured by glucometer (when hypoglycaemia occurred)
- Reasons for hypoglycaemia (unknown, no diet or delay of diet, performed intense exercise, others)
- Time of last diet and study medication before hypoglycaemia occurred.

Further details will be outlined in the eCRF manual.

Cardiovascular events

An Event Adjudication Committee (EAC) will be set up to evaluate the cardiovascular events.

Cardiovascular events are defined as below: Death; Myocardial Infarction; Hospitalisation for Unstable Angina; Stroke & Transient Ischaemic Attack (TIA) (fatal & non-fatal); Urgent Revascularisation Procedures; Hospitalisation for Heart Failure

The detailed review procedure will be developed in a booklet prior to initiating the trial.

Adverse Events

All AEs that occur during the study from the signing of informed consent form through to 14 days after the final dose of the study drug are to be collected and reported on the eCRF, regardless of whether they are reported by the subject, elicited by investigator questioning, detected through physical examination, or by other means.

As far as possible, each AE is described by:

- duration (start and end dates)
- severity grade (mild, moderate, severe)

- investigator causality assessment (relationship to the study product)
- action taken (change of study medication)
- outcome
- seriousness

Definitions and Handling of Adverse Events

AE

An AE is any untoward medical occurrence (change in anatomical, physiological, metabolic function, or clinically significant laboratory abnormality) in a subject, which does not necessarily have any causal relationship with the product under investigation.

SAE

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (Note: the term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe)
- requires subject hospitalisation or prolongation of existing hospitalisation (for the purpose of this study, a hospitalisation is defined as a hospital stay of at least 8 hours and/or an overnight stay)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

or

- other medically important condition

Events that require intervention to prevent one or more of the outcomes listed in the definition above are also to be considered as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalisation, or development of drug dependency or drug abuse.

However, medical judgement has to be exercised in deciding whether an event is serious in any other situations considered medically relevant.

The evaluation of the AE as serious or not-serious is made independently of any attribution of causality.

Events NOT considered to be SAEs are those that require:

- treatment, which is elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and does not worsen
- treatment on an emergency, outpatient basis for an event NOT fulfilling any of the definitions of serious given above and NOT resulting in hospital admission for the purpose of this study, a hospitalisation is defined as a hospital stay of at least 8 hours and/or an overnight stay).

AE severity

AE severity determined by the clinical investigator on the basis of his/her direct observations or the subject's reporting:

- Mild: causes no limitation of usual activities; the subject may experience slight discomfort
- Moderate: causes some limitation of usual activities; the subject may experience annoying discomfort
- Severe: causes inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

AE causality (relationship guide)

Any AE has to be judged for causality (relationship to study medication).

The relationship of an AE to the study product is to be graded on the basis of the following:

• Reasonable possibility	The relationship of the clinical event to the investigational product administration is "related", "possible related", "Possibly not related" or "unassessable" will be regarded as "reasonable possibility".
• No reasonable possibility	The relationship of the clinical event to the investigational product administration is "not related" will be regarded as "no reasonable possibility".

Handling of AEs

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the study product has to be discontinued if appropriate. Follow-up evaluations of the subject are to be performed, whenever possible, until the subject recovers or until the investigator considers the situation to be no longer clinically significant.

If clinically significant laboratory abnormalities appear at Week 24 or Early termination visit, appropriate additional tests may be performed to clarify the nature of any clinically significant laboratory abnormalities that occur. If an abnormal laboratory

value or assessment is clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values. All clinically significant abnormal laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilise, or until they are judged by the Investigator to be no longer clinically significant. Further details will be outlined in the eCRF manual.

AEs are monitored and registered on the AE form of the eCRF at each visit. The AEs caused from the signing of informed consent form through to 14 days after the final dose of the study drug are collected and reported on eCRF. In absence of a specific diagnosis, an individual AE form has to be filled in for each sign or symptom.

Persistent AEs will be entered once in the eCRF until they are resolved or if a new event has to be documented due to deterioration. These AEs will be carefully monitored; further details of monitoring of persistent AEs will be provided in the monitoring plan. If an AE is still not resolved at the end of the study, this will documented as ongoing.

For recurrent AEs, i.e., AEs of the same nature, but with a different date of onset, an individual AE form has to be completed for each of them.

If the AE is classified as serious, the clinical investigator has also to complete the SAE report form. It is the responsibility of the investigator to send the SAE report form by fax to the Drug Safety Department of the CRO within 24 hours of receipt and to retain the original copy of the form (keeping a photocopy in the Investigator Site File). At the earliest possible date, the SAE report form has to be followed by a detailed report and any documentation that may be available, e.g., hospital case records, autopsy reports, and/or other pertinent documents. All such reports will identify subjects by unique code numbers assigned to the study subjects only, and will not include the subjects' names, personal identification numbers, or addresses.

All the above documents will be sent by fax to the Drug Safety Department of the CRO within 24 hours of receipt. The responsibility for reporting the SAE to local ethics committees and the respective health authorities are complied with the national regulatory requirements.

Pregnancies

If the subject or the subject's partner is found to be pregnant during the study, and the embryo-foetus may potentially be exposed to the study medication, the investigator should immediately discontinue the study treatment in the relevant subject and report to the Sponsor accordingly. If the subject wishes to give birth to the child, the investigator will follow up the subject until delivery as far as possible in order to investigate the presence/absence of impact of the study medication on the born baby.

Information obtained from the investigation will be reported in writing to the sponsor in the same way as a significant AE.

6.7 Appropriateness of Measurements

All clinical and laboratory procedures that will be used in this study are standard and generally accepted.

6.8 Data Quality Assurance

Detailed procedures will be separately provided in the data management, monitoring, and quality plans.

6.8.1 Data Collection

Data of all subjects who gave informed consent have to be reported on the eCRFs in an anonymous fashion. Subjects are identified only by screening number.

The investigator will be responsible for the completeness, accuracy, and legibility of the information in the eCRF and other study documents. For documents other than eCRF, only ballpoint pen is to be used and any change of data is to be done by striking out the incorrect data with a single line and dating and initialing the changes made.

The study monitors then have to check the eCRFs against the source documents for accuracy and validity as per the monitoring schedule, as applicable. Any data recorded directly on the eCRF (for example, no prior written or electronic record of data) are considered source data. Also, any step in creation of source data is to be identified at which a computerized system is to be used to create, modify, maintain, archive, retrieve, or transmit source data.

The subject diary will remain as source at site and will only be source data verified by the monitors but not collected. Source data verification will include the diary data, eCRF data, and drug accountability of blisters.

Upon completion of the examination, eCRF completion is expected at each site to ensure quality of data and subject safety. Once eCRFs are completed, they will be available for review by the monitor and the designated CRO Clinical Data Management department. Completed eCRFs will be reviewed remotely for logical discrepancies. The monitor will ensure that all data queries and subsequent amendments in the eCRF documentation are made according to GCP guidelines.

A copy of the eCRF is to be archived by the investigator together with the study documents, source data, and laboratory records for the time required by the national regulation.

Confidentiality/Property

Adequate records have to be maintained for the study, including subject medical records, eCRFs, laboratory reports, worksheets, nursing notes, signed informed consent forms, product forms, SAE forms, and information regarding subject discontinuation and reasons for discontinuation. The confidentiality of each record with subject identification is to be guaranteed by the clinical investigator.

This study protocol and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The investigator agrees to use this information only in conducting this study and is not allowed to use it for other purposes without written consent from the Sponsor. Results obtained from this study are the property of the Sponsor.

Retention of Records

The investigator agrees to retain copies of the eCRFs (usually on compact discs) with other study documents (e.g., the protocol and any protocol amendments, IEC approval, signed consent forms, and source documents for each subject in the study [eg, all demographic and medical information, including laboratory data, ECG, medication disposal and subject diaries]) in a secure place as long as needed to comply with national and international regulations (generally for 5 years). These records have to be made available for inspection upon reasonable request by a representative of the Sponsor or regulatory authorities.

In the event the investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required (e.g. lack of storage capabilities), custody of the records has to be transferred to any other person who accepts responsibility for the records, e.g., a third party, an Institutional Review Board, or another investigator. Notice of such transfer has to be given in writing to the sponsor in advance.

Routine Monitoring

For protocol monitoring and compliance, a site visit will be held prior to initiation of subject enrolment. The protocol, eCRFs, study treatment supplies, and study procedures will be explained in detail.

The purpose of monitoring is to verify the rights and well-being of human subjects are protected; that study data are accurate, complete, and verifiable with source data; and that the study is conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

A monitor assigned by the CRO will conduct regular site visits for the purpose of study monitoring.

The investigator must agree to allow the study monitor and authorised representatives of the CRO or the sponsor to inspect all eCRFs and corresponding source documents (e.g., original medical records, subject records and laboratory raw data); to allow access to the clinical supplies, dispensing, and storage areas; and to agree to assist with their activities, if requested. The investigator should provide adequate time and space for monitoring visits.

The monitor will query any missing or spurious data with the investigator, which should be resolved in a timely manner. A monitoring log will be maintained to record each visit, the reason for the visit, the monitor's signature, and the investigator's or designee's confirmation signature.

6.8.2 Site Audits

The sponsor or its designee may carry out an audit at any time. Investigators will be given adequate notice before the audit occurs. The purpose of an audit is to confirm that the study is conducted as per protocol, GCP and applicable regulatory requirements, that the rights and well-being of the subjects enrolled have been protected, and that the data relevant for the evaluation of the investigational product have been captured, processed and reported in compliance with the planned arrangements. The investigator will permit direct access to all study documents, drug accountability records, medical records, and source data.

Regulatory authorities may perform an inspection of the study, even up to several years after its completion. If an inspection is announced, the investigator or the site must inform the sponsor immediately.

6.8.3 Database Management and Quality Control

The CRO will be responsible for the activities associated with the data management of this study, including the production of an eCRF, setting up a relevant database, along with appropriate validation of data and resolution of queries. All data will be entered into an eCRF. Automated and manual checks will be made against the data entered into eCRF to ensure completeness and consistency. Resolution of queries will be implemented in the database.

AEs will be standardised for terminology and classification, using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be classified by site of action and therapeutic and clinical characteristics using the World Health Organisation (WHO) DRUG dictionary. Versions of the dictionaries to be used will be documented in the Data Management Plan and the statistical analysis plan (SAP).

6.9 Statistical Methods and Determination of Sample Size

6.9.1 Statistical and Analytical Plans

Full details will be given in the SAP before database lock.

6.9.1.1 General Considerations

All significance tests will be carried out at a 5%, 2-sided significance level. Statistical tests will be supported by presenting estimates and 95% confidence intervals 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.

6.9.1.2 Handling of dropouts and missing data

The last observation carried forward (LOCF) approach will be implemented to replace missing efficacy values excepting postprandial parameters for all those subjects who do not present a data value at Week 12 and Week 24. Baseline value will not be used to impute missing data.

6.9.1.3 Analysis Populations

Randomized Set: The Randomized Set includes all subjects who randomized.

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 and have at least one post-baseline safety observation..

Full Analysis Set: The Full Analysis Set (FAS) includes all subjects in the randomized set who have received at least one dose of study medication during the double-blind treatment period and have at least one post-baseline efficacy observation. Subjects who were not diagnosed type 2 diabetes mellitus will be excluded.

Per-Protocol Set: The Per-protocol Set (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. 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.

6.9.1.4 Demography and Baseline Characteristics

Demography and Baseline Characteristics summaries will be based on FAS and the Safety Analysis Set unless otherwise indicated. No formal statistical test would be performed to determine statistical significance between treatment groups.

6.9.1.5 Efficacy Parameters

(1) Primary efficacy endpoint

The primary efficacy endpoint is the change in HbA1c from baseline to Week 24.

Primary analysis: The change in HbA1c from baseline to Week 24 between treatment groups will be analysed using analysis of covariance (ANCOVA), with treatment as fixed effect and baseline value as a covariate. Missing values at Week 24 will be imputed using LOCF approach. Primary analysis on primary efficacy endpoint will be presented for FAS.

Supportive analysis: The same statistical methodology as described for primary analysis will be performed for PPS. The change in HbA1c from baseline to Week 24 between treatment groups will be analysed using mixed-effects model for repeated measures, with treatment, visit and interaction of treatment and visit as fixed effects and baseline value as a covariate. An unstructured covariance matrix will be used to model the covariance of within-patient scores. No imputation will be implemented for missing values. This analysis will be presented for FAS.

(2) Secondary efficacy endpoint

The secondary efficacy endpoints are the change in FPG from baseline to Week 24.

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

(3) Other efficacy endpoints

The other efficacy endpoints are;

- 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 body weight from baseline to Week 12

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

For the others, the same statistical methodology as described for primary analysis on primary efficacy endpoint will be used. Analyses on other efficacy endpoint will be presented for FAS.

6.9.1.6 Safety Parameters

Safety endpoints are:

- AEs
- ADRs
- Hypoglycaemic episodes
- Cardiovascular events
- laboratory measurements
- Vital signs (blood pressure, pulse rate and body temperature)
- 12-lead ECG

All safety summaries will be performed on the Safety Analysis Set. No formal statistical test would be performed to determine statistical significance between treatment groups.

6.9.2 Subgroup Analyses

Change in HbA1c from baseline to Week 24 will be analysed for the subgroup of baseline characteristics.

6.9.3 Interim Analyses

No interim analysis is planned.

6.9.4 Determination of Sample Size

[redacted]

7. Study Report and Publication Policy

Any formal presentation or publication of data from this trial will be considered by the appropriate sponsor personnel. For multi-centre studies it is mandatory that the first publication is based on data from all centres, analysed as stipulated in the protocol. Investigators agree not to present data gathered from one centre or a small group of centres before the full publication. In any case, the Sponsor will review any publications/communications/abstracts for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that proprietary, confidential information is not being inadvertently divulged, and provide any relevant supplementary information.

8 References

[1] EMA 2012

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus 14 May 2012 CPMP/EWP/1080/00 Rev. 1 Committee for Medicinal Products for Human Use (CHMP)

[2] ADA 2014

Diagnosis and Classification of Diabetes Mellitus. Diabetes Mellitus, Volume 36, Supplement 1, January 2014, S81-90