NOVARTIS

Clinical Development

LAF237/Galvus

Clinical Study Protocol CLAF237A23156 / NCT01528254

A 5-year study to compare the durability of glycemic control of a combination regimen with vildagliptin & metformin versus standard-of-care monotherapy with metformin, initiated in treatment-naïve patients with type 2 diabetes mellitus

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Document type:	Amended Protocol Version
EUDRACT number:	2011-003712-23
Version number:	V04 (clean)
Development phase:	IV
Release date:	22-Oct-2019

[redacted]

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
AUC	area under the curve
bid	*bis in die* (twice a day)
BL	baseline
BMI	body mass index (=body mass (kg)/(body height (m))^2)
CFR	United States code of federal regulation
CHF	congestive heart failure
CK-MB	creatinine kinase muscle-brain-type isoenzyme
CPK	phosphocreatine kinase
CRF	case record form
CRO	contract research organisation
CV	cardiovascular
DMC	Data Monitoring Committee
DPP-4	dipeptidyl peptidase-4
DS&E	drug safety & epidemiology
ECG	electrocardiogram
EDC	electronic data capture
EOS	end of study
FAS	full analysis set
FPG	fasting plasma glucose
γ-GT	γ-glutamyl transferase
GCP	good clinical practice
GFR	glomerular filtration rate
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen

[redacted]

hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high density lipoprotein
[redacted]	[redacted]
IB	investigator brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IN	investigator notification
IgM	immunoglobulin M
IRB	institutional review board
IRT	interactive response technology
ISR	insulin secretion rate
LDL	low density lipoprotein
LFT	liver function tests
M	molar (mol/L)
MDRD	modification of diet in renal disease
MI	myocardial infarction
NYHA	New York health association
OAD	oral anti-diabetic drug
OGIS	oral glucose insulin sensitivity
PK	pharmacokinetics
PPS	per protocol set
PSD	premature subject discontinuation
qd	*quaque die* (once daily)
RAN	randomised
RBC	red blood cells
REB	research ethics board
SAE	serious adverse event
SAF	safety
SCR	screening-only
SDD	study drug discontinuation

[redacted]

SOC	system organ class
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
T2DM	type-2 diabetes mellitus
TG	triglyceride
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
ULN	upper limit of normal
VLDL	very low density lipoprotein
WBC	white blood cells

Glossary of terms

Assessment	A procedure used to generate data required by this study protocol.
Background therapy	Oral anti-diabetic drug (OAD), if any, that is being used by the patients at screening (see also "Treatment-naïve patient" below).
Baseline (BL)	Day when patient takes first dose of study medication.
Completion of the study	Point/time when all randomised patients have completed the 5-years treatment period or discontinued the study prematurely.
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with United States Code of Federal Regulation (CFR) 21 Section 312.3 and is synonymous with "investigational new drug".
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an interactive response technology (IRT) system.
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study (see Section 5.5.1).
Period	A subdivision of the study. In this study the 3 periods are likely to be different between patients (see Section 3.1).
Premature subject discontinuation	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomisation number	A unique identifier assigned to each randomised patient, corresponding to a specific treatment arm assignment.
Rescue medication	Rescue medication is medication to treat the patient for type 2 diabetes mellitus (T2DM) when the patient temporarily cannot use the study drug regimen due to adverse events (AEs) or untoward events that require temporary dose adjustments. In this study, insulin should preferably be used as rescue medication (see Section 5.5.6).
Run-in period	The time between Visit 2 and Visit 3 where metformin will be initiated or up-titrated as described in Section 3.1.1.
Study drug discontinuation	Point/time at which the last dose of study drug was taken (in this protocol, this can be earlier but no later than at Visit 23).
Study drug	Any drug administered to the patient as part of the required study procedures; includes the investigational drugs metformin, vildagliptin (or matching placebo in Period 1 only), insulin (in Period 3 only).
Study drug regimen	The combination of study drugs taken by a patient in this study. The combination will be different depending on the period in the study in which the patient is at a given time.
Time to insulin initiation	The time to insulin initiation is defined as the time from randomization (Visit 3) to the date of initiation of insulin therapy prescribed in Period 3 (i.e. for treatment intensification according to local guidelines) or to the date of discontinuation from the study in Period 2 due to not being able or unwillingness to initiate insulin therapy for treatment intensification in Period 3 (see Section 9.5.2.2).
Treatment-naïve patient	Patients not having ever received any anti-diabetic medication, or patients who, after the diagnosis of T2DM ≤24 months ago, have received anti-

[redacted]

	diabetic medication cumulatively for not more than 3 months, and have not received any anti-diabetic treatment within 3 months prior to Visit 1 (only metformin up to 2000mg daily is allowed within 1 month prior to Visit 1).
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

[redacted]

Amendment 4

Amendment rationale

The protocol is being amended based on a health authority request to incorporate the redefined order of analysis in the protocol to align with the final, published statistical analysis plan. The loss of glycaemic control was analysed as a secondary endpoint instead of a primary endpoint, and an additional detail was provided for the confirmatory visit for the primary analysis of time to initial treatment failure. Following this, only one primary endpoint approach was included in the statistical analysis plan analysis and the multiple testing method was removed.

Changes to the protocol

The second primary endpoint was removed from Section 2.1 and moved to Section 2.2 as a secondary endpoint. References to appropriate sections in the statements were updated.

In Section 6.4, the second primary endpoint was removed and entered as a secondary endpoint.

In Section 9.4.1 and Section 9.4.2 only the remaining primary endpoint was described, and reference to the (previously existing) second primary endpoint was removed. The text was further adjusted to clarify the initial treatment failure (confirmed by the second of the two HbA1c measurements ≥7.0%). Text referring to the (previously existing) second primary endpoint was removed from Section 9.4.3. In Section 9.4.4 the time to first treatment failure was clarified, as well as the descriptive subgroup analysis.

The (previously existing) second primary endpoint was described as secondary endpoint in Section 9.5.2.2, as well as various other related corrections.

The text on the power calculation for the removed primary endpoint was deleted from Section 9.6, as well as the text for the overall power of the study. The significance levels were adjusted.

The appropriate changes were also made in the protocol synopsis.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

[redacted]

Amendment 3

Amendment rationale

The protocol is being amended to accommodate the inclusion of an adjudication committee and a data monitoring committee (DMC), and specify timelines for safety reporting. Furthermore, due to a metformin 500mg tablet variant introduced in the study with organoleptic properties which were not well perceived by subjects, the protocol now allows the temporary use of commercial metformin 500mg tablets.

There are some minor corrections as well.

Changes to the protocol

[redacted]

Section 3.1.1 has been amended to clarify that the minimum dose of metformin required at randomisation is 1000mg per day; this is now in line with the rest of the study protocol.

Section 3.1.2 has been amended to clarify that the metformin dose must not exceed 2000mg daily during the dose adjustments permitted in the first 4 weeks of Period 1.

In Section 4.2, a typographical error has been corrected to clarify the permitted use of anti-diabetic medication prior to Visit 1.

In Section 5.1, a sentence has been added to clarify that in untoward situations where patients cannot use the study open label metformin 500mg tablets, temporarily commercial open label metformin 500mg tablets can be used.

In Section 5.5.5, a clarification has been added regarding the permitted dose adjustments and interruptions. In Section 6.1 and Section 7.1, timelines applicable to safety reporting have been clarified. According to the amended protocol, adverse event and serious adverse event reporting must now commence at the time of informed consent.

Table 6-3 has been expanded to clarify that C-peptide is measured as part of the standard chemistry laboratory panel.

Section 7.4 and Section 9.8 now include an outline on involvement of a DMC requested by the Steering Committee. There is limited evidence with DPP-4 inhibitors in the early T2DM population with mild hyperglycaemia or systematically collected safety data up to 5 years which demands looking into early cardiovascular outcomes but also safety of oral antidiabetic medications. The LAF237A23156 study provides a new territory for retrieval of a considerable pool of independently validated safety data (up to 10’000 patient years).

Section 7.5 now includes an outline on involvement of an adjudication committee. Results of recent studies with oral antidiabetic medications (reported after the start of the LAF237A23156 study) led the Steering Committee to request the addition of a cardiovascular adjudication committee. The importance of LAF237A23156 from the perspective of early

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cardiovascular outcomes requires adjudicated events that will satisfy a need for independently validated cardiovascular event data.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

[redacted]

Amendment 2

Amendment rationale

The protocol is being amended to include additional clarification related to the occurrence of a contraindication against the treatment with metformin or vildagliptin during the study and to ensure only patients who received appropriate diet and exercise training with respect to lifestyle modifications prior to enrolment may be included.

Changes to the protocol

In Section 4.1, a new inclusion criterion has been added to emphasise the need for patients to having received appropriate diet and exercise regime instructions related to lifestyle modifications prior to enrolment.

In Section 5.5.9, the occurrence of a contraindication against treatment with metformin or vildagliptin during the study has been added as a reason to discontinue a patient prematurely from the study.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

[redacted]

Amendment 1

Amendment rationale

The protocol is being amended to include an additional meal-test for patients who are participating in the meal-test sub-study at Visit 4. This change, together with the additional meal-tests, will enable the evaluation of the rate of loss in β-cell function and the rate of change in insulin sensitivity based on the meal-test. Furthermore, clarification related to the timing of administration of the study drug at the visits when the meal-test is performed is inserted.

Changes to the protocol

In Table 6-1, the meal-test has been added for Visit 4. Additionally, in Section 6.4 the rate of loss in β-cell function has been corrected to be calculated from Visit 4 (week 13) onwards instead of baseline.

In Section 6.4.3, it is clarified that at baseline (Visit 3), the study drug regimen will be administered to the patient after the meal-test. For the subsequent tests the study drug regimen will be administered 15 minutes before the start of the meal.

Corrections have been made to Section 9.5.2.1 and Section 9.5.2.2 to describe that the rate of loss in β-cell function is being calculated from Visit 4 (week 13) onwards instead of baseline.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the institutional review board (IRBs)/independent ethics committee (IECs) and health authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the informed consent, sites are required to update and submit for approval a revised informed consent that takes into account the changes described in this amended protocol.

Protocol synopsis

Title of study: a 5-year study to compare the durability of glycemic control of a combination regimen with vildagliptin & metformin versus standard-of-care monotherapy with metformin, initiated in treatment-naïve patients with type 2 diabetes mellitus.

Purpose and rationale: the purpose of this study is to determine whether the initiation of a vildagliptin plus metformin combination regimen would result in more durable glycemic control than metformin monotherapy in treatment-naïve patients (see Glossary of terms) with T2DM. The results of this study may be used to support decision-making of national and international diabetes guidelines working groups.

Objectives:

Primary objectives:

To demonstrate the superiority of combination of vildagliptin 50mg bid and metformin over metformin monotherapy in treatment-naïve patients with T2DM by testing the hypothesis that the risk of confirmed initial treatment failure (defined as HbA1c ≥ 7.0%, see Section 9.4.1) is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy.

Secondary objectives:

To evaluate the effect of initiation of combination regimen with vildagliptin plus metformin compared with metformin monotherapy in treatment-naïve patient with T2DM within up to 5 years of treatment, with regards to:

- The long-term efficacy of combination of vildagliptin 50mg bid and metformin over metformin monotherapy in treatment-naïve patients with T2DM by comparing the *rate of loss in glycemic control over time* (estimated annualised slope of HbA1c over time using a random coefficient model, see Section 9.5.2) between the combination vildagliptin plus metformin and metformin monotherapy.
- Progression of HbA1c from 26 weeks after the start of Period 2 to the end of Period 2 (see Section 3.1.3) assessed by rate of loss in glycemic control over time.
- Progression of FPG evaluated by the rate of loss in glycemic control over time assessed by estimated annualised slope of FPG over time for periods defined in Section 6.4.
- Change in HbA1c as defined in Section 6.4.
- Safety and tolerability.

In a subgroup of patients, to evaluate the effect of initiation of combination regimen with vildagliptin plus metformin compared with metformin monotherapy, with regards to:

- β-cell function assessed by insulin secretion rate (ISR)/glucose area under the curve ($AUC_{glucose}$) during a standard meal-test (see Section 3.1.5, Section 6.4.3 & Section 9.5.2.1) at timepoints indicated in Table 6-1 & Table 6-2 for periods defined in Section 6.4.
- Insulin resistance assessed by oral glucose insulin sensitivity (OGIS) during a standard meal-test at timepoints indicated in Table 6-1 & Table 6-2 for periods defined in Section 6.4.

[redacted]

[redacted]

[redacted]

Population: The population will consist of males and females (non-fertile or of childbearing potential using a medically approved birth control method) with T2DM. It is expected to screen approximately 4000 patients in order to randomise 2000 patients in this outpatient, international, multi-center clinical study.

A standard meal-test to evaluate β-cell function and insulin sensitivity (see Section 3.1.5) will be performed in a subgroup of patients.

[redacted]

Inclusion/Exclusion criteria:

Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Confirmed diagnosis of T2DM by standard criteria.
3. T2DM diagnosed ≤ 24 months ago.
4. HbA1c ≥6.5% and ≤7.5% at Visit 1.
5. Patients who are treatment-naïve, defined in this protocol as:
   - Patients not having ever received any anti-diabetic medication.
   - Patients who, after the diagnosis of T2DM ≤24 months ago, have received anti-diabetic medication cumulatively for not more than 3 months, and have not received any anti-diabetic treatment within 3 months prior to Visit 1 (only metformin ≤2000mg daily is allowed within 1 month prior to Visit 1), see also Section 4.2.
   - Patients who initiated metformin within 1 month prior to Visit 1 and take a total daily dose of maximum 2000mg metformin at Visit 1.
6. Age ≥18 and ≤70 years old at Visit 1.
7. Body mass index (BMI) ≥22 and ≤40 kg/m^2 at Visit 1.
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use effective methods of contraception during dosing of study treatment. Effective contraception is defined as a method accepted as per local regulations and include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilisation (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilisation (at least 6 months prior to screening). For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

[redacted]

- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- Placement of an intrauterine device or intrauterine system.
- In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

9. Agreement to take the study medication as required by the study procedures.
10. Lifestyle interventions:
    - Agreement to continue current diet and exercise regime throughout the duration of the study, unless otherwise instructed by the investigator.
    - Only patients who receive appropriate diet and exercise training with respect to lifestyle modifications prior to enrolment may be included in the clinical study.
11. .Ability to comply with all study requirements and willingness to participate in a 5-year study.

Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
2. Use of any of the following medications as assessed at Visit 1:
    - Any anti-diabetic treatment within 3 months prior to visit 1 (except for metformin which is allowed within 1 month prior to Visit 1, see Section 3.1 and Section 4.1) or any anti-diabetic treatment for more than 3 consecutive months or adding up to a total of more than 3 months in the last 2 years.
    - Use of weight control products including weight-loss medications in the previous 3 months.
    - Chronic oral (>7 consecutive days), parenteral or intra-articular corticosteroid treatment within 8 weeks prior to Visit 1.
    - Treatment with growth hormone within the previous 6 months.
    - Treatment with any drug or use of herbal medicine of known and frequent toxicity to a major organ, or that may interfere with the interpretation of the efficacy and safety data during the study.
3. A history or evidence of any of the following:
    - Acute metabolic conditions such a ketoacidosis, lactic acidosis or hyperosmolar state (including coma) within the past 6 months.
    - Current diagnosis of congestive heart failure (NYHA III or IV).
    - Myocardial infarction (MI) within the past 6 months.
    - Coronary artery bypass surgery or percutaneous coronary intervention within the past 6 months.
    - Stroke or transient ischemic attack (TIA) within the past 6 months.
    - Unstable angina within the past 3 months.
    - Sustained and clinically relevant ventricular arrhythmia.

[redacted]

- Active substance abuse, alcohol abuse (as defined by consumption of more than 24 alcohol units per week) and alcohol related history of disease within the past 2 years.
- Type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes (e.g. Cushing's syndrome or acromegaly-associated diabetes).
- Malignancy of an organ system (other than localised basal cell carcinoma of the skin) treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Hepatic disorder defined as:
- acute or chronic liver disease, evidence of hepatitis, cirrhosis or portal hypertension.
- history of imaging abnormalities that suggest liver disease (except hepatic steatosis), such as portal hypertension, capsule scalloping, cirrhosis.

4. Any of the following significant laboratory abnormalities as assessed at Visit 1:
    - Clinically significant thyroid stimulating hormone (TSH) outside of the normal range.
    - Renal dysfunction defined as calculated creatinine clearance <60ml/min/1.73m^2 via modified diet in renal disease (MDRD) formula.
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN) at Visit 1, confirmed by repeat measure within 3 working days.
    - Total bilirubin > 2 x ULN and/or direct bilirubin > 1 x ULN confirmed by repeat measure within 3 working days.
    - Positive Hepatitis B surface antigen (HbsAg).
    - Positive Hepatitis C antibody test (anti-hepatitis C virus (HCV)).
    - Elevated fasting triglycerides (TGs) >500mg/dL.
    - Clinically significant laboratory abnormalities which, in the opinion of the investigator, cause the patient to be considered inappropriate for inclusion in the study.
5. Any of the following electrocardiogram (ECG) abnormalities at Visit 1:
    - Second or third degree atrio-ventricular block without a pacemaker.
    - Long QT syndrome or corrected QT >500ms.
6. Previous or current participation in any vildagliptin clinical study.
7. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
8. Concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study.
9. Donation of ≥500mL or more of blood, significant blood loss equaling to at least one unit of blood within the past 2 weeks or a blood transfusion within the past 8 weeks.
10. Potentially unreliable and/or those judged by the investigator to be unsuitable for the study.
11. Use of an investigative drug within 30 days or 5 half-lives of the drug, whichever is longer.
12. Inability to comply with the study procedures or medications.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Investigational and control therapy: The sponsor will provide the following double-blind study medication (Period 1):

- Vildagliptin 50mg tablets.
- Vildagliptin 50mg matching placebo tablets.

The sponsor will provide the following single-blind study medication (Period 2 and Period 3):

[redacted]

- Vildagliptin 50mg tablets.

The sponsor will provide the following open label study medication (Period 1, 2 and 3):

- Metformin 500mg tablets.

No other drugs will be supplied. Medication will be supplied in bottles. Sufficient medication will be provided for treatment according to the study protocol.

Study design: this is a multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (see Figure 3-1).

Efficacy assessments:

Primary

- HbA1c measurements at visits indicated in Table 6-1 & Table 6-2 to determine the *time to confirmed initial treatment failure* (see Section 9.4.1).

Secondary

- HbA1c measurements at visits indicated in Table 6-1 & Table 6-2 to determine the *rate of loss in glycemic control over time* (estimated annualised slope of HbA1c over time using a random coefficient model), from Visit 5 to the end of Period 1 (see Section 9.5.2).
- HbA1c measurements at visits indicated in Table 6-1 & Table 6-2 to determine the rate of loss in glycemic control from 26 weeks after the start of Period 2 to end of Period 2 (see Section 3.1.3).
- FPG measurements at visits indicated in Table 6-1 & Table 6-2 to determine the rate of loss in glycemic control, i) from Visit 5 to the end of Period 1; ii) from 26 weeks after start of Period 2 to end of Period 2 (see Section 3.1.3).
- HbA1c measurements at visits indicated in Table 6-1 & Table 6-2 to determine the change in HbA1c from BL to end of study (EOS).
- C-peptide measurements collected during a meal-test performed at visits indicated in Table 6-1 & Table 6-2 to determine:
- The change in AUC of ISR/G as an assessment of β-cell function (see Section 6.4.3 & Section 3.1.5) from BL to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.
- The rate of loss of β-cell function from Visit 4 (week 13) to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.
- Insulin measurements collected during a meal-test performed at visits indicated in Table 6-1 & Table 6-2 to determine:
- OGIS as an assessment of change in insulin sensitivity (see Section 3.1.5 & Section 6.4.3) from BL to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.
- Rate of change in insulin sensitivity from Visit 4 (week 13) to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.

[redacted]

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[redacted]

Other assessments: physical examination, vital signs, [redacted] monitoring of hematology, blood chemistry and urine tests, ECG, incidence of hypoglycemia events, AEs/SAEs (see Section 7), new or progression of existing micro-vascular and macro-vascular complications, new onset micro-albuminuria, progression to renal insufficiency, [redacted].

Data analysis: the primary statistical hypothesis of time to confirmed initial treatment failure will be assessed by a 1-sided test of superiority of the combination treatment with vildagliptin + metformin versus metformin monotherapy with α-level of 0.025 of the hazard-ratio between the combination treatment vildagliptin + metformin and metformin monotherapy being equal or greater than 1 as the null hypothesis, versus the 1-sided alternative hypothesis that the hazard-ratio is less than 1: H_{01}: $\lambda_{vildagliptin+metformin}/\lambda_{metformin} \geq 1$ *versus* H_{a1}: $\lambda_{vildagliptin+metformin}/\lambda_{metformin} < 1$, where $\lambda_{vildagliptin+metformin}$ and $\lambda_{metformin}$ are the hazard-rates of the confirmed initial treatment failure for vildagliptin 50mg bid + metformin up to 1000mg bid and metformin up to 1000mg bid monotherapy respectively. The time to failure will be derived as the time from randomization to the second of two consecutive visits at which HbA1c ≥7.0% is measured, starting from Visit 4 (13 weeks after randomization). The primary efficacy analysis will use a Cox proportional hazard regression model to assess the probability of confirmed initial treatment failure, with treatment as classification variable and BL HbA1c as a covariate. The hazard-ratio and associated 95% confidence interval as well as the p-value estimated from the above model will be presented by treatment.

The secondary [redacted] efficacy endpoints will be analysed in the full FAS as appropriate. Demographic and background data as well as safety data will be summarised by treatment appropriately.

[redacted]

1 Introduction

1.1 Background

T2DM is a chronic progressive disease characterised by insulin resistance, pancreatic β-cell dysfunction and hyperglucagonemia resulting in chronic hyperglycemia. Patients with uncontrolled T2DM are at significantly increased risk of long-term micro- and macrovascular complications that increase morbidity, mortality and healthcare costs (IDF, 2009). In the United Kingdom Prospective Diabetes Study (UKPDS) intensive treatment policy compared with conventional therapy in newly diagnosed patients with T2DM resulted in significant reduction of microvascular and macrovascular complications (UKPDS 33, 1998; UKPDS 34, 1998). This protective effect seen in the intensive group was further maintained during the observational study period, despite the loss of difference in glycosylated hemoglobin (HbA1c), suggesting a legacy effect of maintaining strict glycemic control already from diagnosis (Holman et al, 2008).

Life-style intervention targeted to reduce body weight is regarded as the first-line treatment for T2DM, but its success rates and long-term efficacy are limited. Therefore consensus guidelines recommend that metformin should be concurrently initiated with life-style interventions (ADA-EASD, 2009). Metformin is a biguanide which reduces hepatic glucose output and food consumption, and long-term follow up has suggested that it has positive effect on cardiovascular (CV) outcomes in overweight and obese patients (UKPDS 34, 1998). Other OADs, such as sulfonylureas (SU) and pioglitazone, are usually considered as second-line therapies, as they are associated with safety concerns, including side effects such as hypoglycemia and weight gain or increasing the risk of congestive heart failure (CHF), and bone fractures in women (ADA-EASD, 2009). In the UKPDS, SU and metformin initially improved glycemic control, followed by progressive deterioration of HbA1c over the 12 years of follow-up (UKPDS 33, 1998; UKPDS 34, 1998). Furthermore, evaluation of the β-cell function indicated that at the time of diagnosis of T2DM 50% of the β-cell function was lost with further decline of around 4% per year (UKPDS 16, 1995). More recently, the ADOPT study found an annual reduction of β-cell function with metformin of 3.1% versus 2.0% with rosiglitazone in patients with T2DM with a diabetes duration of up to 3 years who had not received (systematically) antidiabetic treatment. The cumulative incidence of monotherapy failure, defined as fasting plasma glucose (FPG) exceeding 180mg/dL (10.0mM), at 5 years was 21% with metformin and 15% with rosiglitazone (32% risk reduction, $p<0.001$), at failure rates 4.3 and 2.9 per 100 patient-years, respectively (Kahn et al, 2006).

The most recent addition to the antidiabetic drugs are the glucagon-like peptide-1 (GLP-1)-based therapies. Both GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors have shown significant improvement in glycemic control with low risk of hypoglycemia and weight neutrality or weight reduction (Nauck et al, 2010). In addition, GLP-1 appears to have a role in pancreatic islet development and regeneration. Studies in rodents show that GLP-1 and its analogs stimulate β-cell growth and replication to increase islet mass (Drucker et al, 2003; Stoffers et al, 2000; Xu et al, 1999). GLP-1 supports the differentiation of pancreatic duct cells into insulin-producing cells (Bulotta et al, 2002; Hardikar et al, 2002), and also may inhibit β-cell apoptosis (Farilla et al, 2002; Li et al, 2003; Wang et al, 2001).

[redacted]

Vildagliptin is a member of the DPP-4 inhibitor drug class. It is a highly-selective substrate for the DPP-4 catalytic site with a slow reaction rate, which blocks the usually rapid degradation of GLP-1 and glucose-dependent insulinotropic peptide (GIP) (Villhauer et al, 2003). Vildagliptin increases plasma level of GLP-1 and GIP, which improves the sensitivity of the β- and α-cell to glucose; there are also extra-pancreatic effects which contribute to improved insulin sensitivity and attenuate weight gain (Ahrén et al, 2011). In clinical studies, vildagliptin has been shown to reduce HbA1c, FPG & postprandial plasma glucose levels (Rosenstock et al, 2007; Goke et al, 2008; Kikuchi et al, 2009; D'Alessio et al, 2009; Ahrén et al, 2004; Bosi et al, 2009; Garber et al, 2008; Fonseca et al, 2007). The human data available with vildagliptin at present show good safety and tolerability at the dose levels used clinically (up to 100mg daily) (Ligueros-Saylan et al, 2010; Schweizer et al, 2011). Additional information regarding vildagliptin is available in the investigator brochure (IB).

The pharmacological actions of vildagliptin, particularly related to enhancement of glucose-dependent insulin secretion, are complementary to those of metformin. The safety and efficacy of co-administration of vildagliptin and metformin for treatment of T2DM, either as separate tablets or as a fixed dose combination, has been demonstrated in numerous clinical studies (Ahrén et al, 2004; Bosi et al, 2009; Matthews et al, 2010). In a 24-week study in T2DM patients with HbA1c between 7.5% and 11.0%, the combination of vildagliptin 50mg/metformin 1000mg has shown superior glycemic control to each of the components in the combination (Bosi et al, 2009), however it is not known how this initial difference in the glycemic control would evolve over time. No long term data related to the effect of combination anti-diabetic therapies including a DPP-4 inhibitor on the durability of glycemic control are available in patients with more preserved β-cell function, i.e. newly diagnosed, or treatment-naïve patients with mild hyperglycemia.

While some guidelines advocate initiation of therapy with metformin already at diagnosis with consequent stepwise addition of other anti-diabetic treatments (ADA-EASD 2009), others recommend initiation combination therapy if patient's HbA1c is in the range 7.6%-9.0% (AACE/ACE, 2009). A more proactive approach with early combination treatment has been suggested (Del Prato et al, 2005). So far no long-term study has compared treatment initiation with combination therapy versus the standard-of-care metformin monotherapy in newly diagnosed or treatment-naïve patients. Considering the protective effect on the β-cell which vildagliptin may have in treatment-naïve patients with mild hyperglycemia (Scherbaum et al, 2008; Mathieu, 2008), it is of scientific and clinical practice interest to address the question if a combination regimen including vildagliptin/metformin given as initial therapy can provide more durable glycemic control compared with the standard-of-care metformin monotherapy.

1.2 Purpose

The purpose of this study is to determine whether the initiation of a vildagliptin plus metformin combination regimen would result in more durable glycemic control than metformin monotherapy in treatment-naïve patients (see Glossary of terms) with T2DM. The results of this study may be used to support decision-making of national and international diabetes guidelines working groups.

[redacted]

2 Study objectives

2.1 Primary objectives

- To demonstrate the superiority of combination of vildagliptin 50mg bid and metformin over metformin monotherapy in treatment-naïve patients with T2DM by testing the hypothesis that the risk of *confirmed initial treatment failure* (defined as HbA1c ≥ 7.0%, see Section 9.4.1) is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy.

2.2 Secondary objectives

To evaluate the effect of initiation of combination regimen with vildagliptin plus metformin compared with metformin monotherapy in treatment-naïve patient with T2DM within up to 5 years of treatment, with regards to:

- The long-term efficacy of combination of vildagliptin 50mg bid and metformin over metformin monotherapy in treatment-naïve patients with T2DM by comparing the *rate of loss in glycemic control over time* (estimated annualised slope of HbA1c over time using a random coefficient model, see Section 9.5.2) between the combination vildagliptin plus metformin and metformin monotherapy.
- Progression of HbA1c from 26 weeks after the start of Period 2 to the end of Period 2 (see Section 3.1.3) assessed by rate of loss in glycemic control over time.
- Progression of FPG evaluated by the rate of loss in glycemic control over time assessed by estimated annualised slope of FPG over time for periods defined in Section 6.4.
- Change in HbA1c as defined in Section 6.4.
- Safety and tolerability.

In a subgroup of patients, to evaluate the effect of initiation of combination regimen with vildagliptin plus metformin compared with metformin monotherapy, with regards to:

- β-cell function assessed by insulin secretion rate (ISR)/glucose area under the curve ($AUC_{glucose(0\text{-}2h)}$) during a standard meal-test (see Section 3.1.5, Section 6.4.3 & Section 9.5.2.1) at timepoints indicated in Table 6-1 & Table 6-2 for periods defined in Section 6.4.
- Insulin resistance assessed by oral glucose insulin sensitivity (OGIS) during a standard meal-test at timepoints indicated in Table 6-1 & Table 6-2 for periods defined in Section 6.4.

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This is a multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (see Figure 3-1). Following a screening visit (Visit 1) and a screening period of up to 2 weeks, treatment-naïve patients (see Section 4.1 or Glossary of terms), meeting all eligibility criteria will enter the run-in period at Visit 2.

3.1.1 Run-in period

At Visit 2, all eligible patients will receive lifestyle instructions (diet and exercise) according to local practice. Metformin treatment will be initiated and/or up-titrated as follows:

Treatment-naïve patients

Metformin will be initiated at a dose 500mg qd. Patients will be instructed to up-titrate metformin to 1000mg daily after one week if gastrointestinal (GI) side effects have not occurred and to 1000mg or 1500mg daily two weeks after Visit 2. If GI side effects occur, patients may stay another week on the same dose of metformin. An unscheduled visit can be performed in order to adjust the metformin dose if deemed necessary.

Up to three weeks after Visit 2 patients will return to the site for Visit 3. Patients who are able to tolerate a total dose of at least 1000mg daily will be randomised.

Patients who have initiated metformin within 1 month prior to Visit 1

Patients taking a daily dose of ≥500mg and <1000mg will be instructed to up-titrate their dose weekly (for 2 weeks or 1 week, respectively) in 500mg increments to 1500mg or a maximum tolerated dose (see Figure 3-1). Patients on a dose ≥500mg and <1000mg will have first up-titration to 1000mg daily. If GI side effects occur during up-titration, the patient should be instructed to go back to the previously tolerated dose, and then try to increase the dose again by 500mg. Patients who are able to tolerate a total dose of at least 1000mg daily will be randomised.

Patients taking metformin ≥1000mg and ≤2000mg daily at Visit 1 will directly proceed to randomisation and start in Period 1.

3.1.2 Period 1: vildagliptin/metformin combination *versus* metformin

At Visit 3, patients will be randomised 1:1 to one of the following study regimens:

- Metformin up to 1000mg bid plus vildagliptin 50mg bid or
- Metformin up to 1000mg bid plus matching placebo bid.

[redacted]

During the first 4 weeks of Period 1 the metformin dose can be adjusted (increased or decreased, but not below 1000mg daily or above 2000mg). An unscheduled visit can be performed in order to adjust the metformin dose if deemed necessary. The objective is to optimise metformin dose to 2000mg daily or to the maximum tolerated dose. Patients who are unable to tolerate a total daily dose of 1000mg metformin will be discontinued. The metformin dose at week 4 post-randomisation and the vildagliptin 50mg bid or matching placebo bid dose should remain unchanged throughout the duration of the study, except for AEs or untoward events that may require dose reduction or interruption (see Section 5.5.5).

Any anti-diabetic medication other than the study drug regimen is not allowed during Period 1, except if the patient had temporarily reduced/interrupted the treatment regimen due to AEs or untoward events that require temporary dose adjustments. In such cases dose adjustments or interruptions of the study drug are permitted (see Section 5.5.5). Patients who, during Period 1, take anti-diabetic medication other than the study drug regimen (except for AEs or untoward events that require temporary dose adjustments, see Section 5.5.5) will be discontinued from the study.

The duration of Period 1 may differ between patients depending on the time when the second of two HbA1c measurements taken at two consecutive visits after randomisation (Table 6-1 & Table 6-2) confirms HbA1c ≥ 7.0%.

3.1.3 Period 2: vildagliptin/metformin combination *versus* vildagliptin add-on to metformin

In the case of two consecutive HbA1c measurements ≥7.0% from two consecutive study visits during Period 1, scheduled according to Table 6-1 & Table 6-2, patients in both arms will receive new vildagliptin study medication packs. The investigator will contact the IRT system within 2 weeks after the receipt of the second of the two elevated HbA1c measurements. The IRT system will assign the new vildagliptin study medication packs. Patients who were randomised to the placebo arm in Period 1 will now receive vildagliptin 50mg bid. Patients who were randomised to the active vildagliptin 50mg bid arm in Period 1 will continue to receive vildagliptin 50mg bid. All patients will continue to take their metformin dose unchanged. Period 2 will remain masked to the patient and both patients and investigators will remain masked to the treatment allocation in Period 1.

Any anti-diabetic medication other than the study regimen is not allowed during Period 2, except if the patient had temporarily reduced/interrupted the treatment regimen due to AEs or untoward events that require temporary dose adjustment/interruption (see Section 5.5.5).

If, during Period 2, therapy intensification is required in accordance with the local guidelines, the patient will enter Period 3.

The duration of Period 2 may differ between patients. End of Period 2 is considered when insulin treatment is initiated, or alternatively when the patient is discontinued because insulin treatment is not initiated in Period 3 (see Section 3.1.4).

3.1.4 Period 3: insulin initiation

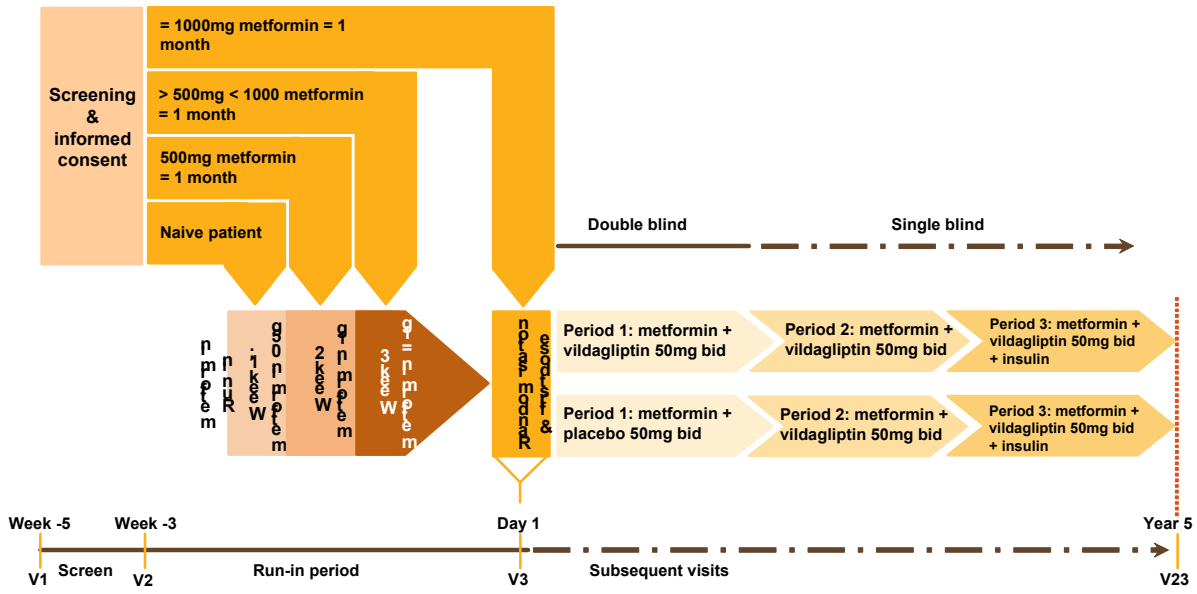
In Period 3, patients must be initiated on insulin. Patients who will have their therapy intensified with anti-diabetic treatment other than insulin must be discontinued from the study.

[redacted]

Reasons for intensifying treatment with other anti-diabetic treatment may be (but are not limited to) the patient being unwilling to initiate insulin therapy or insulin cannot be initiated according to local diabetes treatment guidelines.

Open-label insulin, preferably basal insulin, should be initiated if local guidelines criteria for insulin initiation are met during Period 2. The type of insulin and insulin regimen are at investigator's discretion. The study drug regimen will continue unchanged and will remain masked to the patient in Period 3 and both patients and investigators will remain masked to the treatment allocation in Period 1.

Figure 3-1 Study design



3.1.5 Meal-test

A standard meal-test will be performed in selected experienced sites at visits indicated in Table 6-1 & Table 6-2 in a subgroup of 380 patients in order to assess the progression of β-cell function and insulin sensitivity (see Section 6.4.3).

3.2 Rationale of study design

Up to 2-week screening period will be used to ensure that the entry criteria are met and to allow time for test results to be received and evaluated prior to randomisation. Up to 3-week run-in period is foreseen for the up-titration of metformin in order to minimise its GI side effects for treatment-naïve patients. After randomisation, study visits are scheduled every 13 weeks in order to monitor HbA1c progression over time and determine the time to failure. In case initial treatment fails to maintain HbA1c<7.0%, confirmed at two consecutive study visits (according to Table 6-1 & Table 6-2), vildagliptin will be added to metformin in the metformin-only arm in Period 2. In Period 3, insulin is considered based on local guidelines. This is a standard parallel-group 2-arm study comparing the two different treatment approaches.

[redacted]

3.3 Rationale of dose/regimen, duration of treatment

The selected doses and regimen (vildagliptin 50mg bid/metformin up to 1000mg bid and matching placebo bid/metformin up to 1000mg bid) are approved for use in patients with T2DM and are optimal doses achieving therapeutic effect in this population.

A 5-year study period will allow demonstrating a difference in the durability of the glycemic effect between a combination regimen with vildagliptin/metformin and the current standard-of-care, metformin monotherapy (Kahn et al, 2006). Vildagliptin is chosen as add-on to metformin since it has similar efficacy as other OADs suitable for add-on therapy to metformin (SUs or TZDs), but with a better weight profile than SUs and TZDs, and lower risk of hypoglycemia than SUs. Insulin is chosen as therapy in Period 3 as it is proposed in guidelines after failure of dual combination therapy (ADA, 2009).

3.4 Rationale for choice of comparator

Metformin up to 1000mg bid is chosen as the comparator treatment as it is currently recommended as initial treatment by diabetes guidelines. Metformin improves glycemic control and, when used as monotherapy, is associated with very low risk of hypoglycemia and weight neutrality or weight loss.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks

At the doses currently marketed in many countries, vildagliptin alone and in combination treatment with metformin is an effective treatment and overall tolerability and safety are good.

A study performed with initiation of vildagliptin + metformin in drug-naïve patients with T2DM (CLAF237A2302) showed that this combination is effective and safe and carries no risk of hypoglycemia. Therefore it is expected that the early introduction of vildagliptin in this study will have positive effect without additional risk for the patient. Hence, the use of a combination of metformin and vildagliptin, as proposed in the study, can be justified and patients treated with vildagliptin in the study are expected to benefit from HbA1c reductions. For patients with T2DM whose hyperglycemia is not optimally controlled on a therapy with metformin, even if only moderately above the target threshold, combination therapy with a second OAD is typically started in line with treatment guidelines. The vildagliptin dose of 50mg bid is in accordance with the approved product information of vildagliptin as add-on therapy to metformin.

The risks of the study are judged to be acceptable. Metformin and vildagliptin are both well-profiled and their risks well known. The safety profile of vildagliptin is also well documented and this study does not deviate from the dosages or treatment durations already studied. Safety laboratory tests are performed regularly and a range of AEs of interest are reviewed on an ongoing basis. The study, as designed, does not expose patients to unacceptable risks and, within the constraints of a robust clinical study, conforms to current practice in the treatment of T2DM.

[redacted]

4 Population

The population will consist of males and females (non-fertile or of childbearing potential using a medically approved birth control method) with T2DM.

It is expected to screen approximately 4000 patients in order to randomise 2000 patients in this outpatient, international, multi-center clinical study.

A standard meal-test to evaluate β-cell function and insulin sensitivity (see Section 3.1.5) will be performed in a subgroup of patients.

[redacted]

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Confirmed diagnosis of T2DM by standard criteria.
3. T2DM diagnosed ≤ 24 months ago.
4. HbA1c ≥6.5% and ≤7.5% at Visit 1.
5. Patients who are treatment-naïve, defined in this protocol as:
   - Patients not having ever received any anti-diabetic medication.
   - Patients who, after the diagnosis of T2DM ≤24 months ago, have received anti-diabetic medication cumulatively for not more than 3 months, and have not received any anti-diabetic treatment within 3 months prior to Visit 1 (only metformin ≤2000mg daily is allowed within 1 month prior to Visit 1), see also Section 4.2.
   - Patients who initiated metformin within 1 month prior to Visit 1 and take a total daily dose of maximum 2000mg metformin at Visit 1.
6. Age ≥18 and ≤70 years old at Visit 1.
7. Body mass index (BMI) ≥22 and ≤40 kg/m^2 at Visit 1.
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use effective methods of contraception during dosing of study treatment. Effective contraception is a method accepted as per local regulations and include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilisation (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilisation (at least 6 months prior to screening). For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.

[redacted]

- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- Placement of an intrauterine device or intrauterine system.
- In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

9. Agreement to take the study medication as required by the study procedures.
10. Lifestyle interventions:
    - Agreement to continue current diet and exercise regime throughout the duration of the study, unless otherwise instructed by the investigator.
    - Only patients who receive appropriate diet and exercise training with respect to lifestyle modifications prior to enrolment may be included in the clinical study.
11. Ability to comply with all study requirements and willingness to participate in a 5-year study.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
2. Use of any of the following medications as assessed at Visit 1:
    a. Any anti-diabetic treatment within 3 months prior to visit 1 (except for metformin which is allowed within 1 month prior to visit 1, see Section 3.1 and Section 4.1) or any anti-diabetic treatment for more than 3 consecutive months or adding up to a total of more than 3 months in the last 2 years.
    b. Use of weight control products including weight-loss medications in the previous 3 months.
    c. Chronic oral (>7 consecutive days), parenteral or intra-articular corticosteroid treatment within 8 weeks prior to Visit 1.
    d. Treatment with growth hormone within the previous 6 months.
    e. Treatment with any drug or use of herbal medicine of known and frequent toxicity to a major organ, or that may interfere with the interpretation of the efficacy and safety data during the study.

[redacted]

3. A history or evidence of any of the following:
   a. Acute metabolic conditions such a ketoacidosis, lactic acidosis or hyperosmolar state (including coma) within the past 6 months.
   b. Current diagnosis of congestive heart failure (NYHA III or IV).
   c. Myocardial infarction (MI) within the past 6 months.
   d. Coronary artery bypass surgery or percutaneous coronary intervention within the past 6 months.
   e. Stroke or transient ischemic attack (TIA) within the past 6 months.
   f. Unstable angina within the past 3 months.
   g. Sustained and clinically relevant ventricular arrhythmia.
   h. Active substance abuse, alcohol abuse (as defined by consumption of more than 24 alcohol units per week) and alcohol related history of disease within the past 2 years.
   i. Type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes (e.g. Cushing's syndrome or acromegaly-associated diabetes).
   j. Malignancy of an organ system (other than localised basal cell carcinoma of the skin) treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
   k. Hepatic disorder defined as:
      - acute or chronic liver disease, evidence of hepatitis, cirrhosis or portal hypertension.
      - history of imaging abnormalities that suggest liver disease (except hepatic steatosis), such as portal hypertension, capsule scalloping, cirrhosis.
4. Any of the following significant laboratory abnormalities as assessed at Visit 1:
   a. Clinically significant thyroid stimulating hormone (TSH) outside of the normal range.
   b. Renal dysfunction defined as calculated creatinine clearance <60ml/min/1.73m^2 via modified diet in renal disease (MDRD) formula.
   c. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN) at Visit 1, confirmed by repeat measure within 3 working days.
   d. Total bilirubin > 2 x ULN and/or direct bilirubin > 1 x ULN confirmed by repeat measure within 3 working days.
   e. Positive Hepatitis B surface antigen (HbsAg).
   f. Positive Hepatitis C antibody test (anti-hepatitis C virus (HCV)).
   g. Elevated fasting triglycerides (TGs) >500mg/dL.
   h. Clinically significant laboratory abnormalities which, in the opinion of the investigator, cause the patient to be considered inappropriate for inclusion in the study.
5. Any of the following electrocardiogram (ECG) abnormalities at Visit 1:
   1. Second or third degree atrio-ventricular block without a pacemaker.
   2. Long QT syndrome or corrected QT >500ms.
6. Previous or current participation in any vildagliptin clinical study.
7. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.

[redacted]

8. Concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study.
9. Donation of ≥500mL or more of blood, significant blood loss equaling to at least one unit of blood within the past 2 weeks or a blood transfusion within the past 8 weeks.
10. Potentially unreliable and/or those judged by the investigator to be unsuitable for the study.
11. Use of an investigative drug within 30 days or 5 half-lives of the drug, whichever is longer.
12. Inability to comply with the study procedures or medications.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Investigational and control treatment

The sponsor will provide the following double-blind study medication (Period 1):

- Vildagliptin 50mg tablets.
- Vildagliptin 50mg matching placebo tablets.

The sponsor will provide the following single-blind study medication (Period 2 and Period 3):

- Vildagliptin 50mg tablets.

The sponsor will provide the following open label study medication (Period 1, 2 and 3):

- Metformin 500mg tablets.

Temporarily, in untoward situations where a subject cannot use the study open label metformin 500mg tablets, open label commercial metformin 500mg can be used.

No other drugs will be supplied. Medication will be supplied in bottles. Sufficient medication will be provided for treatment according to the study protocol.

5.2 Treatment arms

Patients will be assigned in a ratio of 1:1 to one of two treatment arms:

- Metformin up to 1000mg bid plus vildagliptin 50mg bid (Period 1). In Period 2 and 3 these patients will receive metformin up to 1000mg bid plus vildagliptin 50mg bid.
- Metformin up to 1000mg bid plus vildagliptin placebo 50mg bid (Period 1). In Period 2 and 3 these patients will receive metformin up to 1000mg bid plus vildagliptin 50mg bid.

5.3 Treatment assignment

At Visit 3 all eligible patients will be randomised via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT system after confirming that the patient meets all the inclusion criteria and no exclusion criterion. The IRT system will assign a randomisation number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomisation number will not be communicated to the user.

[redacted]

The randomisation numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomisation list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomisation numbers. These randomisation numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis drug supply management using a validated system that automates the random assignment of medication numbers to study drug packs containing each of the study drugs.

The randomisation scheme for patients will be reviewed and approved by a member of the randomisation office within the Audit Readiness, Validation and Randomisation department.

5.4 Treatment masking

Patients, investigator staff, persons performing the assessments, and data analysts will remain masked to the identity of the treatment from the time of randomisation until database lock, using the following methods: (1) randomisation data are kept strictly confidential until the time of unmasking, and will not be accessible by anyone else involved in the study & (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

Unmasking will only occur in the case of patient emergencies (see Section 5.5.10) and at the completion of the study (see Section 5.5.11).

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3 etc.). The investigator or his/her staff will contact the IRT system and provide the requested identifying information for the patient to register them into the IRT system. For studies using electronic case record forms (eCRFs), only the assigned patient number should be entered in the field labeled “Patient ID” on the electronic data capturing (EDC) data entry screen (e.g. enter ‘1’, ‘2’, etc.). Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomised for any reason, the IRT system must be notified within 2 days that the patient was not randomised. The reason for not being randomised will be entered on the screening log, and the Demography eCRF should be completed.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with study drug. The study drug packaging has a 2-part label. A unique number is printed on each part of this label which corresponds to one of the 2 treatment arms. Investigator staff will identify the study drug package(s) to dispense to

[redacted]

the patient by contacting the IRT system and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (drug label form) for that patient's unique patient number.

All drug kits assigned by the IRT system will be recorded in the IRT database.

5.5.3 Supply, storage and tracking of study drug

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will comply with the legal requirements of each country. They will contain no information about the patient but will carry the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study drug and packaging to the study center at each study visit, at the time of study drug discontinuation or premature subject withdrawal.

At the completion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.4 Instructions for prescribing and taking study drug

The investigator should ensure that the patient clearly understands the dosing instructions outlined below.

- At Visit 2, each patient will be dispensed study drug consisting of 1 bottle of metformin 500mg oral tablets. This is sufficient medication for the run-in period of up to 3 weeks until Visit 3.
- From Visit 3 to Visit 22, each patient will be dispensed the study medication consisting of 3 bottles of vildagliptin 50mg oral tablets (or matching placebo in Period 1) and 3 bottles of metformin 500mg oral tablets. This is sufficient medication for the period of 13 weeks between subsequent visits.

Patients will be instructed to take one tablet of vildagliptin (or matching placebo in Period 1) in the morning and one tablet in the evening with or without food. Metformin should be taken in a bid regimen (depending on the total daily dose) during or after meals at the same time as vildagliptin (or matching placebo). Study drug should be taken the same time throughout the study.

No study drug should be taken on the morning of a study visit. Patients should arrive in the fasting state; i.e. no food or drinks (except water) minimum 8h before the next scheduled visit.

[redacted]

The study medication will be taken after the completion of all study procedures for that visit prior to the first meal of the day (for patients performing a meal-test, see Section 6.4.3). If the patient has not fasted for an adequate period of time, the collection of fasting laboratory evaluations must be rescheduled. The study drug regimen (or, if applicable, rescue medication as defined in Section 5.5.6) should not be taken prior to obtaining the fasting laboratory test samples.

If a dose is missed and the patient realizes this within 3h, the study drugs should be taken otherwise the patient should take the next scheduled dose.

Previously dispensed medication bottles, including any remaining study medication, must be returned to the study center at each study visit.

All prescribed dosages, all study drugs dispensed to the patient and all dose changes during the study must be recorded on the appropriate Study Drug Dosage Administration Record eCRF(s).

During each study visit, the investigator should encourage compliance with study medication by instructing the patient to take the study drug exactly as prescribed to maintain the validity of the study and to optimise any potential effect of the study drug regimen. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug regimen as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study drug

During the first 4 weeks of Period 1, the metformin dose can be adjusted if GI side effects occur (see also Section 3.1.2).

For patients who suffer AEs or untoward events that require temporary dose adjustments, dose adjustments or interruptions are permitted in order to keep the patient on the regimen:

- Study drug regimen adjustments are restricted to a period of maximum of 4 consecutive weeks.
- No more than 3 periods of study drug regimen adjustments are allowed for each individual patient during the whole study after randomisation.
- Patients are allowed to receive rescue medication during this period, as described in Section 5.5.6.

Any study regimen changes must be recorded on the appropriate Dosage Administration Record eCRF(s).

5.5.6 Rescue medication

Use of rescue medication (defined in the Glossary of terms) is not allowed, except for patients who suffer AEs or untoward events that require temporary dose adjustments (see Section 5.5.5). During these temporary dose adjustment periods, patients may receive rescue medication (preferably insulin).

Any rescue medication must be recorded on the Concomitant Medications/Significant Non-Drug Therapies eCRF.

[redacted]

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant Medications/Significant Non-Drug Therapies eCRF.

5.5.8 Prohibited treatment

Use of the following medications is prohibited during the course of this study:

- Treatment with any OAD other than the study drug regimen (see Glossary of terms) as detailed in the study protocol, except rescue medication as described in Section 5.5.6 (e.g. following a permitted dose adjustment as described in Section 5.5.5).
- Long-term (>4 consecutive weeks) oral, parenteral or intra-articular corticosteroid treatment.
- Weight control products including weight-loss medications.
- Treatment with growth hormones or growth hormone analogs.
- Treatment with any drug with a known and frequent toxicity to a major organ or that may interfere with the interpretation of the efficacy and safety data.
- Treatment with an investigational drug other than study drug.

All other prior and concomitant non-study medications (not specifically contra-indicated in the exclusion criteria, see Section 4.2) are allowed.

5.5.9 Discontinuation of study drug and premature subject withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion eCRF.

The investigator can be guided by the following criteria but may discontinue patients from study participation at anytime during the study based on clinical judgment.

Study drug must be discontinued for a given patient and the patient withdrawn from participation in the study if the investigator determines that continuation would result in a significant safety risk for that patient. In addition, the following circumstances require that study drug treatment and patient participation in the study be discontinued:

1. Patient withdrawal of informed consent.
2. The occurrence of an AE or clinically significant laboratory change or abnormality that, in the judgment of the investigator, warrants discontinuation from the study.

[redacted]

3. Occurrence of ketoacidosis or clinically significant ketosis. Patients with evidence of ketoacidosis/ketosis should be discontinued from the study and treated appropriately according to local guidelines.
4. Liver enzyme elevations (see Section 6.5.5 and Table 6-4 for specific actions, reporting and follow-up).
5. Use of prohibited treatment as per Section 5.5.8.
6. Patients in Period 2 requiring treatment intensification according to local guidelines (see Section 3.1.3) who do not initiate insulin treatment in Period 3 (see Section 3.1.4).
7. Any protocol deviation that results in a significant risk to the patient's safety.
8. Patients becoming pregnant during the study (see Section 6.5.8).
9. Occurrence of a contraindication against treatment with metformin or vildagliptin during the study.

The appropriate personnel from the site and Novartis will assess whether study drug treatment should be discontinued for any patient whose treatment was inadvertently unmasked for any reason.

The investigator must contact the IRT system to register the patient's discontinuation from study drug.

Patients who are prematurely withdrawn from study participation will not be replaced by newly enrolled patients.

5.5.10 Emergency unmasking of treatment assignment

Emergency unmasking should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency unmasking is performed using the IRT system. When the investigator contacts the system to unmask the treatment for a patient, he/she must provide the requested patient identifying information and confirm the necessity to unmask the treatment of the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head that a patient's study drug regimen was unmasked.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT system in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study drug name if available, patient number, and instructions for contacting the local Novartis office, or any entity to which it has delegated responsibility for emergency unmasking, to the patient in case emergency unmasking is required at a time when the investigator and backup are unavailable.

5.5.11 Study completion and post-study treatment

The study will be considered completed for an individual patient when he/she completes the 5 years treatment period. The study as a whole will be considered completed when all randomised patients have completed the 5 years treatment period or discontinued the study prematurely.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.12 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing institutional review boards (IRBs) and/or independent ethics committees (IECs) of the early termination of the study.

6 Visit schedule and assessments

Visits are scheduled as indicated in Table 6-1 & Table 6-2. An "X" in Table 6-1 & Table 6-2 indicates which assessments are to be performed during each visit.

Patients who discontinue study drug before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (Visit 23) will be performed. At a minimum, they will be contacted for safety evaluations during the 30 days following the last intake of study drug, including final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documents.

Table 6-1 Assessment schedule (year 1-2)

Visit	1	2	3	4	5	6	7	8	9	10	11
Week	**-5**	**-3**	**BL**	**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**
Assessments											
Screening log (see Section 6.1)	X										
Informed consent	S										
Inclusion/exclusion criteria (see Section 4.1 & Section 4.2)	S	S									
Demography (see Section 6.2)	X										
Medical history/current conditions	X										
Smoking history	X										
History of diabetes & complications	X										
Hepatitis screen (see Section 6.5.4)	X										
TSH (see Section 6.5.4)	X										
Serum pregnancy test (see Section 6.5.8)	X		X								
Physical examination (see Section 6.5.1)	S										
Randomisation			S								
Efficacy											
HbA1c (see Section 6.4.1)	X	X	X	X	X	X	X	X	X	X	X
FPG (see Section 6.4.2)	X	X	X	X	X	X	X	X	X	X	X
Fasting insulin (see Section 6.4.2)			X				X				X
Safety											
Vital signs including height (see Section 6.5.2)	X										
Vital signs (see Section 6.5.2)		X	X	X	X	X	X	X	X	X	X
[redacted]											
ECG (see Section 6.5.7)	X						X				X
Hematology (see Section 6.5.4)	X		X				X				X
Chemistry (see Section 6.5.4)	X		X				X				X
Liver function test (LFT) testing only (see Section 6.5.4)				X	X	X			X		

[redacted]

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week	**-5**	**-3**	**BL**	**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**
Fasting lipid profile & TGs (see Section 6.5.4)	X		X				X				X
Urinalysis (incl. albumin/creatinin ratio, see Section 6.5.4)	X		X				X				X
Urine pregnancy test (see Section 6.5.8)	X		X				X				X
AEs (see Section 7.1)		X	X	X	X	X	X	X	X	X	X
Serious adverse events (SAEs, see Section 7.2)		X	X	X	X	X	X	X	X	X	X
Medication Records											
History of anti-diabetic medication therapy	X										
Dose administration record – vildagliptin			X	X	X	X	X	X	X	X	X
Dose administration record – metformin		X	X	X	X	X	X	X	X	X	X
Dose administration record – insulin						X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Drug dispensing		S	S	S	S	S	S	S	S	S	S
Drug accountability/medication check			S	S	S	S	S	S	S	S	S
Administrative procedures											
Call IRT system	S	S	S	S	S	S	S	S	S	S	S
Dispense glucometer and instructions		S									
Glycaemia study diary review			S	S	S	S	S	S	S	S	S
[redacted]											
Study completion (see Section 5.5.11)											
Sub-studies											
Meal-test (see Section 6.4.3)			X	X			X				X
[redacted]											

S = Source documents only; X = Assessment to be recorded in the eCRF.

[redacted]

Table 6-2 Assessment schedule (year 3-5)

Visit	12	13	14	15	16	17	18	19	20	21	22	23 SDD and/or PSD
Week	**117**	**130**	**143**	**156**	**169**	**182**	**195**	**208**	**221**	**234**	**247**	**260**
Assessments												
Screening log (see Section 6.1)												
Informed consent												
Inclusion/exclusion criteria (see Section 4.1 & Section 4.2)												
Demography (see Section 6.2)												
Medical history/current conditions												
Smoking history												
History of diabetes & complications												
Hepatitis screen (see Section 6.5.4)												
TSH (see Section 6.5.4)												
Serum pregnancy test (see Section 6.5.8)												X
Physical examination (see Section 6.5.1)												S
Randomisation												
Efficacy												
HbA1c (see Section 6.4.1)	X	X	X	X	X	X	X	X	X	X	X	X
FPG (see Section 6.4.2)	X	X	X	X	X	X	X	X	X	X	X	X
Fasting insulin (see Section 6.4.2)				X				X				X
Safety												
Vital signs including height (see Section 6.5.2)												
Vital signs (see Section 6.5.2)	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
ECG (see Section 6.5.7)				X				X				X
Hematology (see Section 6.5.4)				X				X				X
Chemistry (see Section 6.5.4)				X				X				X

[redacted]

Visit	12	13	14	15	16	17	18	19	20	21	22	23 SDD and/or PSD
Week	**117**	**130**	**143**	**156**	**169**	**182**	**195**	**208**	**221**	**234**	**247**	**260**
LFT testing only (see Section 6.5.4)		X				X				X		
Fasting lipid profile & TGs (see Section 6.5.4)				X				X				X
Urinalysis (incl. albumin/creatinin ratio, see Section 6.5.4)				X				X				X
Urine pregnancy test (see Section 6.5.8)				X				X				X
AEs (see Section 7.1)	X	X	X	X	X	X	X	X	X	X	X	X
SAEs (see Section 7.2)	X	X	X	X	X	X	X	X	X	X	X	X
Medication Records												
History of anti-diabetic medication therapy												
Dose administration record – vildagliptin	X	X	X	X	X	X	X	X	X	X	X	X
Dose administration record – metformin	X	X	X	X	X	X	X	X	X	X	X	X
Dose administration record – insulin	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Drug dispensing	S	S	S	S	S	S	S	S	S	S	S	
Drug accountability/medication check	S	S	S	S	S	S	S	S	S	S	S	S
Administrative procedures												
Call IRT system	S	S	S	S	S	S	S	S	S	S	S	S
Dispense glucometer and instructions												
Glycaemia study diary review	S	S	S	S	S	S	S	S	S	S	S	S
[redacted]												
Study completion (see Section 5.5.11)												X
Sub-studies												
Meal-test (see Section 6.4.3)				X				X				X
[redacted]												

SDD = Study Drug Discontinuation; PSD = Premature Subject Discontinuation; S = Source documents only; X = Assessment to be recorded in the eCRF.

[redacted]

6.1 Information to be collected on screening failures

Patients who were screened for participation in the study, but never took study drug nor were randomised into the study (Visit 3) are considered screening failures.

The following information must be recorded on the respective eCRFs for all screening failures: demography (Demography eCRF) and primary reason for why the patient was not randomised (Screened Subject Entering Next Phase eCRF).

Hypoglycemic events occurring between Visit 1 and Visit 3 will only be captured for those patients who are randomised at Visit 3. AE reporting will start at the time of informed consent.

The site must access the IRT system to record screening failures.

6.2 Patient demographics/other BL characteristics

Demography information such as date of birth, sex, race & ethnicity will be collected at visits indicated in Table 6-1. BMI will be calculated from the height measured at BL and [redacted] measured at visits indicated in Table 6-1 & Table 6-2. The detailed medical history will be collected including previous liver and/or bile duct disease (e.g. viral liver infections, fatty liver, steatohepatitis, chronic hepatitis, cirrhosis, gallstones, hepatobiliary surgery, primary biliary cirrhosis, primary sclerosing cholangitis, portal hypertension, etc.).

Smoking history and history of diabetes and complications (date of diabetes diagnosis, whether proliferative retinopathy, non-proliferative retinopathy, nephropathy or neuropathy, prior/concomitant CV conditions (e.g. angina, MI, CHF, cardiac arrhythmia, coronary revascularisation, TIA, stroke, subarachnoid hemorrhage) are present and their respective dates of diagnosis) will be collected at visits indicated in Table 6-1.

Protocol required tests will be analysed by the central laboratory for samples taken at Visit 1 to determine patient eligibility. The ECG will be performed locally.

At Visit 1 prior discontinued and continuing medications must be recorded (e.g. anti-diabetic medication, metformin history, insulin history, anti-hypertension and lipid-lowering medications) on the appropriate eCRFs.

6.3 Treatment exposure and compliance

Compliance with study drug administration will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information must be captured in the source documents. The site will also be required to complete the appropriate Dosage Administration Record eCRF(s) to record any study drug regimen changes or interruptions.

Study drug regimen

Patients must remain on the study drug regimen for the duration of the study. For treatment-naïve patients at BL, no anti-diabetic medication other than the study drug regimen can be used, except according to Section 5.5.6. For patients who had started use of up to 2000mg daily metformin up to 1 month before Visit 1 (see Section 4.1 & Section 4.2), information

[redacted]

regarding the metformin use including the start date of the metformin use & the daily dose prior to entry into the study will be collected on the Anti-diabetic Medication Taken Prior To Entry Into The Study eCRF. The total daily dose of drug administered during the study will be collected on the appropriate Dosage Administration Record eCRF(s).

On-treatment medication

For all medications (other than the study drug regimen) initiated after the start of study, the reason for prescribing the medication, and the start and, where applicable, end dates will be recorded on the Concomitant Medications/Significant Non-Drug Therapies eCRF.

Rescue medication

Information regarding the administration of rescue medication will be recorded on the appropriate eCRF as per Section 5.5.6.

6.4 Efficacy

The following efficacy measurements and assessments will be made at time-points indicated in Table 6-1 & Table 6-2.

Primary

- HbA1c measurements at visits indicated in Table 6-1 & Table 6-2 to determine the *time to confirmed initial treatment failure* (see Section 9.4.1).

Secondary

- HbA1c measurements at visits indicated in Table 6-1 & Table 6-2 to determine the *rate of loss in glycemic control over time* (estimated annualised slope of HbA1c over time using a random coefficient model), from Visit 5 to the end of Period 1 (see Section 9.5.2).
- HbA1c measurements at visits indicated in Table 6-1 & Table 6-2 to determine the rate of loss in glycemic control from 26 weeks after the start of Period 2 to end of Period 2 (see Section 3.1.3).
- FPG measurements at visits indicated in Table 6-1 & Table 6-2 to determine the rate of loss in glycemic control, i) from Visit 5 to the end of Period 1; ii) from 26 weeks after start of Period 2 to end of Period 2 (see Section 3.1.3).
- Descriptive summary of HbA1c measurements at visits indicated in Table 6-1 & Table 6-2.
- C-peptide measurements collected during a meal-test performed at visits indicated in Table 6-1 & Table 6-2 to determine:
  - The change in AUC of ISR/G as an assessment of β-cell function (see Section 6.4.3 & Section 3.1.5) from BL to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.
  - The rate of loss of β-cell function from Visit 4 (week 13) to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.
- Insulin measurements collected during a meal-test performed at visits indicated in Table 6-1 & Table 6-2 to determine:

[redacted]

- OGIS as an assessment of change in insulin sensitivity (see Section 3.1.5 & Section 6.4.3) from BL to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.
- Rate of change in insulin sensitivity from Visit 4 (week 13) to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.

6.4.1 HbA1c

HbA1c will be measured on a blood sample obtained at visits indicated in Table 6-1 & Table 6-2 and analysed at a central laboratory.

6.4.2 FPG and indices of β-cell function and insulin resistance

Samples for FPG and fasting insulin will be collected at visits indicated in Table 6-1 & Table 6-2.

6.4.3 Meal-test

A standard breakfast meal-test will be performed at visits indicated in Table 6-1 & Table 6-2 in a subgroup of patients (see Section 3.1.5 & Section 4). Blood samples will be collected at -20min, 0min (start of the meal test), 15min, 30min, 60min, 90min & 120min. Plasma glucose, insulin and C-peptide will be determined in these samples. Indices of β-cell function and insulin sensitivity will be calculated as defined in Section 2.2.

The standard breakfast (500kcal; 60% carbohydrate, 30% fat and 10% protein (Pratley et al, 2008)) may consist of the following:

- 180mL orange juice (grapefruit juice is not allowed).
- 2 slices (60g) bread; white, wheat or rye, plain or toasted.
- 2 tablespoons (30g) jam or preserves.
- 1 tablespoon (15g) butter (regular or salted) or margarine.
- 120mL whole milk (3-4% fat) or equivalent amount of cheese plus 120mL water.

- Decaffeinated coffee or tea if desired.

Samples will be analysed by a central laboratory. Laboratory manuals will be provided to participating sites with detailed information on sample collection, handling, and shipment.

At BL, the study drugs will be administered to the patient after the meal-test. For the subsequent tests (see Table 6-1 and Table 6-2) the study drugs will be administered 15min before the start of the meal.

6.4.4 Appropriateness of efficacy assessments

The efficacy variables selected are standard for a clinical study evaluating the long-term effect of different treatments on the durability of glycemic control in patients with T2DM.

6.5 Safety

- Physical examination.
- Vital signs.
- [redacted]
- Monitoring of hematology, blood chemistry and urine tests.
- LFT.
- ECG.
- Pregnancy (see Section 6.5.8 & Section 7.3).
- Incidence of hypoglycemia events.
- All treatment emergent AEs/SAEs (see Section 7).
- [redacted]

The endpoints for the safety objective include treatment emergent AEs (including hypoglycemia events), SAEs, laboratory test results and vital signs.

Incidence of confirmed hypoglycemic events, of all symptomatic episodes and of severe hypoglycemia (defined as an event requiring assistance from another person and associated with either self-monitoring blood glucose ≤3.1mM (≤ 56mg/dL), see Table 6-5).

6.5.1 Physical examination

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions eCRF (see also Section 6.2). Significant findings made after the start of study drug which meet the definition of an AE must be recorded on the AE eCRF.

[redacted]

6.5.2 Vital signs

Vital signs include blood pressure and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Clinically notable vital signs are defined in Appendix 1.

[redacted]

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Laboratory evaluations are listed in Table 6-3.

Hematology

Hematology as listed in Table 6-3 will be analysed at visits indicated in Table 6-1 & Table 6-2.

Clinical chemistry (standard)

Clinical chemistry (standard) as listed in Table 6-3 will be analysed at visits indicated in Table 6-1 & Table 6-2.

Clinical chemistry (LFTs only)

Clinical chemistry (LFTs only) as listed in Table 6-3 will be analysed at visits indicated in Table 6-1 & Table 6-2.

Urinalysis

Urine will be analysed as listed in Table 6-3 at visits indicated in Table 6-1 & Table 6-2. The urine albumin/creatinine ratio will be assessed at visits indicated in Table 6-1 & Table 6-2. Urine will also be used to assess pregnancy (see Section 6.5.8).

Fasting lipid profile & TGs

Fasting lipid profile and TGs will be measured at visits indicated in Table 6-1 & Table 6-2. TGs, total cholesterol, HDL and LDL cholesterol will be measured. VLDL and non-HDL cholesterol will be calculated. LDL cholesterol will be calculated if TGs ≤400mg/dL (4.52mM). If TGs >400mg/dL (4.52mM), then direct LDL cholesterol measurement will be done.

[redacted]

Other measurements

TSH will be measured at visits indicated in Table 6-1.

Hepatitis screen (including hepatitis B test, surface antigen HBsAg, hepatitis C test, HCV antibodies) will be measured at visits indicated in Table 6-1, and will be repeated in the event of an elevated LFT test result according to Table 6-4.

Table 6-3 Laboratory evaluations

Category	Parameter
Hematology with differential	RBC (total), WBC (total), platelet count (direct), hemoglobin, hematocrit, basophils (absolute, %), eosinophils (absolute, %), lymphocytes (absolute, %), monocytes (absolute, %), neutrophils (absolute, %)
Chemistry (standard)	ALT, albumin, alkaline phosphatase, AST, bilirubin (direct), bilirubin (total), blood urea nitrogen, calcium (total), chloride, high-sensitivity c-reactive protein (hsCRP), phosphocreatine kinase (CPK), CK-MB if CPK elevated, creatinine, γ-glutamyl transferase (γ-GT), GFR via MDRD formula, lactate dehydrogenase, potassium, protein (total), sodium, uric acid, c-peptide
Chemistry (LFT only)	ALT, AST, bilirubin (direct), bilirubin (total), alkaline phosphatase
Chemistry (fasting lipid profile & TGs)	TG, total cholesterol, HDL, LDL, VLDL (calculated), non-HDL cholesterol (calculated), LDL (calculated if TGs ≤400mg/dL (4.52mM) or directly measured if TGs >400mg/dL (4.52 mM))
Chemistry (hepatitis screen)	HBsAg, hepatitis C antibody, HCV antibodies
Chemistry (TSH)	TSH
Chemistry (serum pregnancy)	β-hCG
Urinalysis	blood, glucose, ketones, leukocytes, pH, protein, pregnancy (β-hCG), urine albumin/creatinine ratio

6.5.5 Abnormal LFTs

Elevations of AST and/or ALT ≥3 x ULN, with or without elevations of bilirubin, are considered clinically significant. Sources of liver injury/toxicity should be sought before ascribing the cause of the elevation to the study drug.

Table 6-4 Guidance for abnormal liver enzymes and related tests

Category	Definition	Action
Clinical symptoms	Icterus. Any SAE indicative of hepatitis, liver failure or its complications.	Immediately discontinue patient. Ensure appropriate specialist assessment & care. Report as an SAE within 24h to Novartis. Establish diagnosis/causality.
ALT or AST	≥ 3x ULN + total bilirubin > 2x ULN.	Immediately discontinue study drug and retest, if confirmed then discontinue the patient. Ensure appropriate specialist assessment & care. Report as an SAE within 24h to Novartis. Establish diagnosis/causality.
	Asymptomatic, isolated	Ensure appropriate assessment and care.

[redacted]

Category	Definition	Action
	elevation ≥ 3 to < 5x ULN.	Repeat LFT on weekly basis. If LFT elevation ≥3 to <5 x ULN persists >4 weeks, discontinue the patient, and report as an AE on the eCRF.
	Asymptomatic, isolated elevation ≥ 5 to < 8x ULN.	Ensure appropriate specialist assessment & care. If LFT elevation persists (repeat at 3 days), discontinue the patient. Report as an AE on the eCRF. Establish diagnosis/causality.
	Asymptomatic, isolated elevation ≥ 8x ULN.	Immediately discontinue study drug and retest. If confirmed, then discontinue the patient. Ensure appropriate specialist assessment & care. Report as an SAE within 24h to Novartis. Establish diagnosis/causality.
Total bilirubin	Asymptomatic, isolated elevation ≥ 3 x ULN.	Ensure appropriate specialist assessment and care. Report as an AE on the eCRF. If elevation persists >2 weeks, discontinue the patient. Establish diagnosis/causality.

Whenever possible, every attempt should be made to identify and treat the underlying cause(s). Additional medical history should be sought for recent events:

- Alcoholic history: specific query, quantified by drink per day/week/month, recent celebration or binges.
- Over the counter medication, herbal agents or alternative medical therapies, illicit drug use, e.g. cocaine, methamphetamine, etc.
- New symptoms that suggest viral infection or autoimmune events.
- Other active medical conditions, with special mention of heart failure, palpitation, syncope or episode of hypotension, sepsis or parenteral nutrition.
- Symptoms at the time of onset, specifically mentioning rash, fever, abdominal pain, fatigue and itching. Search for alternative medical causes such as cholelithiasis and ascending cholangitis, history of intercurrent illness (e.g. viral syndrome), hepatitis, or potential exposure to viral hepatitis (e.g. transfusion).
- Potential exposure to environmental or chemical hepatotoxins (e.g., carbon tetrachloride, benzene) should also be assessed.
- Drug-related causes of hepatitis should be considered (e.g. acetaminophen, amiodarone, aspirin, chlorpromazine, dantrolene, erythromycin, halothane, isoniazid, methyldopa, nitrofurantoin, oxyphenisatin, perhexiline maleate, phenytoin, propylthiouracil, rifampin, sulfonamides, tetracyclines).

At any time during the study if any of the criteria in Table 6-4 are met, repeat the test, then complete the specified action. Refer to Appendix 2, Panel A, and perform laboratory tests and

[redacted]

abdominal ultrasound as recommended. Additional investigations after the assessment by specialist might include tests described in Appendix 2, Panel B.

In all cases, maintain progress reports of the event until resolution or stabilisation occurs. Any laboratory findings must be documented in the AE eCRF.

6.5.6 Hypoglycemic events

At Visit 1, patient education regarding hypoglycemic symptoms and treatment should occur. This education should include general review of hypoglycemia:

- Explanation of possible triggers of hypoglycemia (e.g., strenuous exercise, delayed meals, changes in meal composition, illness, Ramadan-period, etc.).
- Identification of the symptoms of hypoglycemia (e.g., adrenergic symptoms such as tachycardia, palpitations, shakiness, cholinergic symptoms such as sweating, central symptoms such as dizziness, hunger, blurred vision, impairment of motor function, confusion or inappropriate behavior).
- Review of appropriate treatment for events (oral glucose intake).

At Visit 2 (or Visit 3 for patients who proceed directly to Visit 3 after Visit 1 according to Section 3.1.1), the home glucose monitor and glycaemia study diary should be given to the patient and the hypoglycemic information discussed at Visit 1 should be reviewed:

- The use of a home glucose monitor must be explained. A home glucose monitor will be provided with all appropriate supplies. Blood glucose should be measured each time the patient experiences symptoms which may be suggestive of hypoglycemia, as well as other time points which may be recommended by the investigator.
- Review of the glycemia study diary. Any time the patient experiences symptoms which he/she suspects are related to hypoglycemia, the patient should be instructed to take a blood glucose measurement and treat the event as appropriate. Patients should record the event in the study diary, including:
  - The glucose value.
  - Any relevant associated information.
  - Time of occurrence in relation to the last medication and to the last meal intake.
  - The treatment used.
  - The response to the treatment used.
  - Additionally, if a patient performs routine measurements of blood glucose, any asymptomatic plasma glucose < 56mg/dL (< 3.1mM) - corresponding to a whole blood glucose level < 50mg/dL or < 2.8mM - should be treated and recorded in the glycemia study diary.
- The patient should return the study diary at the next scheduled visit.

Data entry

The glycemia study diary will be reviewed by the study staff at each visit and assessed according to Table 6-5.

[redacted]

Table 6-5 Recording and classification of glycemia study diary data

Severity	Symptoms	Plasma glucose	Action taken	Classification
Patient able to initiate self-treatment if necessary	Symptoms suggestive of hypoglycemia	< 3.1mM (56mg/dL)	Enter in Glycemia Study Diary eCRF	Hypoglycemic event, grade 1
	Symptoms suggestive of hypoglycemia	≥ 3.1mM (56mg/dL)	Enter in Glycemia Study Diary eCRF	AE
	Symptoms suggestive of hypoglycemia	Not taken	Enter in Glycemia Study Diary eCRF	AE
	Asymptomatic	< 3.1mM (56mg/dL)	Enter in Glycemia Study Diary eCRF	Asymptomatic low blood glucose
Patient is unable to initiate self-treatment and requires assistance of another person or hospitalisation	Symptoms suggestive of hypoglycemia	< 3.1mM (56mg/dL)	Enter in Glycemia Study Diary eCRF & report as SAE	Hypoglycemic event, grade 2 & SAE
	Symptoms suggestive of hypoglycemia	Not taken	Enter in Glycemia Study Diary eCRF & report as SAE	Suspected hypoglycemic event, grade 2 & SAE

6.5.7 ECG

Standard 12-lead ECGs will be performed at visits indicated in Table 6-1 & Table 6-2. They will be analysed locally and interpretation of the tracing must be made by a qualified physician and documented on the 12-lead ECG Evaluation eCRF. Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Only clinically significant abnormalities should be reported on the 12-Lead ECG Evaluation eCRF. Clinically significant abnormalities should also be recorded on the Relevant Medical History/Current Medical Conditions eCRF.

6.5.8 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have urine pregnancy tests (see Section 6.5.4). A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the study (see Section 5.5.9).

Pregnancy will also be tested on a serum sample at visits indicated in Table 6-1 & Table 6-2.

6.5.9 Appropriateness of safety measurements

The safety measurements are standard for this type of study.

[redacted]

6.6 Other assessments

[redacted]

6.6.2 Resource utilisation

Not applicable.

[redacted]

6.6.4 Pharmacokinetics (PK)

Not applicable.

6.6.5 Pharmacogenetics/pharmacogenomics

Not applicable.

[redacted]

[redacted]

7 Safety monitoring

7.1 AEs

An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after informed consent even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All AEs must be recorded on the AE CRF with the following information:

1. The severity grade [mild, moderate, severe].
2. Relationship to the study drug(s) (suspected/not suspected).
3. Duration (start and end dates or if continuing at final visit).
4. Whether it constitutes an SAE.

An SAE is defined as an event which:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, unless hospitalisation is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 7.2.

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only), study drug dosage adjusted/temporarily interrupted, study drug permanently discontinued due to this AE, concomitant medication given, non-drug therapy given, patient hospitalised/patient's hospitalisation prolonged. The action taken to treat the AE should be recorded on the AE eCRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of investigator notifications (INs). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.2 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24h of learning of its occurrence.

Any SAEs experienced after this 30-day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be

[redacted]

submitted within 24h of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE report form. The investigator must assess the relationship of any SAE to study drug, complete the SAE report form in English, and send the completed, signed form by fax within 24h to the local Novartis drug safety & epidemiology (DS&E) department. The telephone and telefax number of the contact persons in the local DS&E department, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE report form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE report form was sent, using a new SAE report form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the treatment was unmasked or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the IB or package insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with European community directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24h of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a “clinical study pregnancy form” and reported by the investigator to the local Novartis DS&E department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE report form.

7.4 Data monitoring committee

An independent data monitoring committee (DMC) is overseeing this study. This committee, comprised of external experts in diabetes, cardiology and statistics, reviews the safety experience for this study at regular intervals.

[redacted]

7.5 Adjudication committees

Program wide selected clinical events will be reviewed by independent adjudication committees. This measure is designed to ensure the objectivity, reliability and validity of the event classification. Details of the committee and procedures for reporting and case definitions are detailed in a separate document (adjudication charter).

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to good clinical practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. The identity of the subjects will remain confidential.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRFs using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate data queries, allow the data to be confirmed or corrected before transfer of the data to the contract research organisation (CRO) working on behalf of Novartis. The investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive the patient data in an appropriate form for archiving at the investigational site.

8.3 Database management and quality control

Novartis or CRO staff working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Obvious errors are corrected by Novartis personnel (or a CRO working on behalf of Novartis). Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper data query form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff (or CRO staff working on behalf of Novartis) who will make the correction to the database. The signed copy of the data query form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the World Health Organisation Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system (ATC). Medical history/current medical conditions and AEs will be coded using the medical dictionary for regulatory activities terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomisation codes and data about all study drug dispensed to the patient and all IRT recorded dosage changes will be tracked using an IRT system. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of an unmasking via IRT will be reported to the clinical team and the monitor. The unmasking functionality will remain available until completion or upon request of Novartis.

9 Data analysis

9.1 Analysis sets

The following analysis data sets will be defined for this study.

Screened-only (SCR) set: consists of all patients who were screen failed after the first visit or who entered the run-in phase but were not randomised. Except for the tabulation and listing of individual patients in this SCR set with the reasons for not being randomised, no other analysis will be performed in this analysis set.

Randomised (RAN) set: consists of all randomised patients.

Full-analysis set (FAS): consists of all randomised patients who received at least one dose of study medication and had at least one post-randomization assessment of any efficacy parameter. Following the intent-to-treat principle, subjects will be analysed according to the treatment they were assigned to at randomization.

Safety (SAF) set: consists of all patients who received at least one dose of study medication. Patients will be analysed according to the treatment received.

The Per-protocol set (PPS) is a subset of the FAS. It consists of all randomised patients in the FAS patients who take at least one dose of study medication and have no major protocol deviations affecting the primary endpoint analyses.

The major protocol deviations leading to exclusion from the PPS will be specified prior to unbinding the database with respect to treatment.

9.2 Patient demographics and other BL characteristics

Demographic, background data and key efficacy variables at BL will be summarised for all randomised patients (RAN set) by treatment group that patients were assigned to at randomization using frequency and percentage for qualitative variables (gender, race, ethnicity, age group, smoker status, BMI group, and BL HbA1c group, groupings as for the subgroups described in Section 9.4.4), and mean, standard deviation, median, minimum and maximum for quantitative variables (age, height, weight, BMI, duration of T2DM, BL HbA1c and FPG).

BMI will be calculated from the collected variables height (in m) and weight (in kg) at Visit 1. BL HbA1c and FPG are the values obtained at randomization (Visit 3) or at an earlier visit (scheduled or unscheduled) which was closest to Day 1 (visit 3) if Day 1 values are missing.

BL comparability among the treatment groups will be examined using a χ^2 test for the qualitative variables, and using a two-sample t-test for the quantitative variables (these p-values are provided for descriptive purposes, and are not to be considered to define any formal basis for determining factors which should be included in statistical analysis model).

In addition, all relevant medical history and history of diabetes and complications will be summarised by primary system organ class (SOC), preferred term and treatment using frequency tables.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

The duration on the study medication (in weeks) during the overall randomised treatment period will be computed for all patients using the following algorithm:

(last study drug date – Visit 3 date)/7 or

(last study visit date – Visit 3 date + 1)/7 if the last study drug date is missing or incomplete.

Duration will be set to 0 for patients who did not take any study drug.

The above defined duration will be summarised according to the treatment patients are assigned to at randomization for the RAN set both descriptively (i.e., mean, standard deviation, median, minimum and maximum) and by duration category (≥0 and <13 weeks, ≥13 and <26 weeks..., in 13-week intervals cumulatively up to ≥260 weeks).

The study Period 1 duration (in weeks) will be also similarly summarised in the RAN set. The study Period 1 duration is defined as (initiation date of new study vildagliptin packs due to treatment failure – visit 3 date)/7 for patients who entered study Period 2. The study Period 1 duration is the same as overall study duration for patients who did not enter into Period 2.

[redacted]

The study period from randomization to the end of Period 2 will be computed for all patients who initiate insulin in Period 3 and for patients discontinuing the study in Period 2 due to being unable or unwillingness to initiate insulin for treatment intensification in Period 3.

Prior and concomitant therapies taken during the randomised double-blind period will be summarised by ATC class and preferred term according to the treatment patients are assigned to at randomization in the RAN set.

9.4 Analysis of the primary variable(s)

9.4.1 Variable

The primary efficacy variable is time to confirmed initial treatment failure. The confirmed initial treatment failure is defined as a patient with HbA1c measurements ≥7.0% at two consecutive scheduled visits as defined in Table 6-1 & Table 6-2, starting from Visit 4 (Week 13). The time to confirmed initial treatment failure is defined as the time from randomization until the time when the second of the two HbA1c measurement ≥7.0% was determined after at least 13 weeks of treatment (Visit 4). The rationale of starting the treatment failures count from Visit 4 is that treatment guidelines consider as treatment failure patients who do not achieve HbA1c <7.0% after 3 months of treatment (ADA-EASD, 2009).

9.4.2 Statistical model, hypothesis, and method of analysis

Time to initial treatment failure

The primary statistical hypothesis of time to confirmed initial treatment failure will be assessed by a 1-sided test of superiority of the combination treatment with vildagliptin + metformin versus metformin monotherapy with α-level of 0.025 of the hazard-ratio between the combination treatment vildagliptin + metformin and metformin monotherapy being equal or greater than 1 as the null hypothesis, versus the 1-sided alternative hypothesis that the hazard-ratio is less than 1:

$H_{01}: \lambda_{vildagliptin+metformin}/\lambda_{metformin} \geq 1$

versus

$H_{a1}: \lambda_{vildagliptin+metformin}/\lambda_{metformin} < 1$

where $\lambda_{vildagliptin+metformin}$ and $\lambda_{metformin}$ are the hazard-rates of the confirmed initial treatment failure for vildagliptin 50mg bid + metformin up to 1000mg bid and metformin up to 1000mg bid monotherapy respectively.

The time to confirmed failure will be derived as the time from randomization to the second of two consecutive visits at which HbA1c ≥7.0% is measured, starting from Visit 4 (13 weeks after randomization).

The primary efficacy analysis will use a Cox proportional hazard regression model to assess the probability of confirmed initial treatment failure, with treatment as classification variable and BL HbA1c as a covariate. The hazard-ratio and associated 95% confidence interval as well as the p-value estimated from the above model will be presented by treatment.

[redacted]

The confirmed initial treatment failure rate over time by treatment will be summarised and plotted with associated 95% confidence intervals, using estimates from a Kaplan-Meier analysis.

The primary analysis for this primary efficacy variable will be performed using the FAS. It will be performed in the PP set as supportive analysis as well.

9.4.3 Handling of missing values/censoring/discontinuations

In the analysis for the primary efficacy variable of time to confirmed initial treatment failure, patients who discontinue the study for any reason during Period 1 (lack of efficacy, lost to follow-up, AE or abnormal laboratory values etc.) will be treated as censored values at the time of discontinuation. Patients who remain under the threshold (or whose measurement above the threshold is not confirmed at next scheduled visit) will be censored at the time of last study visit.

9.4.4 Supportive analyses

Time to first treatment failure

The time to first treatment failure will be derived as the time from randomization to the first of two consecutive scheduled visits (after remapping in section 1.3.3 has been applied), at which HbA1c $\geq$7.0% is measured, starting from Visit 4 (13 weeks after randomization).

Time to first treatment failure will be analyzed in the similar way as primary analysis.

Descriptive analysis in HbA1c over time

Summaries of absolute values and change from BL to end of Period 1 in HbA1c by treatment group and visit will be presented in the FAS. Figures will be produced showing the mean HbA1c by visit during the study Period 1 for each treatment group.

In addition, the above descriptive analysis (including summary table and figure) will be performed on HbA1c data collected up to the end of Period 2, as well as data collected during the entire duration of the study.

Descriptive subgroup analysis

Summaries of absolute values and changes from BL to end of Period 1 in HbA1c will be presented for the following subgroups in the FAS:

1. BL HbA1c category (<7% vs. $\geq$7%).
2. BMI (<30kg/m^2, $\geq$30kg/m^2 at Visit 1).
3. Age at Visit 1 by tertiles.
4. Gender.
5. Race.
6. Smoking status.
7. Geographical regions.

[redacted]

[redacted]

9. Other baseline demographic subgroups may be added as appropriate.

9.5 Analysis of secondary variables

9.5.1 Key secondary variables

Not applicable.

9.5.2 Other efficacy secondary [redacted] variables

9.5.2.1 Secondary [redacted] efficacy variables

The following secondary [redacted] efficacy variables will be analysed. They were grouped by type of analyses for the convenience of describing the related analysis methods.

[redacted]

Variables related to the rate of change of β-cell function and insulin sensitivity

- Rate of loss of β-cell function (assessed using the AUC of ISR/G) from Visit 4 (week 13) to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.
- Rate of change in insulin sensitivity (assessed using the OGIS) from Visit 4 (week 13) to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.

Variables related to the rate of loss in glycemic control over time

- Rate of loss in glycemic control in HbA1c from 26 weeks after the start of Period 2 to end of Period 2 (see Section 3.1.3).
- Rate of loss in glycemic control in FPG, i) from Visit 5 to the end of Period 1; ii) from 26 weeks after start of Period 2 to end of Period 2 (see Section 3.1.3).

Variables related to change from BL to endpoint

- Change in AUC of ISR/G (as an assessment of β-cell function) from BL to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.
- Change in OGIS (as an assessment of insulin sensitivity) from BL to: i) initial treatment failure; ii) end of Period 2 (see Section 3.1.3); iii) EOS.

[redacted]

[redacted]

[redacted]

9.5.2.2 Statistical analysis methods

Rate of loss in glycemic control over time

The rate of loss in glycemic control over time will be estimated by the slope of HbA1c over time (in years) as a random coefficient in a linear mixed effect model: the model will be fitted to HbA1c data collected from Week 26 and onwards, up to and including the end of the Period 1 visit, i.e. up to and including the initial treatment failure date. It includes treatment approach, geographic region, baseline HbA1c, time (of HbA1c measurements, in years) and the interaction of treatment approach by time as the fixed effects, and time and intercept as a random effects. Treatment approach and geographic region will be considered as classification variables while baseline HbA1c and time are the covariates. The unstructured covariance will be used as the covariance structure within patients. The actual hypothesis will be tested using the treatment approach by time interaction term. Note that it is not an issue that patients who 'fail' at Week 26 will only contribute one data point to the analysis, as this is expected in only a few patients.

The mean slopes within each treatment approach and the difference in mean slopes between two treatment approaches as well as the p-value obtained from the test using the above model will be presented. Graphical representation will also be produced as required.

The analysis will be performed using the FAS. It will be performed in the PPS as supportive analysis as well.

The assumptions for inference using the model as described above (i.e., errors are independently normally distributed with constant variance) will be checked using CSR Section 16 table(s) by subjective examination of the presented residual plots: normal probability plot and residuals versus fitted values plots.

[redacted]

[redacted]

Variables related to the rate of loss in glycemic control over time

The rate of loss in glycemic control in FPG from 26 weeks to the end of Period 1 will be assessed using the same random coefficient linear mixed effect model as used in the analysis of 'rate of loss in glycemic control in HbA1c from Visit 5 (Week 26) to the end of Period 1'. This analysis is performed in the FAS only.

The rate of loss in glycemic control in HbA1c or FPG from 26 weeks after the start of Period 2 to the end of Period 2 (see Section 3.1.3) will be assessed for patients who start insulin therapy in Period 3 (i.e. for treatment intensification) or discontinue the study during Period 2 due to not being able or unwillingness to initiate insulin therapy in Period 3. The random coefficient linear mixed effect model used in the analysis of 'rate of loss in glycemic control in HbA1c from Visit 5 (Week 26) to the end of Period 1' will be used in this secondary variable. Only data collected between initiation of Period 2 to insulin initiation on patients who take insulin therapy in Period 3 (i.e. for treatment intensification) or who discontinued the study in Period 2 due to not being able or unwillingness to initiate insulin therapy in Period 3 will be included in this model. The analysis will be performed in the FAS only.

Variables related to the rate of change of β-cell function and insulin sensitivity over time

The rate of change of β-cell function and insulin sensitivity (assessed using the AUC of ISR/G and OGIS respectively) from Visit 4 (week 13) to the end of Period 1, or from Visit 4 (week 13) to the end of Period 2, or from Visit 4 (week 13) to the end of study will be assessed using a similar random coefficient linear mixed effect model used in the analysis of 'rate of loss in glycemic control in HbA1c from Visit 5 (Week 26) to the end of Period 1'. This analysis is performed in the FAS only. Data collected up to the end of Period 1, or the end of Period 2, or to the end of the study will be used in the analysis for assessing the rate of change from baseline to end of Period 1, or from baseline to end of Period 2, or from baseline to the end of the study respectively.

Note that the above analyses will be performed only when sufficient patient's data warrant such analyses.

Variables related to change from BL to endpoint

An analysis of covariance (ANCOVA) model with treatment, geographic region as classification variables and BL value as a covariate will be used to assess all secondary efficacy variables related to change from BL to endpoint. The least squares mean ("adjusted mean") change from BL for each treatment group, the difference in the least squares mean changes between the two treatment groups, and the two-sided adjusted 95% confidence interval along with the p-value for the difference will be obtained from this analysis model and presented.

The endpoint is defined differently for these secondary endpoints as follows.

- For change in AUC of ISR/G, OGIS, [redacted] from BL to EOS, the endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled) up to final

[redacted]

scheduled study visit (Visit 23, Week 260). [redacted]

- For change in AUC of ISR/G, OGIS, [redacted] from BL to end of Period 2 (see Section 3.1.3), the endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to or at the initiation of insulin therapy, up to final scheduled study visit (Visit 23, Week 260).
- For change in AUC of ISR/G, OGIS, [redacted] from BL to initial treatment failure, the endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to or at the start of additional new vildagliptin medication package use due to initial treatment failure, up to final scheduled study visit (Visit 23, Week 260).

Note that for meal-test related parameters (AUC of ISR/G and OGIS), the above analyses will be performed only when sufficient patient's data warrant such analyses.

Supportive descriptive analysis for secondary [redacted] variables over time

Summaries of absolute values and change from BL to end of Period 1 in secondary or exploratory variables (including FPG, [redacted], AUC of ISR/G, OGIS, [redacted]) by treatment group and visit will be presented in the FAS.

9.5.2.3 Derivation of secondary [redacted] variables

[redacted]

- OGIS = p_4 [($p_1 D_0$ –V(G(120)-G(90))/30)/G(90) + p_3/G(0)] / [I(90)-I(0)+p_2], where D_0 (g/m^2) is the glucose dose included in the standard meal administered to patients who participate in the standard meal-test (D_0 =73.2 g/m^2 for the standard meal as planned in Section 6.4.3), V =10 (ml/m^2) is the assumed glucose distribution volume, G(0), G(90) and G(120) are glucose concentration values at oGTT timepoints 0, 90 and 120 min, I(0) and I(90) are insulin concentration values at timepoints 0 and 90 min, p_1 = 6.5, p_2 = 1951, p_3 =4514 and p_4 =792 are constants (Mari, et al 2001).

AUC of ISR/G is defined as ISR relative to glucose 0-2h (pmol/min/m^2/mM) = $AUC_{0\text{-}2hr}$ of ISR/$AUC_{0\text{-}2hr}$ of glucose.

Calculation of ISR

Separately for each patient and each meal challenge, deconvolution is applied to estimating insulin secretion to assess β-cell function. C-peptide, which is co-secreted with insulin in an equimolar ratio, is preferred to insulin as a basis for estimating insulin secretion. Mathematically, we need to solve for the insulin secretion rate *r* given the impulse response *h*, and plasma C-peptide *c*, where

[redacted]

$$c(t) = \int_{-\infty}^{t} h(t-s)r(s)ds.$$

The impulse response is the PK model for an intravenously administered unit bolus dose of C-peptide when the endogenous C-peptide production has been suppressed, i.e.

$$h(t-s) = (1/V)[fe^{-\alpha(t-s)} + (1-f)e^{-\beta(t-s)}],$$

where V, f, α, and β are a subject's parameters, which are generally unknown. However, from clinical studies these parameters have been estimated, and are related to a subject's disease status, body surface area, age, and gender. Thus, h becomes known.

Insulin secretion rates are modeled by a piecewise continuous linear function with knots at the actual sampling time. Changes in slopes are penalised through a single regularisation parameter that is determined by a root finding method to produce similar residual standard deviation for fitted C-peptide concentrations as would be expected from assay error standard deviations given in the kit instructions.

The IMMULITE 2000 C-peptide kit instructions were used to model intra-assay SD as a function of the true C-peptide concentration $C1$ expressed in conventional units of ng/mL by simple linear regression as:

SD = 0.04056$C1$ + 0.06311ng/mL.

With concentration of C-peptide expressed alternatively in SI units, i.e., $C2$ expressed in nM (1ng/mL C-peptide = 0.331nM C-peptide) the equations for SD becomes:

SD = 0.04056 $C2$ + 0.331 × 0.06311nM.

The following ln-transformation with a shift parameter of observed and fitted C-peptide values is used to stabilize the variance in performing the deconvolution:

ln($C1$ + 0.06311/0.04056) or ln($C2$ + 0.331 × 0.06311/0.04056).

Nonlinear least squares with ISR constrained non-negative using PROC IML function NLPLM in SAS® is used to solve for ISR at the sampling time points using actual sampling times. The bisection method is used to iteratively determine the regularisation parameter such that the sum of squares of the observed C-peptide minus the fitted C-peptide expressed in either units equals 0.040562n where n is the number of non-missing C-peptide concentrations in the meal challenge.

Calculation of AUC

For the patients participating in the meal-test, glucose, insulin and C-peptide are also to be measured at the following 7 time-points (minutes in relation to the meal time): -20min, 0min (immediately prior to meal ingestion), 15min, 30min, 60min, 90min, 120min. Let L_1, L_2, …., L_7 denote the lab measurements at these 7 time-points (i.e., L_1 is the value measured at 20min pre-meal, L_2 is the value measured at 0min pre-meal, …, L_7 is the value which should be measured about 2h after the meal) and T_1, T_2, .., T_7 be the corresponding times (actual times in units of h), the $AUC_{0\text{-}2hr}$ is calculated (using the trapezoidal rule) as:

$AUC_{0\text{-}2h}$ =

[redacted]

$[(L_2 + L_3) \times (T_3 - T_2) + (L_3 + L_4) \times (T_4 - T_3) + (L_4 + L_5) \times (T_5 - T_4) + (L_5 + L_6) \times (T_6 - T_5) + (L_6 + L_7) \times (T_7 - T_6)] / 2$.

9.5.3 Safety variables

The safety and tolerability of vildagliptin 50mg bid as add-on to metformin over 5-years of treatment will be compared to placebo as add-on to metformin based on data collected during the randomised treatment period in SAF set.

The assessment of safety will be based mainly on the frequency of treatment emergent AEs (including overall AEs), SAEs, death, AEs leading to study discontinuation or study drug interruption & pre-specified AE risks on the number of post BL laboratory values that fall outside of pre-determined ranges and on the frequency and severity of hypoglycemic events during the randomised treatment period. Summaries for safety assessment will be presented for the SAF set. Unless specified otherwise, comparison will be made to BL, which will be the measurement taken at Visit 3, or the sample obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1 if Day 1 measurement is missing.

AEs will be summarised by presenting, for each treatment group (vildagliptin 50mg bid + metformin, placebo + metformin), the number and percentage of patients having any AE, having an AE in each primary SOC and having each individual AE. Any other information collected (e.g. severity or relatedness to study medication) will be presented as appropriate.

Laboratory data will be summarised by presenting summary statistics of raw data and change from BL values (means, medians, standard deviations, ranges) and by presenting the number and percentage of patients having notable lab values or having endpoint change from BL meeting pre-specified percent change criteria. The identification of notable values will be based on the pre-specified criteria provided in the investigator binder (will also be included in the analysis plan). The predefined categories of liver enzyme (ALT/AST) and CPK elevations and persistent elevations will be summarised by treatment.

Hypoglycemia events will be included in all AE summaries. In addition, events will be characterised by event profile, such as ability to self-treat, self monitoring of plasma glucose level, precipitating event, time from last meal, time from last dose, and time of the day.

[redacted]

Data from other tests (e.g. vital signs including [redacted], ECGs) will be summarised as appropriate, incidences of notable values will be presented in the tables and notable values will be flagged in the listings.

All above safety analyses will be performed in the SAF on all available data collected during the entire study. In addition, key safety analyses will be performed on data obtained during Period 1 only.

[redacted]

9.5.4 Resource utilisation

Not applicable.

[redacted]

9.5.6 PK

Not applicable.

9.5.7 Pharmacogenetics/pharmacogenomics

Not applicable.

[redacted]

9.5.9 PK/pharmacodynamics

Not applicable.

9.6 Sample size calculation

A total sample size of 1000 randomised patients per treatment arm (in 1:1 allocation ratio to vildagliptin + metformin and metformin monotherapy) is planned.

Power calculation for the time-to-treatment failure variable

The sample size calculation assumes that all randomised patients are to be followed up for 5 years unless patients dropped out from the study for various reasons (lack of efficacy, AEs,

[redacted]

abnormal labs, lost to follow-up etc.), and that the yearly dropout rate is 11% (estimate based on ADOPT data (Kahn S et al, 2006).

The existing vildagliptin study data suggest that approximately 10% of vildagliptin patients will have an HbA1c >7.0% after the first 3 months of the study (initial response phase), since those patients who are randomised with an HbA1c measurement above the failure threshold (7.0%) may never have an HbA1c measurement below the required threshold during the study and will therefore be counted as failures during the first 13 weeks. A similar proportion is assumed for the comparator arm. Hence it is expected that the difference in failure rate is likely to be small early in the study, but will diverge as the study progresses. The power calculations have been adjusted to take this assumption into account using statistical simulations.

The simulations showed that assuming an annual initial treatment failure rate of 7.1% in the metformin monotherapy arm (estimated based on ADOPT data), incorporating a 10% initial failure rate after 13 weeks in each treatment arm (due to some patients with BL HbA1c ≥7.0%), 1000 patients per treatment arm would be sufficient to detect a hazard-ratio of 0.75 between vildagliptin + metformin and metformin alone (corresponding to a risk reduction rate of 25% in vildagliptin + metformin group *versus* metformin alone) with approximate 66% power and a 1-sided significance level of 0.025 (corresponding to a 2-sided test at 0.05).

9.7 Power for analysis of key secondary variables

Not applicable.

9.8 Interim analyses

An external and independent DMC to monitor patient safety data on a regular basis during the course of the study will be established. The DMC may request additional safety data review. Such safety analyses do not inflate the type I error for the primary efficacy hypothesis testing and thus require no multiplicity adjustments.

There is no efficacy interim analysis planed for the study.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guidelines for GCP, with applicable local regulations (including European directive 2001/20/EC, US CFR Title 21, and Japanese ministry of health, labor, and welfare), and with the ethical principles laid down in the declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing

[redacted]

so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis clinical quality assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately of this request.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalisation of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorised deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

12 References

AACE/ACE Consensus Statement (2009) An algorithm for glycemic control. Endocrine Practice; 15:540-559.

ADA-EASD Consensus Statement (2009) Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. Diabetologia; 52:17-30.

ADVANCE Management Committee (2001) Study rationale and design of ADVANCE. Diabetologia; 44: 1118-1120.

Ahren B, Gomis R, Standl E, et al (2004) Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care; 27:2874-80.

Ahren B, Foley J, Bosi E (2011) Clinical evidence and mechanistic basis for vildagliptin's action when added to metformin. Diabetes Obes Metab; 13:193–203.

Bosi E, Dotta F, Jia Y, et al. (2009) Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naïve patients with type 2 diabetes mellitus. Diabetes Obes Metab; 11:506–15.

Bulotta A, Hui H, Anastasi E, et al (2002) Cultured pancreatic ductal cells undergo cell cycle re-distribution and beta-cell-like differentiation in response to glucagon-like peptide-1. J. Mol. Endocrinol. 29:347–360.

D'Alessio DA, Denny A, Hermiller L, et al (2009) Treatment with the DPP-4 inhibitor vildagliptin improves fasting islet-cell function in subjects with type 2 diabetes. J Clin Endo Metab; 94:81-88.

Del Prato et al. (2005) Improving glucose management: ten steps to get more patients with type 2 diabetes to glycaemic goal. Intl J Clin Pract; 59: 1345-1355.

Drucker DJ (2003) Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes. Expert Opin. Investig. Drugs; 12:87-100.

Farilla L, Hui H, Bertolotto C, et al (2002) Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. Endocrinology; 143:4397–4408.

[redacted]

Fonseca V, Schweizer A, Albrecht D, et al. (2007) Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. Diabetologia; 50:1148–55.

Garber A, Foley J, Banerji M, et al. (2008) Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with sulfonylurea. Diabetes Obes Metab; 10:1047-1055.

Goke B, Hershon K, Kerr D, et al. (2008) Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naïve patients with type 2 diabetes: Comparison with metformin. Horm Metab Res; 40:892-95.

Hardikar AA, Wang XY, Williams LJ, et al (2002) Functional maturation of fetal porcine beta-cells by glucagon-like peptide 1 and cholecystokinin. Endocrinology; 143:3505–3514.

Holman R et al. UKPDS 80: 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. NEJM; 359:1577-1589.

Holst JJ (2002) Therapy of type 2 diabetes mellitus based on the actions of glucagon-like peptide 1. Diabetes Metab Res Rev; 18:430-441.

IDF (2009). Diabetes Atlas; The Global Burden. http://www.diabetesatlas.org/content/global-burden.

Kikuchi M, Nobuyuki A, Mitsutoshi K, et al. (2009) Vildagliptin dose-dependently improves glycemic control in Japanese patients with type 2 diabetes mellitus. Diabetes Res Clin Prac; 83: 233-40.

Kahn S et al. for the ADOPT Study Group (2006) Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. NEJM; 355:2427-2443.

Li Y, Hansotia T, Yusta B, et al (2003) Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. J. Biol. Chem.; 278:471–478.

Ligueros-Saylan M, et al. (2010) An assessment of adverse effects of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function from a large pooled database of Phase II and III clinical trials. Diabetes Obes Metab; 12:495-509.

Mari A, Ludvik B, Pacini G, et al (2001) A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes Care; 24: 539-548.

Mathieu C (2008) The scientific evidence: vildagliptin and the benefits of islet enhancement. Diabetes Obes Metab; 11 (Suppl. 2): 9–17.

Matthews DR et al. (2010) Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes Obes Metab; 12:780-789.

Pratley RE et al. (2008) Robust improvements in fasting and prandial measures of β-cell function with vildagliptin in drug-naïve patients: analysis of pooled vildagliptin monotherapy database. Diabetes Obes Metab; 10:931–938.

[redacted]

Rosenstock J, Baron MA, Camisasca RP, et al (2007) Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. Diabetes Obes Metab; 9:175–185.

Scherbaum W, et al. (2008) Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycaemia. Diabetes Obes Metab; 10:1114–1124.

Schweizer et al (2011) Assessing the general safety and tolerability of vildagliptin: value of pooled analyses from a large safety database versus evaluation of individual studies. Journal of Vascular Health and Risk Management; 7 49–57.

Stoffers DA, Kieffer TJ, Hussain MA, et al (2000) Insulinotropic glucagon-like peptide 1 agonists stimulate expression of homeodomain protein IDX-1 and increase islet size in mouse pancreas. Diabetes; 49:741–748.

UKPDS Group (1995) Overview of 6 years' therapy of type II diabetes. A progressive disease. Diabetes; 44:1249-1258.

UKPDS Group (1998a) UK Prospective Diabetes Study 33: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet; 352:837-53.

UKPDS Group (1998b) UK Prospective Diabetes Study 34: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. Lancet; 352:854-65.

Villhauer EB, Brinkman JA, Naderi GB, Burkey BF, Dunning BE, Prasad K, Mangold BL, Russell ME, Hughes TE (2003) 1-[[3-Hydroxy-1-adamantyl) amino]acetyl]-2-cyano-(S)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. J. Med. Chem.; 46:2774-89.

Wallace T, Matthews DR (2002) Coefficient of failure: a methodology for examining longitudinal β-cell function in Type 2 diabetes. Diabetic Medicine; 19: 465–469.

Wang X, Zhou J, Doyle ME, Egan JM (2001) Glucagon-like peptide-1 causes pancreatic duodenal homeobox-1 protein translocation from the cytoplasm to the nucleus of pancreatic beta-cells by a cyclic adenosinemonophosphate/protein kinase A-dependent mechanism. Endocrinology; 142: 820–1827.

Xu G, Stoffers DA, Habener JF, Bonner-Weir S (1999) Exendin-4 stimulates both beta-cell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats. Diabetes; 48:2270–2276.

References will be made available on request.

13 Appendix 1: Clinically notable laboratory values and vital signs

Laboratory notable range deviations will be provided in the investigator binder.

[redacted]

Table 13-1 Vital signs notable range deviations

Vital signs		Notable abnormalities
Pulse (beats/min)		either ≥120 + increase ≥25* or >130
		either ≤50 + decrease ≥30* or < 40
Blood pressure (mmHg)	systolic	either ≥180 + increase ≥30* or > 200
		either ≤90 + decrease ≥30* or < 75
	diastolic	either ≥105 + increase ≥20* or > 115
		either ≤50 + decrease ≥20* or < 40
Weight		a weight change of > 10% during the study

* Refers to post-BL value as compared to BL value.

14 Appendix 2: testing for patients with elevated LFTs

At the first recognition of a liver related AE an immediate blood draw for items listed on Panel A (see below) must be performed. After timely consultation with a gastroenterologist or hepatologist, Panel B below may need to be drawn.

If jaundice is present right upper quadrant ultrasound with Doppler within 24-72h should be performed.

Liver panel A must be performed within 24h of the abnormal LFTs

A urine sample must be collected for toxicology screen. Human immunodeficiency virus status must be established.

A blood sample must be draw for:

- HBsAg, hepatitis B core antibody (HbcAb), Hepatitis C RNA.
- HAV total and immunoglobulin M (IgM).
- Hepatitis E serology: IgM and immunoglobulin G.
- Herpes simplex virus, cytomegalovirus & Epstein-Barr virus serology.

Liver panel B – may be required following consultation with a specialist

After a refreshed history, physical examination, and upon consultation with a gastroenterologist or hepatologist, tests might include:

- Autoimmune disease: antinuclear antibody (ANA), anti–smooth muscle antibody (ASMA), anti–liver-kidney microsomal antibody (anti–LKM-1), antibodies against soluble liver antigen (anti-SLA), antibodies to liver-specific asialo-glycoprotein receptor, anti-mitochondrial antibody (AMA).
- Other infectious disease: malaria, tuberculosis, parasites, West Nile virus.
- Wilson's disease: serum ceruloplasmin.
- Hemochromatosis genotype (C282Y, H63D mutations).
- α-1 anti-trypsin level, and if low then phenotype.

[redacted]

- Tests for hemolysis (LDH, peripheral smear, haptoglobin, reticulocyte count).
- Liver biopsy.

[redacted]