20 May 2021
EMA/402373/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zomarist	vildagliptin / metformin hydrochloride
Eucreas	vildagliptin / metformin hydrochloride
Icandra	vildagliptin / metformin hydrochloride

Procedure No. EMEA/H/C/xxxx/WS/1937/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE Adverse event
ANCOVA Analysis of covariance
ALT Alanine aminotransferase
AST Aspartate aminotransferase
BMI Body mass index
CI Confidence interval
CPK Creatine phosphokinase
CV Cardiovascular
DPP-4 Dipeptidyl peptidase-4
ECG Electrocardiogram
FAS Full analysis set
FPG Fasting plasma glucose
HbA1c Glycosylated haemoglobin A1c
n number of patients in study/treatment group
PPS Per protocol set
SAE Serious adverse event
SAF Safety set
SE Standard error
SOC System organ class
SYE Subject-year exposure
SU Sulphonylurea
T2DM Type 2 diabetes mellitus

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 11 September 2020 an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Modification of approved therapeutic indication to simplify wording. Update of SmPC section 5.1 to add VERIFY study data (new study). Existing warning on drugs that may affect renal function or metformin disposition was expanded to include drugs that inhibit renal transporter (OCT2/MATE inhibitors) and corresponding update in drug interaction (section 4.4 and 4.5). PI update to QRD v10.1.

The grouped worksharing procedure requested amendments to the Summary of Product Characteristics, Package Leaflet and Annex II.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/169/2010 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Kristina Dunder

Timetable	Actual dates
Submission date	11 September 2020
Start of procedure:	31 October 2020
CHMP Rapporteur Assessment Report	21 December 2020
CHMP members comments	20 January 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 January 2021
Request for supplementary information (RSI)	28 January 2021
CHMP Rapporteur Assessment Report	8 March 2021
CHMP members comments	17 March 2021
Updated CHMP Rapporteur Assessment Report	18 March 2021
Request for supplementary information (RSI)	25 March 2021
CHMP Rapporteur Assessment Report	5 May 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur Assessment Report	12 May 2021
Opinion	20 May 2021

2. Scientific discussion

2.1. Introduction

Vildagliptin is an oral antidiabetic agent which belongs to the class of dipeptidyl peptidase 4 (DPP-4) inhibitors. The International Birth Date (IBD) of vildagliptin (Galvus) is 14 Feb 2007 (Mexico) and of vildagliptin/metformin FDC (Eucreas) is 14 Nov 2007 (EU). Both vildagliptin and vildagliptin/metformin FDC is indicated in the treatment of type 2 diabetes mellitus (T2DM) in adults.

The purpose of this application is to provide summary of the findings from the recently concluded 5-year study CLAF237A23156 (VERIFY Study - Vildagliptin Efficacy in combination with metformin for early treatment of type 2 diabetes). The VERIFY study was conducted to determine whether the early initiation of a vildagliptin plus metformin combination regimen would result in more durable glycaemic control than a sequential approach, with metformin monotherapy followed by combination therapy in treatment-naïve patients with T2DM.

The MAH has previously in 2010 submitted results from a 24-week study (LMF23A2302) of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1000 mg twice daily) as initial therapy in drug-naïve patients (var II/006/G). The study demonstrated that vildagliptin/metformin 50 mg/1000 mg twice daily reduced HbA1c by -1.82%, vildagliptin/metformin 50 mg/500 mg twice daily by -1.61%, metformin 1000 mg twice daily by -1.36% and vildagliptin 50 mg twice daily by -1.09% from a mean baseline HbA1c of 8.6%. Information from this study has been reflected in section 5.1 of the SmPC for Eucreas.

With this application the MAH proposes changes in section 4.1, 4.4, 4.5 and 5.1 for Eucreas, Icandra and Zomarist. In the cover letter, the MAH proposes modifications of the approved indication for Eucreas, Icandra and Zomarist to simplify the wording of the indication in section 4.1, in line with the guideline recommendations and the label wording of the other DPP4 inhibitors, and, moreover, proposes to include information on study results from the finalised VERIFY study in section 5.1. However, in the submitted revised product information, the MAH proposes further changes in section 4.1 and to extend the indication to include "initial combination of vildagliptin and metformin, when diabetes is not adequately controlled by diet and exercise alone".

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP, while an updated ERA was required.

2.2.1. Ecotoxicity/environmental risk assessment

As this procedure concerned a change in indication, an updated ERA was required for the originally applied products including the authorised new indications. An updated ERA has been provided on request however some issues remain, and the ERA(s) cannot be considered finalized within this variation.

Regarding vildagliptin: The ERA remains to be updated by the data an OECD TG308 and OECD TG218 study was missing for vildagliptin. A commitment (with time schedule by June 2023) to submit an update has been made by the MAH. Depending on the outcome of the study a risk characterisation of the sediment is deemed necessary. If so, this will also involve recalculating the PEC sediment for which adsorption data on soils and sludges would be needed. Data of adsorption/desorption studies is available for three types of sludges, but not for soils. The MAH intends to use a worst-case KOC_{soil} of 100 000.

Regarding metformin: A previous assessment of metformin degradation in water sediment systems (OECD TG308) within the application EMEA/H/C/2656 (in 2014) found metformin hydrochloride to be persistent. A supportive study ([14C]JNJ-28431754 – Generation of Aerobic Transformation Products for Identification in Aquatic Sediment Systems) on the formation of transformation products was also provided in EMEA/H/C/2656 but has not been noted/included in the present ERA. The following recalculated sediment DT50 value should be used: DT50 (sediment) = 70.5 – 354.8 days (SFO, 20°C). Although metformin has shown to be very persistent (DT50>180d, 12°C) in one of the sediments, several sets of data on Metformin confirm degradation to higher contents, which suggests that the derived DT50 of 70.5 d (20°C) is more reliable. In both sediments a limited amount of extractable parent and a high amount of non-extractable residues (>70%) were observed. Therefore, Metformin hydrochloride is considered to be persistent in sediments (150.5 d, 12°C) which should be noted in an updated ERA.

Additionally, a commitment for a Fish Full Life Cycle Test for Metformin is requested. The applicant is recommended to handle this matter via a letter of access for such a metformin study if possible. The company committed to provide the necessary ERA information and update as a post-authorisation measure by 31.05.2023.

2.2.2. Discussion on non-clinical aspects

This procedure concerned a change in indication and an updated ERA has been provided on request. Some issues regarding vildagliptin and metformin remain, and the ERA(s) cannot be considered finalized within this variation and necessary update will be provided latter as REC commitment. It was also noted

that in section SmPC 6.6. and Package Leaflet there was no disposal advice of the product, therefore disposal statement was included and SmPC and PL updated accordingly.

2.2.3. Conclusion on the non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP, while an updated ERA was required and provided. Remaining ERA information regarding vildagliptin and metformin will be provided, and ERA updated accordingly as a post-authorisation measure (REC) by 31.05.2023.

2.3. Clinical aspects

2.3.1. Introduction

The current application is based on the results of one study CLAF237A23156 (VERIFY), hereafter referred to as study VERIFY.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

2.3.2. Pharmacokinetics

Pharmacokinetic interaction studies

As part of the CDS update, an assessment was conducted against the individual labels of vildagliptin and metformin. In the innovator label of metformin, an interaction was noted with concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin.

A systematic review of information on clinical pharmacology and interactions of metformin and vildagliptin in clinical databases using various key words was performed according to the criteria mentioned below.

Databases: Stockley's drug interactions, Medline, Drug interaction database, Embase and International pharmaceutical abstracts.

Key words: "Metformin", "Vildagliptin", "Pharmacokinetics (PK)", "Pharmacodynamics (PD)", "Metabolism" and "Interactions".

Experiments performed in cell lines expressing hOCT2, hMATE1 and hMATE2-K confirmed the *in vitro* uptake of metformin (Kimura et al 2004 and Tanihara et al 2007). The *in vitro* findings were further confirmed by the clinical drug interaction data where metformin exposure was increased when co-administered with cimetidine, dolutegravir, ranolazine and vandetanib (inhibitors of hOCT2, hMATE1 and hMATE2-K). Due to the unavailability of selective inhibitors of these transporters, the relative contribution of each transporter in the renal uptake of metformin could not be established.

Some of the clinical drug interaction studies of metformin done with OCT2, MATE1 and MATE2-K transporters are summarized in the table below:

Inhibitor	Substrate	Fold increase in AUC	Reference
Cimetidine	Metformin	1.5	Somogyi et al 1987
Dolutegravir	Metformin	2.5	Song et al 2016
Ranolazine	Metformin	1.8	Zack et al 2015
Vandetanib	Metformin	1.7	Johansson et al 2014

The MAH satisfactorily justified why a warning regarding an interaction with metformin and the renal transporter inhibitors OCT2, MATE1 and MATE-2K is being included in the SmPC for Eucreas in section 4.4. and 4.5 and also provided relevant references to support this claim. In section 4.5 of the SmPC, the information about renal inhibitors has as suggested been placed under the subheading *Combinations requiring precautions for use*. The package leaflet has been updated to add the interaction with cimetidine as requested to section 2, Other medicines and <X>.

2.4. Clinical efficacy

2.4.1. Main study(ies)

Study VERIFY

This was a 5-year study in treatment naïve patients with T2DM 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%) is lower with the combination of vildagliptin and metformin compared with metformin monotherapy.

Methods

VERIFY was a phase IV, multi-centric, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (***Figure 1***).

Following a screening visit (Visit 1) and a screening period of up to 2 weeks, treatment-naïve patients, meeting all eligibility criteria entered the run-in period at Visit 2.

Run-in period: At Visit 2, in all eligible patients, metformin treatment was initiated and/or uptitrated. At the end of the 3-week run-in period, patients who were able to tolerate a total dose of at least 1000 mg and up to 2000 mg daily proceeded to randomization and started in Period 1.

Period 1 (vildagliptin/metformin combination versus metformin): At Visit 3, patients were randomized 1:1 to one of the following study regimens:

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

During the first 4 weeks of Period 1 the metformin dose could be adjusted (increased or decreased, but not below 1000 mg daily or above 2000 mg). The objective was to optimise metformin dose to 2000 mg daily or to the maximum tolerated dose. No anti-diabetic medication other than the study drug regimen was 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

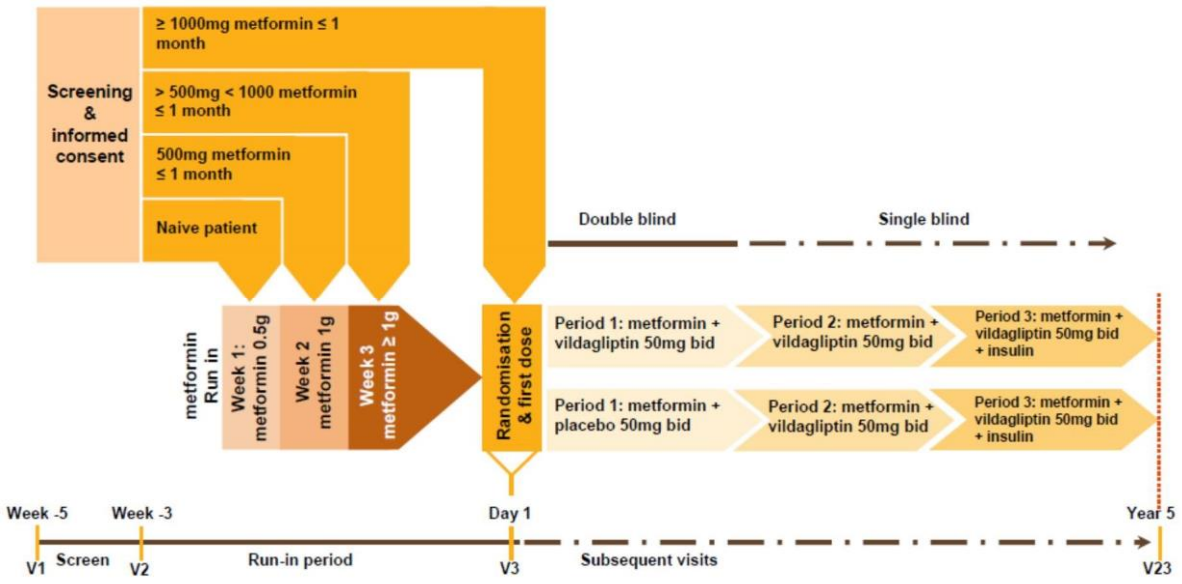
adjustments or interruptions of the study drug were permitted. Patients who, during Period 1, took anti-diabetic medication other than the study drug regimen (except for AEs or untoward events that require temporary dose adjustments) were to be discontinued from the study.

The duration of Period 1 could differ between patients depending on the time when the second of two HbA1c measurements taken at two consecutive visits after randomization confirmed HbA1c ≥ 7.0% (i.e. reached the primary endpoint of the study). When/if patients reached this endpoint, they entered into Period 2 of the study. Otherwise, they remained in Period 1.

Period 2 (vildagliptin/metformin combination versus vildagliptin add-on to metformin): When entering period 2, patients who were randomized to the placebo arm in Period 1 received vildagliptin 50 mg bid. Patients who were randomized to the active vildagliptin 50 mg bid arm in Period 1 continued to receive vildagliptin 50 mg bid. All patients continued to take their metformin dose unchanged. Period 2 remained masked to the patient and both patients and investigators remained masked to the treatment allocation in Period 1. No anti-diabetic medication other than the study regimen was allowed during Period 2, except if the patient had temporarily reduced/interrupted the treatment regimen due to AEs or untoward events that required temporary dose adjustment/interruption.
If, during Period 2, therapy intensification was required in accordance with the local guidelines, the patient entered Period 3. Period 2 was considered ended when insulin treatment was initiated, or, alternatively, when the patient was discontinued because the patient did not initiate insulin treatment in Period 3.

Period 3 (insulin initiation): In Period 3, patients were to be initiated on open-label insulin. The study drug regimen continued unchanged and remained masked to the patient in Period 3 and both patients and investigators remained masked to the treatment allocation in Period 1.

Figure 1 Study Design



Study participants

Population

Main inclusion criteria

- Confirmed diagnosis of T2DM by standard criteria.

T2DM diagnosed ≤ 24 months ago.
HbA1c ≥6.5% and ≤7.5% at Visit 1.

- Patients who were 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, received anti-diabetic medication cumulatively for not more than 3 months, and had not received any antidiabetic treatment within 3 months prior to Visit 1 (only metformin ≤2000mg daily was allowed within 1 month prior to Visit 1).

Patients who initiated metformin within 1 month prior to Visit 1 and took a total daily dose of maximum 2000mg metformin at Visit 1.

- Age ≥18 and ≤70 years old at Visit 1.
- Body mass index (BMI) ≥22 and ≤40 kg/m2 at Visit 1.

Main exclusion criteria

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 was allowed within 1 month prior to visit 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.
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 localized 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 suggested liver disease (except hepatic steatosis), such as portal hypertension, capsule scalloping, cirrhosis.

The inclusion criteria identified a population with a rather short duration of diabetes, but not all of them were strictly treatment naïve since 1 month of previous treatment with metformin was allowed.

Objectives Outcomes/endpoints

Primary objective

The primary objective of the study was to demonstrate the superiority of early combination of vildagliptin 50 mg 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%) is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy. The primary endpoint was "time to initial treatment failure" defined as HbA1c≥7.0%, confirmed at two consecutive scheduled study visits, starting from Visit 4 (Week 13).

Secondary objectives

- Testing the hypothesis that the rate of loss in glycaemic control over time (estimated annualised slope of HbA1c over time using a random coefficient model or by threshold) is lower with the combination vildagliptin plus metformin compared to that with metformin monotherapy.

- Progression of HbA1c from 26 weeks after the start of Period 2 to the end of Period 2 assessed by rate of loss in glycaemic control over time.

- Progression of FPG evaluated by the rate of loss in glycaemic control over time assessed by estimated annualised slope of FPG over time for periods.

- Change in HbA1c

- 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 (AUCglucose(0-2h)) during a standard meal-test at indicated time-points.
- Insulin resistance assessed by oral glucose insulin sensitivity (OGIS) during a standard meal-test at indicated time-points.

Exploratory objectives

- Body weight
- Time to insulin initiation
- β-cell function assessed by homeostasis model assessment for the β-cell (HOMA-B /HOMA-%β)
- Insulin resistance assessed by homeostasis model assessment for insulin resistance (HOMA-IR / HOMA-% sensitivity)
- Health status assessed by EQ-5D questionnaire
- Cardiovascular outcomes; microvascular and macrovascular complications, microalbuminuria, progression to renal insufficiency, and all-cause mortality
- Micro-aneurysm count assessed by retinal imaging in a subgroup of patients

Sample size

A total sample size of 1000 randomized patients per treatment group (in 1:1 allocation ratio to vildagliptin + metformin and metformin monotherapy) was planned. The sample size calculation assumed that all randomized patients were to be followed up for 5 years unless patients dropped out from the study for various reasons (lack of efficacy, AEs, abnormal labs, lost to follow-up etc.), and that the yearly dropout rate is 11%, based on ADOPT data (Kahn et al 2006).

The existing vildagliptin study data suggested that approximately 10% of vildagliptin patients would have an HbA1c >7.0% after the first 3 months of the study (initial response phase), since those patients who were randomized with an HbA1c measurement above the failure threshold (7.0%) might never have an HbA1c measurement below the required threshold during the study and were therefore to be counted as failures during the first 13 weeks. A similar proportion was assumed for the comparator arm. Hence it was expected that the difference in failure rate was likely to be small early in the study but diverges 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 group (due to some patients with baseline HbA1c ≥7.0%), 1000 patients per treatment group 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 75% power and a 1-sided significance level of 0.025 (corresponding to a 2-sided test at 0.05).
The sample size calculation seemed appropriate, even if the power of the primary test was low at the planning stage of the trial. This is, however, not an issue, given the study results. It is acknowledged that the planned sample size remained unchanged when the rate of loss in glycaemic control over time was removed from the primary to the secondary endpoints.

Randomisation

Patients were assigned in a ratio of 1:1 to one of two treatment groups:

- Metformin up to 1000 mg bid plus vildagliptin 50 mg bid (Period 1).
- Metformin up to 1000 mg bid plus vildagliptin placebo 50 mg bid (Period 1).

In Period 2 all patients received metformin up to 1000 mg bid plus vildagliptin 50 mg bid.

A patient randomisation list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. These randomisation numbers were linked to the different treatment groups, which in turn were linked to medication numbers. A separate medication list was produced by or under the responsibility of Novartis drug supply management using a validated system that automated the random assignment of medication numbers to study drug packs containing each of the study drugs. The randomized allocation to treatment approach was provided by centre.

The randomisation numbers were generated for each study centre using an IRT system. The randomisation was not stratified.

Blinding (masking)

As described in the CSR, patients, investigator staff, persons performing the assessments, and data analysts remained masked to the identity of the treatment from the time of randomisation until database lock, using the following methods: (1) randomisation data were kept strictly confidential until the time of unmasking, and were not accessible by anyone else involved in the study; (2) the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, schedule of administration and appearance. Unmasking could only occur in the case of patient emergencies. The database was locked on May 10, 2019.

Protocol amendments

Table 9-7 Protocol amendments

Version and date	Summary of key changes
Amendment no. 1 (released 27-Oct-2011)	An additional meal-test was included for patients who were participating in the meal-test sub-study at Visit 4. This change, together with the additional meal-tests, enabled 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 was performed was inserted.
Amendment no. 2 (released 08-Feb-2012)	Additional clarification was included 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 could be included.
Amendment no. 3 (released 04-Oct-2016)	The protocol was amended to accommodate the inclusion of an adjudication committee and a data monitoring committee (DMC), and to 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 allowed the temporary use of commercial metformin 500mg tablets.
Amendment no. 4 (released 22-Oct-2019)	The protocol was 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 (published before LPLV; Matthews et al 2019b). 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.

Statistical methods

Analysis sets

Screened-only set (SCR)	All patients who were screen-failed after the first visit or who entered the run-in phase but were not randomized.
Randomized set (RAN)	All randomized patients.
Full analysis set (FAS)	All randomized patients who received at least one dose of randomized study medication (vildagliptin or placebo) and had at least one post-randomization assessment of any efficacy parameter. Following the intent-to-treat principle, patients were analysed according to the treatment approach they were assigned to at randomization.
Safety set (SAF)	All patients who received at least one dose of randomized study medication (vildagliptin or placebo). Patients were analysed according to the treatment approach received. If a patient received both vildagliptin and placebo in Period 1, the patient was included in the vildagliptin group. Note that the SAF allowed the inclusion of non-randomized patients who received the study drug in error.

Per protocol set (PPS)	A subset of FAS that consisted of all randomized patients who received at least one dose of randomized study medication (vildagliptin or placebo), had at least one post-randomization assessment of any efficacy parameter in Period 1, did not discontinue the study prior to Week 26, and had no major protocol deviations occurring during Period 1.

Primary efficacy variable

The primary efficacy variable was time to confirmed initial treatment failure, defined as the time from randomization to the second of two consecutive scheduled visits, at which HbA1c ≥ 7.0% was measured, starting from Visit 4 (13 weeks after randomization), i.e. the end of Period 1.

Primary analysis

The primary statistical hypothesis of time to confirmed initial treatment failure was assessed by a 1-sided test of superiority of the combination treatment with vildagliptin + metformin versus metformin monotherapy on alpha level of 0.025. The null hypothesis was that the hazard-ratio (HR) between the combination treatment vildagliptin + metformin and metformin monotherapy was equal or greater than 1, and the 1-sided alternative hypothesis was that the hazard-ratio was less than 1.

The primary efficacy analysis used a Cox proportional hazard regression model to assess the probability of confirmed initial treatment failure, with treatment approach and geographic region as classification variables and baseline HbA1c as a covariate. The hazard-ratio and associated 95% confidence interval as well as the p-value estimated from the above model were presented by treatment approach. The confirmed initial treatment failure rate over time by treatment approach was summarized using estimates and 95% confidence intervals from a Kaplan-Meier analysis. The primary analysis for the primary efficacy variable was performed using the FAS and repeated in the PPS as supportive analysis. Patients who discontinued the study for any reason during Period 1 (lack of efficacy, lost to follow-up, AE or abnormal laboratory values etc.) were treated as censored values at the time of discontinuation. Patients who remained under the threshold (or whose measurement above the threshold was not confirmed at next scheduled visit) were censored at the time of last study visit.

As supportive analyses, time to first treatment failure (derived as the time from randomization to the first of two consecutive scheduled visits, at which HbA1c ≥7.0% was measured, starting from Visit 4, at 13 weeks after randomization), and time to second treatment failure (a post-hoc endpoint, derived as the time from randomization to the second of the two consecutive scheduled visits, at which HbA1c ≥7.0% was measured in Period 2) were analysed in a similar way as in the primary analysis. Patients who discontinued the study for any reason during Period 1 or Period 2 without the treatment failure were censored at the date of discontinuation. Patients that failed in Period 1 and did not fail in Period 2 were censored at the end of Period 2. Patients who did not fail in Period 2 who passed to Period 3 were censored to last study visit prior Period 3.

Subgroup analyses of HbA1c by treatment approach were performed using descriptive statistics.

Secondary analyses

The rate of loss in glycaemic control over time was estimated by the slope of HbA1c over time (in years) as a random coefficient in a linear mixed effect model: the model was fitted to HbA1c data collected from Visit 5 (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 included 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 random effects.

For the time to insulin initiation (defined as the time from treatment start to the date of initiation of insulin therapy prescribed in Period 3 or to the date of discontinuation from the study in Period 2 due to

being unable or unwilling to initiate insulin therapy for treatment intensification in Period 3) the same Cox proportional hazards regression model used in the primary efficacy endpoint was used for this secondary variable as well. Patients who discontinued the study during Period 1 or Period 2 for reasons other than not being able or unwilling to initiate insulin therapy in Period 3 (i.e. for treatment intensification), or who completed the study during Period 1 or Period 2, were censored at the time of last study visit.

Variables related to the rate of change of β-cell function and insulin sensitivity over time, as well as variables related to the rate of loss in glycaemic control over time, were assessed using a similar random coefficient linear mixed effect model as used for the endpoint 'rate of loss in glycaemic control in HbA1c from Visit 5 (Week 26) to the end of Period 1'.

All secondary efficacy variables related to change from baseline to an endpoint were analysed using an analysis of covariance (ANCOVA) model with treatment approach, geographic region as classification variables and baseline value as a covariate. In a subgroup of patients, change in total retinal micro-aneurysm count from Baseline to: i) Year 4 (Week 208 visit); ii) Year 5 (Week 260 visit) was analysed using the same ANCOVA model. The least squares mean ("adjusted mean") change from Baseline for each treatment approach, the difference in the least squares mean changes between the two treatment approaches, and the two-sided adjusted 95% confidence interval along with the p-value for the difference was obtained from this analysis model and presented.

No imputation was used for missing HbA1c measurements. If there was a case where the HbA1c value was missing, then for consecutive scheduled visits only visits with non-missing HbA1c measurements were considered (e.g. if Visit 4 HbA1c ≥7.0%, Visit 5 HbA1c was missing, and Visit 6 HbA1c ≥7.0%, then this was to be considered treatment failure).

Safety analyses: In order to assess safety and tolerability of vildagliptin as compared to placebo as add-on to metformin, key safety variables (overall AEs, SAEs, AEs leading to study drug discontinuation, incidence of hypoglycemia, predefined AE risks, predefined categories of liver enzyme (ALT/AST) and CPK and persistent elevations) as well as other predefined safety assessments were summarized by treatment approach.

No interim analyses were planned for this study.

Changes in the planned analyses were made during development of the statistical analysis plan (SAP) (final version 3, 7 May 2019) and led to the last protocol amendment (number 4, 22 Oct 2019). The major changes were redefining the loss of glycaemic control as a secondary endpoint instead of a primary endpoint as initially planned, and redefining time to initial treatment failure to be time to confirmed initial treatment failure, measured until the second of the two HbA1c measurement ≥7.0% instead of the first as initially planned. Sample size section has been updated to include only the primary endpoint, with no changes in the sample size. Time to first treatment failure and few subgroup analyses of the primary endpoint were also added.

According to the initial CSP, there were two primary efficacy variables defined:

1) time to initial treatment failure, defined as time from randomization until the time when the first of the two HbA1c measurement ≥7.0% was determined after at least 13 weeks of treatment (Visit 4).
2) the rate of loss of glycaemic control over time. It was to be estimated by an annualised slope of HbA1c over time from Visit 5 (Week 26) to the end of Period 1.

Post-hoc analyses include time to second treatment failure and few subgroup analyses by age and baseline GFR.

The planned analyses in general were found appropriate. For the primary analysis, patients who discontinued the study for any reason during Period 1 were censored; however, it was unclear how

treatment discontinuations and any rescue medications were handled. Sensitivity analyses should be performed where also treatment discontinuations and rescue medication intake (if any) are censored or imputed as treatment failures, accompanied by the numbers of observations censored for a specific reason. Sensitivity analyses presented as requested confirmed the results of the primary analysis. It appeared that the MAH had censored treatment discontinuations in the primary analysis and not study discontinuations as was described in the analysis plan. Numbers of study discontinuations were 187 and 216 in Vildagliptin and placebo group, respectively.

The primary statistical hypothesis of superiority of the combination treatment versus metformin was tested on alpha level of 2.5% (1-sided). One-sided superiority tests are not conventional for confirmatory trials but may be acceptable for the assessment of the study results. However, p-values from 2-sided tests are expected to be presented in the SmPC, particularly when the test results are not statistically compelling.

Substantial changes have been made in the planned analyses concerning the primary efficacy endpoint. Two primary efficacy variables were initially planned: time to initial treatment failure and rate of loss of glycaemic control over time. Definition of the initial treatment failure had been changed during the course of the study. After study completion (and unclear if prior to the database lock) the statistical analysis plan was updated to remove the loss of glycaemic control as primary endpoint. These changes have been described in the submitted documentation, but without a clear rationale. Considering that the rate of loss of glycaemic control over time is not statistically significant, it may be suspected that the change of the primary endpoints was data driven and the study integrity undermined. The MAH is expected to provide rationale for the change of the primary endpoints and comment if the decision was data driven.

The MAH considered that two consecutive values were more robust than one due to fluctuation of HbA1c. It was assured by the MAH that removal of the loss of glycaemic control as primary endpoint was not data driven. The main arguments for the change were to focus on a clinically interpretable and predictable measure, and, considering its clinical importance, to enable a full alpha allocation initially. It was further discussed that the change in the multiple testing procedure due to the change to one primary endpoint does not alter the conclusion of statistical significance for the primary endpoint, which has been acknowledged.

Irrespectively of the MAH's specification of the order of importance of the variables, the judgement of what is required for demonstration of efficacy in terms of endpoints, whether it would be both or one, and which one in case of the latter, is in the end made by the regulator. If significance of both initially defined primary variables is required for a positive efficacy conclusion, then the study cannot be deemed as a success in respect to the primary efficacy analyses, despite the change of the primary endpoints. However, it was initially anticipated that significance of either one of the initially defined two primary endpoints was deemed sufficient for the study success with multiplicity being handled using Hochberg's multiple testing step-up procedure, according which the hypothesis relating to the lower of the two obtained p-values was to be rejected if $p<0.0125$ (one-sided). Also, if Bonferroni split is used, then significance on alpha level of 2.5% (2-sided) for any of the initially defined primary endpoints, as the case here, indeed proves the efficacy. Therefore, positive efficacy result for the study could statistically be concluded despite the change of the primary variables. Statistical significance is compelling for the primary endpoint time to confirmed initial treatment failure and supported by the results of the time to first treatment failure. Long-term efficacy in terms of rate of loss in glycaemic control over time (estimated annualised slope of HbA1c over time) is, however, not demonstrated.

Time to second treatment failure has been added as a post-hoc endpoint in the CSR but was not mentioned in the final SAP nor in the amended protocol version 4. However, in the CSR section 9.8.3, time to second treatment failure is listed among the changes related to the protocol amendment made in

2016. Timing for the addition of this endpoint needed to be clarified and a rationale was provided together with a discussion on the importance of this endpoint for the study conclusions.

It was also noted that the primary efficacy analysis presented by HR has been interpreted in terms of relative risk, which is not statistically correct (see for example Janez Stare & Delphine Maucort-Boulch (2016); Odds Ratio, Hazard Ratio and Relative Risk. Metodoloski zvezki, Vol. 13, No. 1, 2016, 59-67). The interpretation was thefore requested to be reworded in the SmPC section 5.1.

Results

Participant flow

It was planned to screen approximately 4000 patients in order to randomize 2000 patients. As per the plan, 2001 patients were randomized, 998 patients into the vildagliptin 50mg bid + metformin group and 1003 into the placebo + metformin group.

Table 1. displays the subject disposition over the entire study period by treatment groups. A total of 811 (81.3%) patients in the early combination group and 787 (78.5%) in the monotherapy group completed the study. The most frequent reason for early discontinuation was administrative problems (9.5% of patients overall). There were no major differences between treatment groups for any reason for discontinuation. Of note, the annualized discontinuation rate is about 4% (20.1%/5), thus lower than the anticipated 11% discontinuation rate.

Table 1 Patient disposition by treatment approach (Randomized) Period: Treatment period (Periods 1, 2, and 3)

Disposition Reason	Vildagliptin 50 mg bid + metformin N=998 n (%)	Placebo + metformin N=1003 n (%)	Total N=2001 n (%)
Completed	811 (81.3)	787 (78.5)	1598 (79.9)
Discontinued	187 (18.7)	216 (21.5)	403 (20.1)
Administrative problems	96 (9.6)	94 (9.4)	190 (9.5)
Adverse event(s)	28 (2.8)	44 (4.4)	72 (3.6)
Lost to follow-up	17 (1.7)	24 (2.4)	41 (2.0)
Death	13 (1.3)	9 (0.9)	22 (1.1)
Protocol deviation	9 (0.9)	19 (1.9)	28 (1.4)
New therapy for study indication	8 (0.8)	6 (0.6)	14 (0.7)
Unsatisfactory therapeutic effect	6 (0.6)	8 (0.8)	14 (0.7)
Subject withdrew consent	5 (0.5)	4 (0.4)	9 (0.4)
Abnormal laboratory value(s)	3 (0.3)	7 (0.7)	10 (0.5)
Abnormal test procedure result(s)	1 (0.1)	0	1 (0.0)
Subject's condition no longer requires study drug	1 (0.1)	1 (0.1)	2 (0.1)

- All randomized patients are included in Treatment period (Periods 1, 2 and 3) summary regardless of whether patients actually started Period 1 or not.

Baseline data

Demographic and other background characteristics were overall well balanced between both treatment groups. The mean age was 54.3 years, and 25.4% of patients were older than 65 years.

The ratio of females and males was balanced (53.0% and 47.0%). Most subjects were Caucasian (60.8%), followed by Asian (18.6%) and Native American (10.5%). The mean body mass index (BMI) was 31.1 kg/m^2. There were only small, non-significant differences between treatment groups for any demographic characteristics.

Mean HbA1c at randomization (Visit 3) was 6.7% in both treatment groups. The majority of all patients (71.3%) had a mean HbA1c of <7.0%. Mean fasting plasma glucose for all patients was 7.1 mmol/L. The mean duration of diabetes was 6.4 months; the median duration was shorter (3.3 months); the higher mean value is driven by few patients (20) with longer than allowed disease duration at baseline (≤ 24 months) which was defined as protocol deviation. Most patients had normal renal function at baseline (66.0%).

Table 2 Patient baseline demographic characteristics by treatment approach

Demographic variable	Vilda 50mg bid + metformin N=998	Placebo + metformin N=1003	Total N=2001
Age (years)			
n	998	1003	2001
Mean	54.1	54.6	54.3
SD	9.54	9.24	9.39
Min	19.0	22.0	19.0
Median	55.0	56.0	55.0
Max	70.0	70.0	70.0
Age group, n (%)			
< 48 years	238 (23.8)	220 (21.9)	458 (22.9)
48 - < 62 years	503 (50.4)	531 (52.9)	1034 (51.7)
>= 62 years	257 (25.8)	252 (25.1)	509 (25.4)
Sex, n (%)			
Male	453 (45.4)	488 (48.7)	941 (47.0)
Female	545 (54.6)	515 (51.3)	1060 (53.0)
Predominant race, n (%)			
Caucasian	605 (60.6)	612 (61.0)	1217 (60.8)
Black	26 (2.6)	23 (2.3)	49 (2.4)
Asian	186 (18.6)	187 (18.6)	373 (18.6)
Native American	103 (10.3)	107 (10.7)	210 (10.5)
Other	78 (7.8)	74 (7.4)	152 (7.6)
Ethnicity, n (%)			
Hispanic/Latino	268 (26.9)	277 (27.6)	545 (27.2)
Chinese	28 (2.8)	25 (2.5)	53 (2.6)
Indian (Indian subcontinent)	94 (9.4)	91 (9.1)	185 (9.2)
Mixed ethnicity	0	2 (0.2)	2 (0.1)
Other	608 (60.9)	608 (60.6)	1216 (60.8)
Height (cm)			
n	998	1003	2001
Mean	165.5	165.4	165.4
SD	10.48	10.54	10.51
Min	133.0	134.6	133.0
Median	165.0	165.0	165.0

Demographic variable	Vilda 50mg bid + metformin N=998	Placebo + metformin N=1003	Total N=2001
Max	200.0	198.0	200.0
Weight (kg)			
n	998	1003	2001
Mean	85.8	85.1	85.5
SD	17.89	17.19	17.54
Min	47.0	43.9	43.9
Median	85.0	84.0	84.3
Max	147.0	139.0	147.0
BMI (kg/m^2)			
n	998	1003	2001
Mean	31.2	31.0	31.1
SD	4.78	4.67	4.72
Min	19.9	22.0	19.9
Median	30.9	30.6	30.8
Max	40.0	45.5	45.5
BMI group			
<30 (kg/m^2)	428 (42.9)	447 (44.6)	875 (43.7)
>=30(kg/m^2)	570 (57.1)	556 (55.4)	1126 (56.3)

Table 3 Patient baseline background characteristics by treatment approach

Background Characteristic	Vilda 50mg bid + metformin N=998	Placebo + metformin N=1003	Total N=2001
HbA1c (percent)			
n	996	1003	1999
Mean	6.7	6.7	6.7
SD	0.45	0.47	0.46
Median	6.7	6.7	6.7
Min	4.4	5.0	4.4

Max	8.6	10.2	10.2
HbA1c (percent)			
< 7	722 (72.3)	705 (70.3)	1427 (71.3)
>= 7	274 (27.5)	298 (29.7)	572 (28.6)
Missing	2 (0.2)	0	2 (0.1)
FPG (mmol/l)			
n	996	1003	1999
Mean	7.1	7.2	7.1
SD	1.40	1.47	1.44
Median	6.9	6.9	6.9
Min	4.1	4.3	4.1
Max	14.2	17.2	17.2
Duration of type 2 diabetes (months)			
n	998	1003	2001
Mean	6.2	6.6	6.4
SD	7.00	8.05	7.55
Median	3.3	3.4	3.3
Min	0.0	0.0	0.0
Max	62.3	113.9	113.9
GFR (MDRD) (mL/min/1.73 m**2)			
Normal (>80)	660 (66.1)	661 (65.9)	1321 (66.0)
Mild (>=50 - <=80)	333 (33.4)	337 (33.6)	670 (33.5)
Moderate (>=30 - <50)	3 (0.3)	4 (0.4)	7 (0.3)
Severe (<30)	0	1 (0.1)	1 (0.0)
Missing	2 (0.2)	0	2 (0.1)
Is subject a current smoker?			
Yes	154 (15.4)	136 (13.6)	290 (14.5)
No	844 (84.6)	867 (86.4)	1711 (85.5)

Medical history

In both treatment groups a similar pattern was observed for all system organ classes (SOCs) and preferred terms. Most frequently reported were conditions within the SOC Vascular disorders (65.0% in the early combination and 66.2% in the monotherapy group); within this system organ class, most frequently reported was hypertension (59.4% vs. 61.3%, respectively). Second frequently reported were conditions within the SOC Metabolism and nutrition disorders (58.6% and 57.7%, respectively); most frequently reported within this SOC were dyslipidemia (30.7% vs, 29.0%) and obesity (17.7% vs. 17.3%, respectively).

Prior and concomitant therapy

Most frequently used was metformin or metformin hydrochloride (40.6% and 41.1% of patients in the early combination group and monotherapy group, respectively). Other antidiabetic medication was used infrequently (<1% for any antidiabetic medication).

Concomitant medication was used by the majority of subjects at any time over the entire study period (93.9% of patients in the early combination group and 93.4% in the monotherapy group. Most frequently used medication included antihypertensives such as angiotensin II antagonists either plain (21.5% vs. 21.8% of patients, respectively) or in combination with other compounds, and lipid-lowering medication, such as statins (41.6% vs. 42.5%, respectively). There was little difference between treatment groups for any specific concomitant medication.

In both treatment groups, the mean duration of metformin taken during the screening and run-in period was 9 weeks, and the average daily metformin dose approximately 1.4 g.

In general the baseline characteristics were balanced; however, the MAH was asked to comment on that patients who did not meet the inclusion criteria on HbA1c (≥6.5% and ≤7.5%), BMI (≥22 and ≤40 kg/m^2) and diabetes duration (≤ 24 months) were included in the study. The MAH has clarified that almost all included patients met the inclusion criteria with respect to BMI and HbA1c.

Numbers analysed

Table 2 provides an overview of the number of patients in the analysis populations. Almost all patients were included in the Safety set (99.9%) and in the Full analysis set (98.6%). The majority of patients was also included into the Per protocol set (92.5%).

Table 2 Number (%) of patients in the analysis populations

Population	Vilda 50mg bid + metformin N=998 n (%)	Placebo + metformin N=1003 n (%)	Total N=2001 n (%)
Randomized	998 (100)	1003 (100)	2001 (100)
Safety	998 (100)	1001 (99.8)	1999 (99.9)
Full analysis set	983 (98.5)	989 (98.6)	1972 (98.6)
Per protocol	919 (92.1)	931 (92.8)	1850 (92.5)
Randomized, meal-test subset	233 (23.3)	230 (22.9)	463 (23.1)
FAS, meal-test subset	228 (22.8)	227 (22.6)	455 (22.7)
Randomized, retinal micro-aneurysm count subset	76 (7.6)	88 (8.8)	164 (8.2)
FAS, retinal micro-aneurysm count subset	75 (7.5)	87 (8.7)	162 (8.1)
Randomized, biomarker subset	234 (23.4)	233 (23.2)	467 (23.3)

Outcomes and estimation

Primary endpoint results

The primary efficacy variable was time to confirmed *initial treatment failure* 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), i.e. the end of Period 1. The results of the analysis are presented in **Table 4**.

The initiation of an early combination regimen of vildagliptin 50 mg bid plus metformin resulted in a statistically significant reduction in the relative risk for time to confirmed initial treatment failure vs metformin monotherapy in treatment-naïve patient with T2DM over the 5-year study duration (Full analysis set). The incidence of initial treatment failure was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the monotherapy group (HR [95%CI]: 0.51 [0.45, 0.58]; p<0.001).

Table 4 Cox regression analysis of time to initial treatment failure (FAS and PPS)

Consistent results were observed in the Per protocol set (PPS).

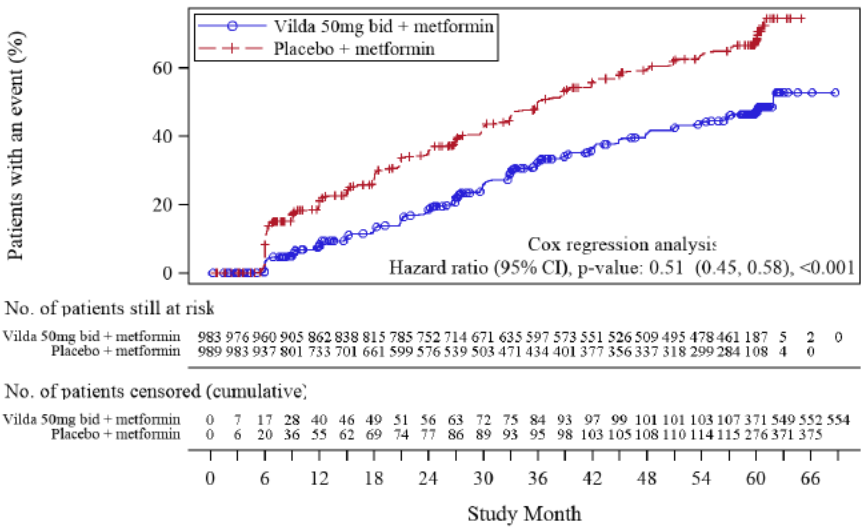
Table 11-1 Cox regression analysis of time to initial treatment failure (FAS and PPS)

Analysis set Treatment approach	n/N' (%)	Vilda 50mg bid + metformin / Placebo + metformin Hazard Ratio	95% CI	p-value
FAS				
Vilda 50mg bid + metformin (N=983)	429/983 (43.6)	0.51	(0.45, 0.58)	<0.001*
Placebo + metformin (N=989)	614/989 (62.1)			
PPS				
Vilda 50mg bid + metformin (N=919)	411/919 (44.7)	0.50	(0.44, 0.57)	<0.001*
Placebo + metformin (N=931)	598/931 (64.2)			

The results in the per protocol set were consistent with those from the full analysis set.

From Month 6, the probability of initial treatment failure (FAS) was lower in the early combination treatment arm compared to the monotherapy treatment group. The median (interquartile range, IQR) observed time to treatment failure in the monotherapy group was 36.1 (15.3, not estimable [NE]) months, while the median treatment failure time for those receiving early combination therapy could only be estimated to be beyond the study duration at 61.9 (29.9, NE) months (post-hoc analyses, on file). At the end of Year 5, the probability of initial treatment failure was 46.4% in the early combination therapy group and 66.6% in the monotherapy group.

Figure 2 Kaplan-Meier estimates of the probability (%) of initial treatment failure (FAS)

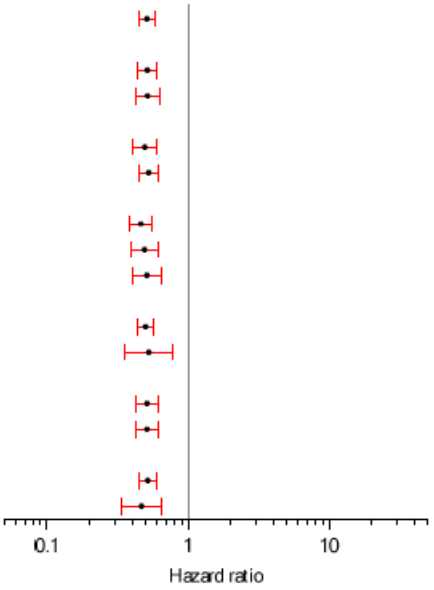


Subgroup analyses for time to initial treatment failure

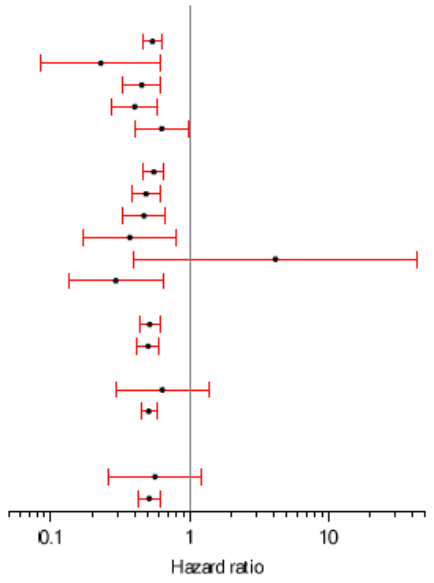
Subgroup analyses for time to initial treatment failure revealed a consistently significant benefit of early combination treatment over monotherapy for the primary outcome (**Figure 3**). This benefit was demonstrated for all of the subgroups of HbA1c, BMI, age, gender, smoking status, race, geographical regions, and estimated glomerular filtration rate (eGFR) categories, with no evidence of heterogeneity (all p-values above 0.05).

Figure 3 Forest plot of hazard ratios (95% CI) in time to confirmed initial treatment failure up to end of Period 1 by treatment approach (FAS)

Subgroup	Vilda n/N (%)	Placebo n/N (%)	HR (95% CI)	p-value
Overall	429/983 (43.64)	614/989 (62.08)	0.510 (0.45,0.58)	<.001
Baseline HbA1c				0.240
<7%	260/714 (36.41)	376/696 (54.02)	0.515 (0.44,0.60)	
>=7%	169/269 (62.83)	238/293 (81.23)	0.516 (0.42,0.63)	
Baseline BMI				0.349
<30 kg/m2	168/418 (40.19)	267/439 (60.82)	0.493 (0.41,0.60)	
>=30 kg/m2	261/565 (46.19)	347/550 (63.09)	0.525 (0.45,0.62)	
Age per tertiles of baseline age				0.455
<=51 years	190/364 (52.20)	239/330 (72.42)	0.463 (0.38,0.56)	
51 - <=59 years	133/294 (45.24)	205/327 (62.69)	0.491 (0.39,0.61)	
>59 years	106/325 (32.62)	170/332 (51.20)	0.510 (0.40,0.65)	
Age				0.394
<65 years	388/842 (46.08)	549/846 (64.89)	0.500 (0.44,0.57)	
>=65 years	41/141 (29.08)	65/143 (45.45)	0.527 (0.35,0.78)	
Gender				0.442
Male	201/443 (45.37)	311/482 (64.52)	0.512 (0.43,0.61)	
Female	228/540 (42.22)	303/507 (59.76)	0.512 (0.43,0.61)	
Baseline smoking status				0.345
No	363/834 (43.53)	524/854 (61.36)	0.518 (0.45,0.59)	
Yes	66/149 (44.30)	90/135 (66.67)	0.468 (0.34,0.65)	



Subgroup	Vilda n/N (%)	Placebo n/N (%)	HR (95% CI)	p-value
Race				0.111
Caucasian	273/595 (45.88)	374/606 (61.72)	0.540 (0.46,0.63)	
Black	8/26 (30.77)	17/22 (77.27)	0.230 (0.08,0.62)	
Asian	67/183 (36.61)	106/183 (57.92)	0.452 (0.33,0.62)	
Native American	44/103 (42.72)	69/105 (65.71)	0.402 (0.27,0.59)	
Other	37/76 (48.68)	48/73 (65.75)	0.631 (0.40,0.99)	
Geographical region				0.066
Europe	234/516 (45.35)	317/518 (61.20)	0.552 (0.47,0.65)	
LatAm	121/261 (46.36)	177/267 (66.29)	0.486 (0.38,0.61)	
South-East Asia	51/123 (41.46)	78/128 (60.94)	0.469 (0.33,0.67)	
East Asia	10/46 (21.74)	20/41 (48.78)	0.371 (0.17,0.80)	
Australia	3/5 (60.00)	1/5 (20.00)	4.157 (0.40,43.59)	
Africa	10/32 (31.25)	21/30 (70.00)	0.294 (0.13,0.64)	
Baseline GFR (mL/min/1.73 m**				0.387
<90	225/560 (40.18)	320/551 (58.08)	0.516 (0.43,0.61)	
>=90	204/423 (48.23)	294/438 (67.12)	0.502 (0.42,0.60)	
Baseline GFR (mL/min/1.73 m**				0.295
<60	13/33 (39.39)	21/38 (55.26)	0.636 (0.29,1.38)	
>=60	416/950 (43.79)	593/951 (62.36)	0.508 (0.45,0.58)	
Baseline GFR (mL/min/1.73 m**				0.387
<30	0/0 (0.00)	0/1 (0.00)	N.E.	
30 - <60	13/33 (39.39)	21/37 (56.76)	0.563 (0.26,1.22)	
60 - <90	212/527 (40.23)	299/513 (58.28)	0.512 (0.43,0.61)	



- p-values presented are one sided, - p-value for the "Overall" are comparison of treatment effects (not interaction)

The study reached its primary endpoint, but the clinical relevance of the results needed to be discussed and the MAH provided further discussion. The mean HbA1c was similar in both treatment groups at the end of study after 5 years, and therefore the clinical relevance of the observed difference up to this time point ("the legacy effect") was still an issue of concern considering that treatment with two products instead of one always increases the risk of adverse events.

It was acknowledged that the clinical relevance of the results cannot be further justified based on data from the VERIFY study. Instead, relevant previous knowledge is what potentially could serve as support. The most relevant study in this context is probably the follow up of the UKPDS (*Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008)10-year follow-up of intensive glucose control in type 2 diabetes.N Engl J Med*). In this study, differences in glycated hemoglobin levels between patients treated with conventional and intensive treatment documented in the original study, were lost after the first year of follow up. In the sulfonylurea–insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, P=0.04) and microvascular disease (24%, P=0.001), and risk reductions for myocardial infarction (15%, P=0.01) and death from any cause (13%, P=0.007) emerged over time. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, P=0.01), myocardial infarction (33%, P=0.005), and death from any cause (27%, P=0.002). This may indicate a sustained legacy effect of an initial intensive glucose-control strategy. The Steno-2 Study reported a similar outcome during a 5.5-year period after earlier multifactorial risk reduction among patients with type 2 diabetes (*Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl JMed 2008*). However, it can be questioned if these results also are of relevance for the current scenario considering that the control group in the UPKDS was treated with diet only and may therefore be at a higher risk of later events compared to "conventional therapy" in the VERIFY study (ie metformin monotherapy). With respect to the Steno-2 trial, multifactorial interventions were used and it may therefore be difficult to tease out the relevance of the legacy effect of reducing glucose.
The long term importance of optimizing glycaemic control in patients with type 2 diabetes has been well documented with respect to reduction of the risk of microvascular complications. However, the importance for the risk of macrovascular complications has been debated. In the ADVANCE trial (*The ADVANCE Collaborative Group (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358:2560–25728*) patients randomized to intensive glucose control had a mean glycated hemoglobin level that was 0.8% lower than that in the standard-control group. They had a reduction in major microvascular events of 14% (95% confidence interval [CI], 3 to 33) but a nonsignificant reduction in major macrovascular events of only 6% (95% CI, −6 to 16) after a median of 5 years of follow-up. Also in the ACCORD trial (*The Action to Control Cardiovascular Risk in Diabetes Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358:2545–2559*) there was a nonsignificant reduction of 10% in the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes among 10,251 patients with type 2 diabetes who were assigned either to a group with a target glycated hemoglobin level of less than 6.0% or to a group with a target level of 7.0 to 7.9%. In addition, when the results of more recent (positive) cardiovascular outcome trials have been analysed, it has often been put forward that the benefit is not only based on the lowering of blood glucose.
In conclusion, current knowledge cannot undisputedly support the clinical relevance of reducing blood glucose as fast as possible in newly diagnosed patients with type 2 diabetes.

Secondary efficacy results

Key secondary endpoints

Rate of loss of glycaemic control

The rate of loss of glycaemic control, assessed by the annualised slope of HbA1c over time from Week 26 to end of Period 1, was carried out using a linear mixed effect model including treatment approach and region as factors, baseline HbA1c and time of HbA1c measurement as covariates and interaction of treatment approach by time. The model assesses the rate of loss of function as a mathematical estimate of annualised slope of HbA1c.

A reduction in rate of loss of glycaemic control, assessed by the annualized slope of HbA1c over time from Week 26 to end of Period 1, was observed in the early combination group compared to the monotherapy group (for FAS: adjusted mean rate of change in HbA1c per year: −0.02, 95% CI [−0.05, 0.00]; one-sided p=0.042). Similar results were observed for the Per Protocol Set (PPS).

Table 5 Analysis of rate of loss in glycaemic control during Period 1 (FAS and PPS)

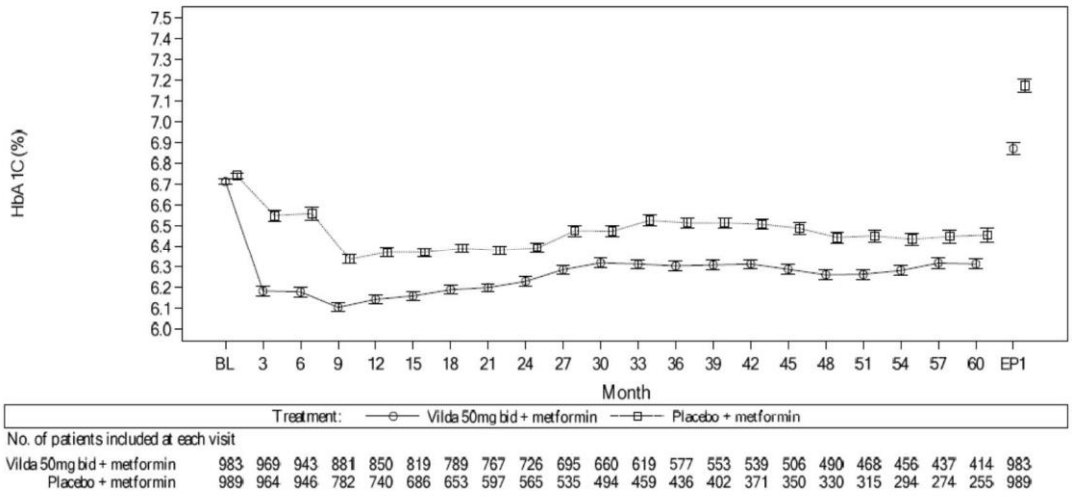
Analysis set Treatment approach	n	Adjusted mean rate of loss (SE)	Slope difference Adjusted mean rate of loss (SE)	(95% CI)	p-value
FAS					
Vilda 50mg bid + metformin (N=983)	961	0.24 (0.01)	-0.02 (0.01)	(-0.05, 0.00)	0.042
Placebo + metformin (N=989)	955	0.27 (0.01)			
PPS					
Vilda 50mg bid + metformin (N=919)	911	0.25 (0.01)	-0.03 (0.01)	(-0.06, 0.00)	0.034
Placebo + metformin (N=931)	914	0.28 (0.01)			

The slope of HbA1c deterioration from week 26 was slightly lower for those receiving the combination therapy versus monotherapy, but the clinical relevance of the magnitude of the effect is difficult to understand. In the opinion of the MAH, the methodology used for the analyses was not optimal in a study design setting mandating rescue medication and, therefore, not applicable for assessment of loss of beta cell function.

Analysis in HbA1c over time

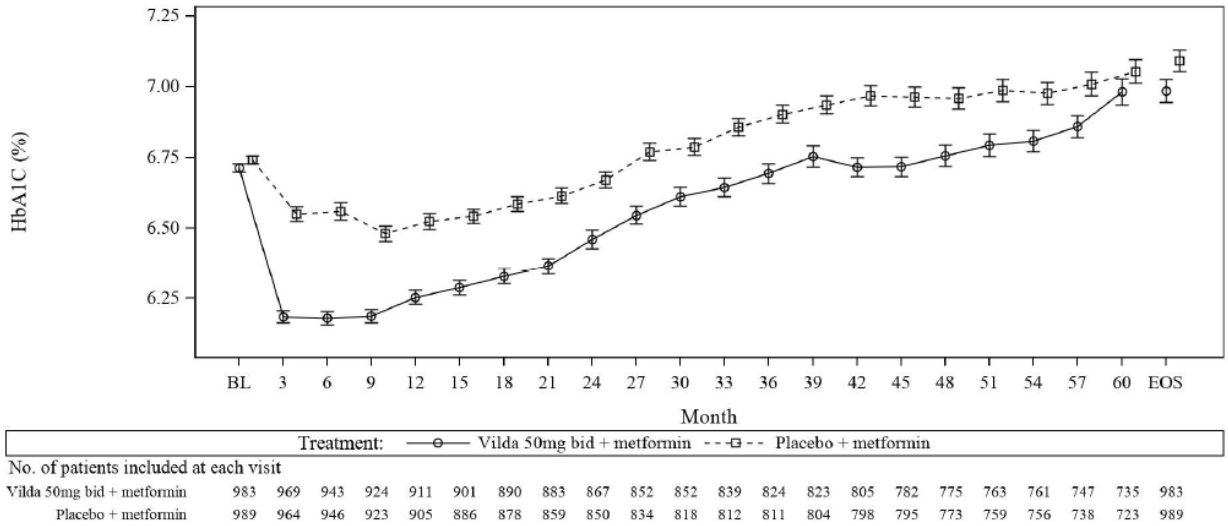
Graphical displays for HbA1c over time for Period 1 are presented in **Error! Reference source not found.** (FAS). Starting from similar baseline values, there was a faster reduction in HbA1c values in patients in the combination group compared to patients in the monotherapy group. Due to the study design, any graphical presentation of HbA1c values per period will display a 'survivor population' pattern as those without a glycaemic response are rescued to the next period.

Figure 4 Mean HbA1c (%) by treatment approach and visit, on HbA1c data collected up to the end of Period 1 (Full Analysis Set)



EPI=end of period 1

Figure 5 Mean HbA1c (%) by treatment approach and visit, on HbA1c data collected up to the end of study (Full Analysis Set)



EOS=end of study

A descriptive analysis in HbA1C over time was performed; from baseline to end of period 1, as well as data collected during the entire study (**Figure *5***). In the analysis on HbA1c data collected during the entire study, HbA1c mean values were in the end of the study increased towards 7% in both treatment groups and were less differentiated.

Time to second treatment failure

The time to secondary glycaemic failure (defined as two consecutive HbA1c readings above or equal to 7.0%, 13 weeks apart, after confirmed initial treatment failure) was assessed in a post-hoc analysis. The time to secondary failure defined the time to insulin initiation when all patients were receiving vildagliptin combination in Period 2.

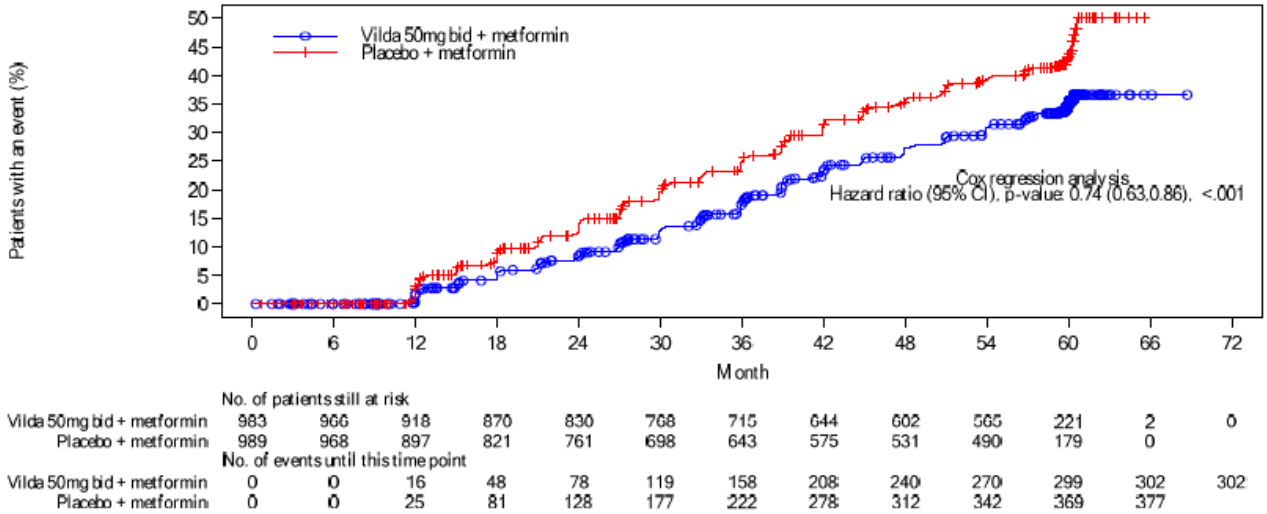
The relative risk for time to second treatment failure by HbA1c threshold during Period 2 was significantly reduced by the early treatment combination strategy vs. monotherapy group (HR [95% CI]: 0.74 [0.63, 0.86], p<0.0001).

Kaplan-Meier estimates of the probability of second treatment failure (i.e. after Period 1 and up to end of Period 2) over time are graphically displayed in **Figure 6**.

Table 6 Cox regression analysis of time to treatment failure after period 1 and up to period 2 (FAS)

Treatment approach	n/N' (%)	Hazard Ratio (95% CI)	p-value
Vilda 50mg bid + metformin (N=983)	302/ 983 (30.7)	0.74 (0.63, 0.86)	<.001
Placebo + metformin (N=989)	377/ 989 (38.1)		

Figure 6 KM plot for time to second treatment failure (after Period 1 and up to Period 2) (FAS)



Time to second treatment failure (defined as ≥7.0% at two consecutive measurements, 13 weeks apart, after confirmed initial treatment failure) was added as a *post-hoc analysis and a protocol amendment to be included in the CSR*. It was questioned how to interpret data considering that the study was not double-blind in this part of the study. The MAH considered that the results indicate that the introduction of the early combination therapy provides unique benefits which cannot be attained after sequential introduction of combination therapy after initial metformin therapy failure. This needed to be further discussed and justified. Time to insulin initiation was analysed as an exploratory endpoint but (surprisingly) there was no difference between the combination and the monotherapy groups in time to insulin from Baseline (HR [95%CI]: 1.04 [0.81, 1.33]; p=0.759).

Considering the timing for the addition of time to second treatment failure as an endpoint, the MAH explained that progression of HbA1c from 26 weeks after the start of Period 2 to the end of Period 2 was part of the protocol and reported in the CSR among the secondary objectives. While this is acknowledged, the corresponding variable to be analysed was defined in terms of rate of loss in glycaemic control in HbA1c, i.e. not as a time-to-event endpoint which was analysed post-hoc. It is therefore understood that both the endpoint and its analysis were defined post-hoc, i.e. after the DBL. The MAH has clarified that 70% of patients in the early combination group who had initial treatment failure actually failed during period 2. This makes sense since they did not get any additional treatment in period 2. The corresponding number in monotherapy group was 61%. These groups are, however, not randomized, and comparison not straightforward. The main question is whether this prolongation of loss of glycaemic control is of relevance for the risk of micro-and macro vascular complications.

Exploratory efficacy results

Change of β-cell function over time

The β-cell function assessed by homeostasis model assessment for the β-cell (HOMA-B). The results of the analysis of rate of change of ß-cell function over time (slope of AUC of ISR/G) in subjects in the meal-test subset are summarized in **Table 7**. Overall, a significant reduction in the slope from Week 13 to end of study was observed among those (n=228) individuals randomized to receive early combination approach vs. those (n=227) in the initial metformin group (slope difference: -0.58, 95% CI: -0.99, -0.17; p=0.006). As expected, there was no difference in the adjusted mean rate of change (slope difference: -0.08, 95% CI: -0.53, 0.38; p=0.744) between groups among patients with a glycaemic response in Period 1. From Week 13 to end of Period 2, a statistically significant difference in the adjusted mean rate of change was observed (slope difference: -0.50, 95% CI: -0.91, -0.09; p=0.017).

Table 7 Analysis of rate of change of ß-cell function over time (FAS, meal-test subset)

Time period Treatment approach	n	Adjusted mean rate of change (SE)	Slope difference Adjusted mean rate of change (SE)	(95% CI)	p-value
From Week 13 to end of Period 1					
Vilda 50mg bid + metformin (N=228)	201	-0.60 (0.15)	-0.08 (0.23)	(-0.53, 0.38)	0.744
Placebo + metformin (N=227)	202	-0.53 (0.18)			
From Week 13 to end of Period 2					
Vilda 50mg bid + metformin (N=228)	202	-0.93 (0.14)	-0.50 (0.21)	(-0.91, -0.09)	0.017
Placebo + metformin (N=227)	204	-0.43 (0.15)			
From Week 13 to end of study					
Vilda 50mg bid + metformin (N=228)	202	-1.04 (0.15)	-0.58 (0.21)	(-0.99, -0.17)	0.006
Placebo + metformin (N=227)	204	-0.46 (0.15)			

Change of insulin sensitivity over time

The results of the analysis of rate of change of insulin sensitivity over time (slope of OGIS) in subjects in the meal-test subset are summarized in **Table 8**. OGIS is an index of insulin sensitivity in dynamic conditions, which predicts glucose clearance by a model-derived formula from the OGTT glucose and insulin concentrations. Statistically significant differences between the combination group over those in the monotherapy in the adjusted mean rate of change were observed for all 3 treatment periods: from Week 13 to end of Period 1 (slope difference -5.03, 95% CI: -9.26, -0.79; p=0.020), end of Period 2 (slope difference: -5.08, 95% CI: -8.46, -1.69; p=0.003), and to end of study (slope difference: -5.38, 95% CI: -8.61, -2.16; p=0.001).

Table 8 Analysis of rate of change of insulin sensitivity over time (FAS, meal-test subset)

Time period Treatment approach	n	Adjusted mean rate of change (SE)	Slope difference Adjusted mean rate of change (SE)	(95% CI)	p-value
From Week 13 to end of Period 1					
Vilda 50mg bid + metformin (N=228)	189	-4.61 (1.38)	-5.03 (2.16)	(-9.26, -0.79)	0.020
Placebo + metformin (N=227)	193	0.41 (1.66)			
From Week 13 to end of Period 2					
Vilda 50mg bid + metformin (N=228)	190	-6.07 (1.20)	-5.08 (1.73)	(-8.46, -1.69)	0.003
Placebo + metformin (N=227)	194	-0.99 (1.24)			
From Week 13 to end of study					
Vilda 50mg bid + metformin (N=228)	190	-6.39 (1.15)	-5.38 (1.64)	(-8.61, -2.16)	0.001
Placebo + metformin (N=227)	194	-1.01 (1.17)			

Change in body weight

ANCOVA results for change from Baseline in body weight are summarized in **Table 9**. Initially, the mean (SE) body weight were 85.44 (0.57) kg and 84.82 (0.54) kg for the combination and monotherapy groups, respectively. From Baseline to the end of Period 1, a trend toward a decrease was observed in both treatment groups; however, mean changes were small (-0.32 kg in the combination group and -0.74 kg in the monotherapy group)

Table 9 ANCOVA results for change in body weight (kg) from baseline to endpoint by treatment approach (FAS)

Endpoint Treatment approach	n	Baseline mean (SE)	Adjusted mean change (SE)	Difference in adjusted mean change (Vilda 50mg bid + metformin) - (Placebo + metformin) mean (SE)	(95% CI)	p-value
End of Period 1						
Vilda 50mg bid + metformin (N=983)	983	85.44 (0.57)	-0.32 (0.32)	0.42 (0.22)	(-0.00, 0.85)	0.052
Placebo + metformin (N=989)	988	84.82 (0.54)	-0.74 (0.32)			
End of Period 2						
Vilda 50mg bid + metformin (N=983)	983	85.44 (0.57)	-0.82 (0.35)	0.27 (0.24)	(-0.21, 0.75)	0.268
Placebo + metformin (N=989)	988	84.82 (0.54)	-1.09 (0.35)			
End of study						
Vilda 50mg bid + metformin (N=983)	983	85.44 (0.57)	-0.91 (0.36)	0.26 (0.25)	(-0.22, 0.75)	0.289
Placebo + metformin (N=989)	988	84.82 (0.54)	-1.17 (0.36)			

There were minor reductions in body weight body in both treatment groups and a slightly larger reduction in the metformin monotherapy group compared with the early treatment group; although not statistically significant.

Change in HOMA-B from baseline to endpoint

ANCOVA results for change in β-cell function assessed by HOMA-B. The mean (SE) baseline index values of HOMA-B were indicative of a relatively good basal beta cell functionality in both treatment approach groups: 120.11 (3.49) and 114.11 (3.20) for those in the early combination and monotherapy groups, respectively. From Baseline to the end of Period 1, independent of the time to initial treatment failure, an increase of 17.21 (9.04) in HOMA-B value was observed in the combination group while the HOMA-B value decreased by 2.02 (9.02) among those receiving metformin monotherapy only. The difference in adjusted mean change from Baseline to end of Period 1 between the combination and the monotherapy group was statistically significant (difference: 19.23 (5.51), 95% CI: 8.42, 30.03; p<0.001).

The HOMA-B value after a confirmed failure continuing on the combination therapy from Baseline to end of Period 2: a mean increase of 10.66 (9.09) in HOMA-B value was observed from Baseline until end of Period 2. Similarly, addition of vildagliptin to the failing metformin monotherapy maintained the beta cell functionality in Period 2 (mean change in HOMA-B value, 0.84 (8.99), indicating no further decline during this period). The difference in adjusted mean change from Baseline to end of Period 2 between the two treatment approaches was now diluted and did not reach statistical significance (difference: 9.83, 95% CI: -0.61, 20.26; p=0.065).

Change in β-cell function was assessed by HOMA-B. The difference in mean change in HOMA-B was improved in the early combination group versus the metformin monotherapy group from baseline to end of period 1; however, the difference between the groups to the end of period 2 and to the end of the study, respectively, was not statistically significant.

Change in HOMA-IR from Baseline to endpoint

The mean (SE) baseline index values of 6.19 (0.18) and 5.97 (0.20) for the early combination and initial metformin monotherapy treatment approach groups, respectively, indicated presence of early, clinically significant insulin resistance in both groups at the time of diabetes diagnosis. From Baseline to the end of Period 1, independent of the time to initial treatment failure, similar, incremental increases in insulin resistance were observed in both treatment groups (adjusted mean index value change of 1.28 (0.44) in the combination group and 1.23 (0.44) in the monotherapy group, difference: 0.05, 95% CI: -0.47, 0.58; p=0.842). Among those who initially received metformin monotherapy, the mean adjusted increase in insulin resistance from Baseline to end of Period 2 was higher, HOMA-IR value of 1.84 (0.58) vs 1.33 (0.59) among those in the early combination treatment group while the difference between the groups did not reach statistical significance (difference: -0.51, 95% CI: -1.19, 0.17; p=0.142). Overall, despite the differences in glycaemic outcomes, the HOMA-IR index values continued to increase in both treatment approach groups from Baseline to the end of study; the mean adjusted change in 5 years was 2.10 (0.80) vs 2.17 (0.79) for the early combination and initial metformin groups, respectively (difference: -0.07, 95% CI: -0.99, 0.85; p=0.887).

Change in insulin resistance was assessed by HOMA-IR. The observed glycaemic durability in patients in the early treatment strategy group cannot be explained by any favourable changes in insulin sensitivity as measured by HOMA-IR index. Overall, neither of the treatment groups seem to be slowing down the incrementally progressive insulin resistance.

Change in total retinal micro-aneurysm count from Baseline to selected visits

In a subgroup of patients (n=162), change in total retinal micro-aneurysm count from Baseline to Year 4 (Week 208 visit) and Year 5 (Week 260 visit) was assessed. ANCOVA results are presented in **Table 10**.

Table 10 ANCOVA results for change in total retinal micro-aneurysm count from baseline to selected visits by treatment approach (FAS, retinal micro-aneurysm count subset)

Endpoint Treatment approach	n	Baseline mean (SE)	Adjusted mean change (SE)	Difference in adjusted mean change (Vilda 50mg bid + metformin) - (Placebo + metformin) mean (SE)	(95% CI)	p-value
Year 4						
Vilda 50mg bid + metformin (N=75)	27	0.63 (0.21)	-0.18 (0.19)	0.10 (0.32)	(-0.53, 0.74)	0.746
Placebo + metformin (N=87)	15	0.73 (0.42)	-0.28 (0.25)			
Year 5						
Vilda 50mg bid + metformin (N=75)	25	0.56 (0.21)	-0.04 (0.23)	-0.49 (0.34)	(-1.17, 0.20)	0.162
Placebo + metformin (N=87)	20	0.45 (0.31)	0.45 (0.25)			

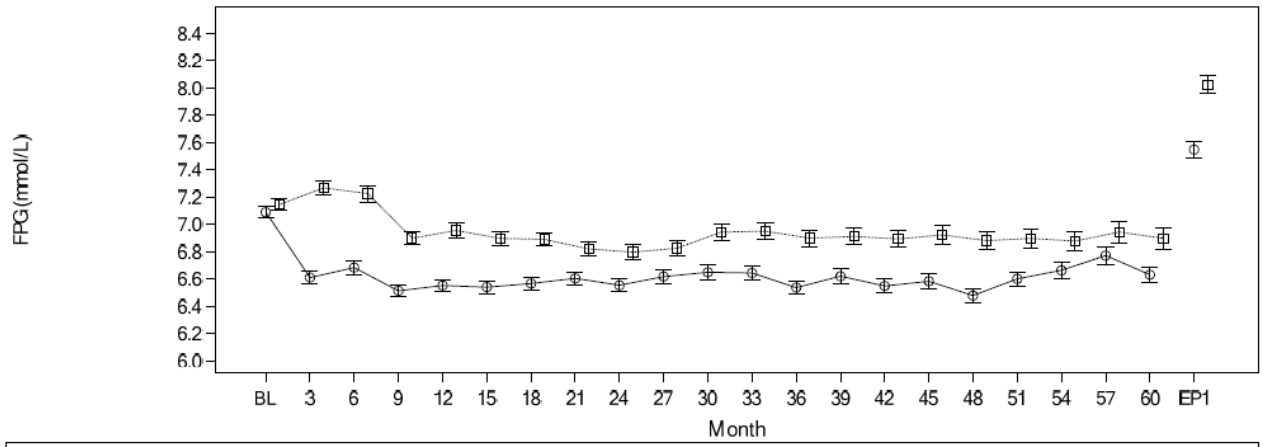
Change in total retinal micro-aneurysm was assessed in a subgroup of patients (n=162). However, the number of patients dropped and were few at year 4 (n=42) and year 5 (n=45), respectively, wherefore difficult to draw any firm conclusions (not statistically significant).

Change from Baseline in FPG

At all post-Baseline visits, decreases in FPGe were observed in the combination group, whereas either no decrease or increases (especially in the later phase of Period 1) were observed in the monotherapy group. Consistent differences favoring combination therapy over monotherapy was observed throughout the entire Period 1.

Absolute value and change from Baseline in FPG (mmol/L) by treatment approach and visit, using data collected up to the end of Period 2 is graphically presented in **Figure 7**. The differences in change from Baseline during Period 2 when all patients were now receiving vildagliptin as well as up to end of study (**Figure 8**) were generally smaller than observed in Period 1.

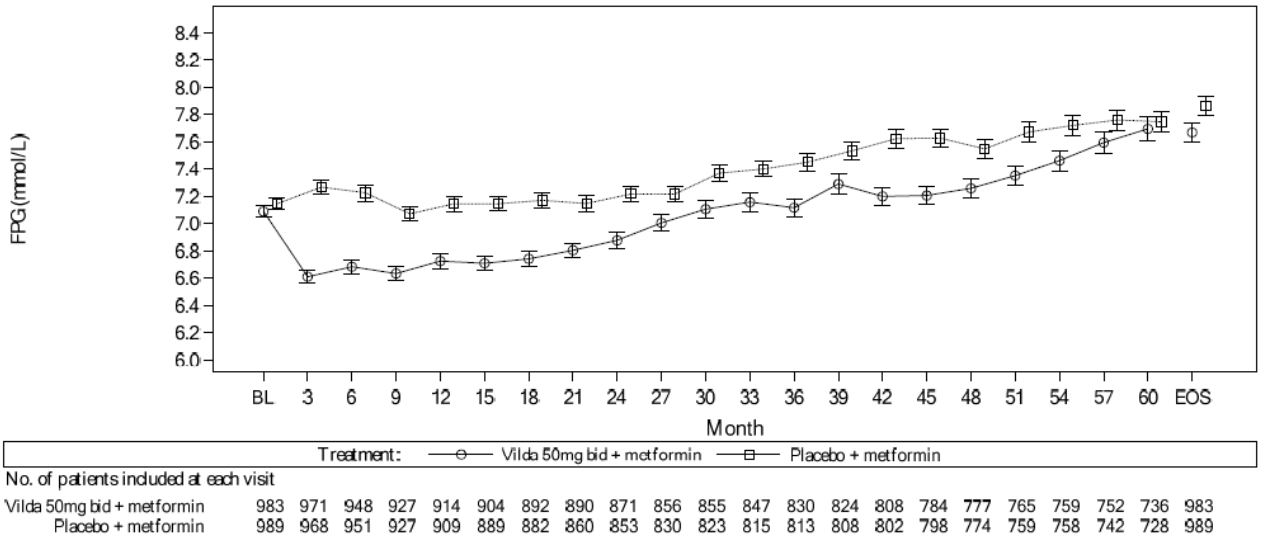
Figure 7 Mean FPG (mmol/L) by treatment approach and visit, on FPG data collected up to the end of Period 2 (FAS)



No. of patients included at each visit

Vilda 50mg bid + metformin	983	971	948	884	853	822	791	771	727	698	663	625	582	553	541	509	494	468	454	440	414	983
Placebo + metformin	989	968	951	787	739	690	657	597	566	532	495	460	435	403	374	352	331	315	295	275	257	989

Figure 8 Mean FPG (mmol/L) by treatment approach and visit, on FPG data collected up to the end of study (FAS)



Differences in change from baseline in FPG up to end of study (when comparing metformin and early added vildagliptin versus metformin and later added vildagliptin) were smaller than observed from baseline to end of period 1 (when comparing early combination treatment and metformin monotherapy).

Overall, the preliminary results of all the exploratory efficacy analyses provided some indicative support of maintained beta-cell function and delayed loss of insulin sensitivity with early combination intervention; however, the MAH has clarified that preliminary results of the exploratory analyses will require more refined and sophisticated methodology outside this CSR. As for example, it is claimed that a more detailed analysis of clinically relevant changes in beta cell functionality by iHOMA2 model are necessitated to understand in the role of improved beta cell function.

Health-related quality of life assessments

Change in EQ-5D score, a measure of quality of life, from baseline to endpoint were generally small and not consistent in both treatment groups, and there were no major differences between treatment groups in EQ-5D score at any time point.

For Visual Analog Scale measurement, a trend toward an increase (improvement) was observed in both treatment groups; changes were generally small and were similar in both treatment groups.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial CLAF237A23156 (VERIFY)

Title: 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	
Study identifier	CLAF237A23156 (EudraCT no. 2011-003712-23)

Design	Multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period. Following a screening visit (Visit 1) and a screening period of up to 2 weeks, treatment-naïve patients, meeting all eligibility criteria entered the run-in period at Visit 2. Patients who were able to tolerate a total metformin dose of at least 1000 mg and up to 2000 mg daily proceeded to randomization and started in Period 1 to receive one the following study regimens: • Metformin up to 1000 mg bid plus vildagliptin 50 mg bid or • Metformin up to 1000 mg bid plus matching placebo bid. When entering period 2, patients who were randomized to the placebo arm in Period 1 received vildagliptin 50 mg bid. If, during Period 2, therapy intensification was required in accordance with the local guidelines, the patient entered Period 3 to be initiated on open-label insulin.		
	Screening period: Duration of Run-in phase: Duration of main phase:		up to 2 weeks 3-weeks up to 5 years
Hypothesis	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%) is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy		
Treatments groups	Metformin bid + vildagliptin		up to 1000 mg bid + 50 mg bid
	Metformin bid + placebo		up to 1000 mg bid
Endpoints and definitions	Primary endpoint	Time to initial treatment failure	Time to confirmed initial treatment failure, defined as the time from randomization to the second of two consecutive scheduled visits, at which HbA1c ≥ 7.0% was measured, starting from Visit 4 (13 weeks after randomization), i.e. the end of Period 1.
	Secondary endpoints	Rate of loss in glycemic control over time	Testing the hypothesis that the rate of loss in glycemic control over time (estimated annualized slope of HbA1c over time using a random coefficient model or by threshold) is lower with the combination vildagliptin + metformin vs metformin alone.
		Progression of HbA1c	Progression of HbA1c from 26 weeks after the start of Period 2 to the end of Period 2 assessed by rate of loss in glycemic control over time
		Progression of FPG	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.
		HbA1c change	Change in HbA1c
		AEs	Safety and tolerability
		ISR/(AUCglucose(0-2h))	In a subgroup of patients β-cell function assessed by insulin secretion rate (ISR)/glucose area under the curve (AUCglucose(0-2h)) during a standard meal-test at indicated time-points
		OGIS	In a subgroup of patients Insulin resistance assessed by oral glucose insulin sensitivity (OGIS) during a standard meal-test at indicated time-points
Database lock	May 10, 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Full analysis set (FAS); All randomized patients who received at least one dose of randomized study medication (vildagliptin or placebo) and had at least one post-randomization assessment of any efficacy parameter. Following the ITT principle, patients were analysed according to the treatment assigned to at randomization. Per protocol set (PPS); A subset of FAS that consisted of all randomized patients who received at least one dose of randomized study medication (vildagliptin or placebo), had at least one post-randomization assessment of any efficacy parameter in Period 1, did not discontinue the study prior to Week 26, and had no major protocol deviations occurring during Period 1.		
Descriptive statistics and estimate variability	Treatment group	Metformin bid + vildagliptin	Metformin bid + placebo
	Number of subjects	983 (FAS) 919 (PPS)	989 (FAS) 931 (PPS)
	Time to initial treatment failure (months)	61.9	36.1
	Median, IQR	29.9, NE	15.3, NE
	Incidence of initial treatment failure (%)	43.6 (FAS) 44.7 (PPS)	62.1 (FAS) 64.2 (PPS)
Effect estimate per comparison	Initial treatment failure	Comparison groups	Metformin bid + vildagliptin vs Metformin bid + placebo
		HR	0.51 (FAS) 0.50 (PPS)
		95% CI	0.45, 0.58 (FAS) 0.44, 0.57 (PPS)
		P-value	<0.001 (FAS, PPS)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Full analysis set (FAS) Per protocol set (PPS)		
Descriptive statistics and estimate variability	Treatment group	Metformin bid + vildagliptin	Metformin bid + placebo
	Number of subjects	983 (FAS; Per.1) 410 (FAS; Per.2)	989 (FAS; Per.1) 588 (FAS; Per.2)
	Rate of loss in glycemic control over time (adjusted mean)	0.24 (FAS) 0.25 (PPS)	0.27 (FAS) 0.28 (PPS)
	SE	0.01 (FAS), 0.01 (PPS)	0.01 (FAS), 0.01 (PPS)
	Progression of HbA1c (adjusted mean)	1.11 (FAS)	1.02 (FAS)
	SE	0.15	0.12
	Progression of FPG (adjusted mean)	0.25 (FAS; end of Per.1) 1.27 (FAS; end of Per.2)	0.26 (FAS; end of Per.1) 1.27 (FAS; end of Per.2)
	SE	0.01 (end of Per.1) 0.25 (end of Per.2)	0.01 (end of Per.1) 0.19 (end of Per.2)
	HbA1c change (mean)	0.16 (FAS; end of Per.1) 0.16 (PPS; end of Per.1) 0.32 (FAS; end of Per.2) 0.27 (FAS; end of study)	0.43 (FAS; end of Per.1) 0.45 (FAS; end of Per.1) 0.43 (FAS; end of Per.2) 0.35 (FAS; end of study)
	SE	0.029 (FAS; end of Per.1) 0.030 (PPS; end of Per.1) 0.040 (FAS; end of Per.2) 0.040 (FAS; end of study)	0.029 (FAS; end of Per.1) 0.030 (PPS; end of Per.1) 0.039 (FAS; end of Per.2) 0.037 (FAS; end of study)
	Safety and tolerability (n with AEs, %)	83.5% (AE) 16.6% (SAE) 1.1% (hypoglycemic event	83.2% (AEs) 18.3% (SAEs) 0.6% (hypolgycemic event)

	Number of subjects	228 (FAS; meal-test subset)	227 (FAS; meal-test subset)
	ISR/(AUCglucose (0-2h)) change (adjusted mean, ANCOVA)	-0.98 (end of Per.1) -2.10 (end of Per.2) -2.26 (end of study)	-3.67 (end of Per.1) -3.65 (end of Per.2) -3.60 (end of study)
	SE	1.10 (end of Per.1) 1.18 (end of Per.2) 1.23 (end of study)	1.08 (end of Per.1) 1.14 (end of Per.2) 1.19 (end of study)
	OGIS change (adjusted mean, ANCOVA)	3.05 (end of Per.1) -3.50 (end of Per.2) -3.15 (end of study)	-7.25 (end of Per.1) -8.36 (end of Per.2) -8.38 (end of study)
	SE	8.11 (end of Per.1) 8.32 (end of Per.2) 8.32 (end of study)	7.94 (end of Per.1) 8.04 (end of Per.2) 8.04 (end of study)
Effect estimate per comparison		Comparison groups	Metformin bid + vildagliptin vs Metformin bid + placebo
	Rate of loss in glycemic control over time (slope difference)	Adjusted mean (SE)	-0.02 (0.01) [FAS] -0.03 (0.01) [PPS]
		95% CI	-0.05, 0.00 [FAS] -0.06, 0.00 [PPS]
		P-value	0.042 [FAS] 0.034 [PPS]
	Progression of HbA1c (slope difference)	Adjusted mean (SE)	0.09 (FAS)
		95% CI	-0.29, 0.47 (FAS)
		P-value	0.635 (FAS)
	Progression of FPG	Adjusted mean (SE)	-0.01 (0.02) [end of Per.1] 0.28 (0.32) [end of Per.2]
		95% CI	(-0.05, 0.02) [end of Per.1] (-0.35, 0.90) [end of Per.2]
		P-value	0.530 [end of Per.1] 0.381 [end of Per.2]
	ISR/(AUCglucose(0-2h)) change difference (mean)	Adjusted mean (SE)	2.69 (0.82) [end of Per.1] 1.55 (0.93) [end of Per.2] 1.34 (0.96) [end of study]
		95% CI	(1.08, 4.30) [end of Per.1] (-0.27, 3.37) [end of Per.2] (-0.56, 3.23) [end of study]
		P-value	0.001 [end of Per.1] 0.095 [end of Per.2] 0.166 [end of study]
	OGIS change (mean)	Adjusted mean (SE)	10.31 (6.10) [end of Per.1] 4.86 (6.59) [end of Per.2] 5.23 (6.59) [end of study]
		95% CI	(-1.69, 22.30) [end of Per.1] (-8.09, 17.82) [end of Per.2] (-7.72, 18.18) [end of study]
		P-value	0.092 [end of Per.1] 0.461 [end of Per.2] 0.428 [end of study]

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The VERIFY study was a double-blind, randomised trial conducted in treatment-naïve patients with T2DM to evaluate the glycaemic durability of the initiation of an early combination of metformin and vildagliptin

(n=998) against initial standard-of-care metformin monotherapy (n=1,103) followed by sequential addition of vildagliptin in patients losing glycaemic control, during a 5-year treatment period.

The mean duration of diabetes in the study population was 6.4 months. Patients were treatment naïve or had received anti-diabetic medication cumulatively for not more than 3 months but not received any antidiabetic treatment within 3 months prior to Visit 1. However, patients who had initiated metformin within 1 month prior to Visit 1 and took a total daily dose of maximum 2000mg metformin at Visit 1 could also be included. Approximately 40% of patients had previously used metformin.
HbA1c at visit 1 should be ≥6.5% and ≤7.5%. It can be questioned if the total study population was treatment naïve, but they still represented a population for which the full effect of metformin monotherapy had not been exhausted (i.e. a population not covered by the currently approved indication for vildagliptin).

Statistical plan

The planned analyses in general were found appropriate. For the primary analysis, patients who discontinued the study for any reason during Period 1 were censored; however, it is unclear how treatment discontinuations and any rescue medications were handled. Sensitivity analyses on request, where treatment discontinuations and rescue medication intake (if any) are censored or imputed as treatment failures, were supportive of the primary endpoint results.

The primary statistical hypothesis of superiority of the combination treatment versus metformin was tested on alpha level of 2.5% (1-sided). One-sided superiority tests are not conventional for confirmatory trials but may be acceptable for the assessment of the study results. However, p-values from 2-sided tests are expected to be presented in the SmPC, particularly when the test results are not statistically compelling.

Substantial changes have been made in the planned analyses concerning the primary efficacy endpoint. Two primary efficacy variables were initially planned: time to initial treatment failure and rate of loss of glycaemic control over time. Definition of the initial treatment failure had been changed during the course of the study. After study completion (and unclear if prior to the database lock) the statistical analysis plan was updated to remove the loss of glycaemic control as primary endpoint. These changes have been described in the submitted documentation, but without a clear rationale. Considering that the rate of loss of glycaemic control over time is not statistically significant, it may be suspected that the change of the primary endpoints was data driven and the study integrity undermined. The MAH has assured that removal of the loss of glycaemic control as primary endpoint was not data driven. The main arguments for the change were to focus on a clinically interpretable and predictable measure, and, considering its clinical importance, to enable a full alpha allocation initially.

Time to second treatment failure has been added as a post-hoc endpoint in the CSR but was not mentioned in the final SAP nor in the amended protocol version 4. It is understood that both the endpoint and its analysis were defined post-hoc.

It was noted that the primary efficacy analysis presented by HR has been interpreted in terms of relative risk, which is not statistically correct. The interpretation was reworded in the SmPC section 5.1.

Efficacy data and additional analyses

The study met its primary objective, to demonstrate the superiority of early combination of vildagliptin 50mg bid and metformin over metformin monotherapy by testing the hypothesis that the risk of confirmed initial treatment failure (defined as HbA1c ≥ 7.0% at two consecutive measurements) is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy.

However, the clinical relevance of this result is not obvious considering that as soon as a patient fails on metformin monotherapy, several other treatment options are readily available, and in fact, at the end of study, HbA1c was very similar in the two study groups. The clinical relevance is also not fully supported by literature data or by the recommendations from learned societies.

To further assess the benefit of initial combination compared to sequentially added vildagliptin an analysis of a second treatment failure was performed as a post hoc analyses in period 2 of the study. The RR for time to second treatment failure during period 2 of the study was significantly reduced in the combination treatment group compared with the sequential metformin treatment; HR 0.74 [95% CI 0.63, 0.86; p<0.001]. Thus, even if both groups now were receiving the same treatment, patients in the initial combination group had a longer time to treatment failure. However, also in this situation, additional treatments are available which was also reflected in the study with the introduction of insulin treatment in patients with second treatment failure.

Key secondary endpoints were rate of loss of glycaemic control, assessed by the annualized slope of HbA1c over time from week 26 to end of period 1, and change from baseline in HbA1c during the study. A slight reduction in rate of loss of glycaemic control (−0.02, 95% CI [−0.05, 0.00]; one-sided p=0.042) was observed in the early combination group compared with the monotherapy group, but the clinical relevance is not easily understood. The HbA1c values remained consistently lower in the combination group compared with the monotherapy group up to the end of period 1, but as mentioned above, at end of study the results were rather similar in both groups.

The preliminary results of all the exploratory efficacy analyses provided some indicative support of maintained beta-cell function and delayed loss of insulin sensitivity with early combination intervention; however, the MAH considers that preliminary results of the exploratory analyses will require more refined and sophisticated methodology outside this CSR.

There were minor reductions in body weight body in both treatment groups and a slightly larger reduction in the metformin monotherapy group compared with the early treatment group; although not statistically significant.

Change in total retinal micro-aneurysm count was assessed as an exploratory analysis in a subgroup of patients (n=162). However, the number of patients dropped and were few at year 4 (n=42) and year 5 (n=45), respectively, wherefore difficult to draw any firm conclusions (not statistically significant).

2.4.3. Conclusions on the clinical efficacy

The guidelines for management of hyperglycaemia in type II diabetes recommends metformin as first-line choice of therapy with sequential addition of other oral antidiabetic drugs. The VERIFY study has been performed with the aim to show that the risk of initial treatment failure is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy in a patient population with newly diagnosed type 2 diabetes.

The VERIFY study met its primary endpoint; the provided data show that early combination therapy with metformin and vildagliptin was superior to metformin monotherapy with regards to initial treatment failure (defined as HbA1c ≥ 7.0% at two consecutive analyses) in patients with recent onset of diabetes with mild hyperglycaemia. Also, the post hoc analyses time to second treatment failure was significantly reduced in the early combination group compared with metformin and sequentially added vildagliptin.

Based on the results of this study, the MAH has proposed to extend the indication to include "initial combination of vildagliptin and metformin, when diabetes is not adequately controlled by diet and exercise alone" in section 4.1. However, the clinical relevance of initial combination therapy in patients with newly diagnosed type 2 diabetes is not fully supported by literature data or by the recommendations

from learned societies. Therefore the CHMP did not agree to include "include initial combination therapy" in section 4.1. of the SmPC. but agreed to reflect the results of the "VERIFY" in section 5.1. of the SmPC. The CHMP proposed wording was agreed by the MAH.

The MAH also applied to change the wording in section 4.1. of the SmPC with regards to the use of vildagliptin in combination with other glucose lowering agents i.e. to make a general cross-reference to section 5.1. of combination use instead of reflecting specific combinations in section 4.1. This is in line with the wording of other oral anti-diabetic drugs and has been agreed by the CHMP.

2.5. Clinical safety

Patient exposure

Subject exposure

Mean exposure to study medication was similar in both treatment groups (53.6 months in the early combination therapy group and 52.4 months in the monotherapy group; median exposure was 59.8 months for both arms) (**Table 11**). Also, for exposure categories for the entire study duration a similar pattern was observed in both treatment groups.

The duration of Period 1 was significantly longer in patients in the early combination therapy group (i.e., who remained at their initially assigned treatment) compared to patients in the monotherapy group (median duration 50.8 vs. 30.1 months, respectively). Also, the proportion of patients who remained at their initial therapy over the entire 5-year study duration was significantly higher in the early combination therapy group compared to the monotherapy group (≥57 months: 46.5% vs 28.5%).

About 81.3% of patients in the early combination therapy group and 78.5% patients in the monotherapy group have completed the entire 5-year study period. The median exposure was 59.8 months in both groups.

Total subject exposure

For the entire study period, the exposure to study drug was comparable (4456 subject years in the early combination group and 4376 subject years in the monotherapy group). For Period 1, subject year exposure to study drug was higher in the early combination group than in the monotherapy group (3453 vs. 2724 subject years).

Since patients in the early combination group received vildagliptin from the start of the study, the higher subject year exposure over the entire study period for this group is expected (4457 subject years vs. 1631 subject years in the monotherapy group).

Table 11 Duration of exposure to study drug during the treatment period (Periods 1, 2 and 3) by treatment approach (RAN) Period: Treatment period (Periods 1, 2 and 3)

Duration in months	Vilda 50mg bid + metformin N=998	Placebo + metformin N=1003	Total N=2001
Exposure to study medication			
n	998	1003	2001
Mean	53.6	52.4	53.0
SD	15.32	16.94	16.16
Min	0.0	0.0	0.0
Median	59.8	59.8	59.8
Max	75.6	66.2	75.6
Exposure categories - n (%)			
0 - < 3 months	20 (2.0)	24 (2.4)	44 (2.2)
3 - < 6 months	14 (1.4)	15 (1.5)	29 (1.4)
6 - < 9 months	11 (1.1)	23 (2.3)	34 (1.7)
9 - < 12 months	16 (1.6)	21 (2.1)	37 (1.8)
12 - < 15 months	6 (0.6)	5 (0.5)	11 (0.5)
15 - < 18 months	5 (0.5)	13 (1.3)	18 (0.9)
18 - < 21 months	5 (0.5)	9 (0.9)	14 (0.7)
21 - < 24 months	7 (0.7)	6 (0.6)	13 (0.6)
24 - < 27 months	13 (1.3)	13 (1.3)	26 (1.3)
27 - < 30 months	8 (0.8)	4 (0.4)	12 (0.6)
30 - < 33 months	4 (0.4)	5 (0.5)	9 (0.4)
33 - < 36 months	13 (1.3)	5 (0.5)	18 (0.9)
36 - < 39 months	7 (0.7)	8 (0.8)	15 (0.7)
39 - < 42 months	17 (1.7)	12 (1.2)	29 (1.4)
42 - < 45 months	11 (1.1)	10 (1.0)	21 (1.0)
45 - < 48 months	8 (0.8)	11 (1.1)	19 (0.9)
48 - < 51 months	10 (1.0)	7 (0.7)	17 (0.8)
51 - < 54 months	3 (0.3)	10 (1.0)	13 (0.6)
54 - < 57 months	8 (0.8)	7 (0.7)	15 (0.7)
57 - < 60 months	529 (53.0)	507 (50.5)	1036 (51.8)
>= 60 months	283 (28.4)	288 (28.7)	571 (28.5)

Adverse events

Overview of adverse events during period 1-3

The overall incidence of AEs over the entire study was similar between the treatment groups (83.5% in the early combination therapy group vs. 83.2% in the monotherapy group, respectively, see **Table 12**). All safety outcomes are presented by treatment approach (SAF) and no major differences between treatment groups was observed for any primary system organ class (SOC). Most frequently reported preferred terms (PTs) were within the SOCs Infections and infestations (48.8% vs. 46.1%), Musculoskeletal and connective tissue disorders (33.0% vs. 34.4%), Gastrointestinal disorders (31.5% vs. 31.4%) and Nervous system disorders (25.6% vs. 22.1%).

Table 12 Number (%) of patients with AEs by primary system organ class and treatment approach (SAF) Period: Treatment period (Periods 1, 2 and 3)

Primary system organ class	Vilda 50mg bid + metformin N=998 n (%)	Placebo + metformin N=1001 n (%)
Any primary system organ class	833 (83.5)	833 (83.2)
Blood and lymphatic system disorders	51 (5.1)	42 (4.2)
Cardiac disorders	104 (10.4)	107 (10.7)
Congenital, familial and genetic disorders	4 (0.4)	10 (1.0)
Ear and labyrinth disorders	38 (3.8)	42 (4.2)
Endocrine disorders	23 (2.3)	17 (1.7)
Eye disorders	82 (8.2)	86 (8.6)
Gastrointestinal disorders	314 (31.5)	314 (31.4)
General disorders and administration site conditions	139 (13.9)	107 (10.7)
Hepatobiliary disorders	63 (6.3)	69 (6.9)
Immune system disorders	15 (1.5)	10 (1.0)
Infections and infestations	487 (48.8)	461 (46.1)
Injury, poisoning and procedural complications	120 (12.0)	132 (13.2)
Investigations	79 (7.9)	102 (10.2)
Metabolism and nutrition disorders	158 (15.8)	168 (16.8)
Musculoskeletal and connective tissue disorders	329 (33.0)	344 (34.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	62 (6.2)	54 (5.4)
Nervous system disorders	255 (25.6)	221 (22.1)
Pregnancy, puerperium and perinatal conditions	2 (0.2)	4 (0.4)
Product issues	0	1 (0.1)
Psychiatric disorders	94 (9.4)	90 (9.0)
Renal and urinary disorders	77 (7.7)	96 (9.6)
Reproductive system and breast disorders	48 (4.8)	64 (6.4)
Respiratory, thoracic and mediastinal disorders	108 (10.8)	105 (10.5)
Skin and subcutaneous tissue disorders	97 (9.7)	93 (9.3)
Social circumstances	4 (0.4)	0
Vascular disorders	162 (16.2)	177 (17.7)

There were only minor differences between both treatment groups for any preferred terms. The most frequently reported AEs (≥10% in any group) were back pain, diarrhoea, hypertension, nasopharyngitis and arthralgia (**Table 13**).

Table 13 Number (%) of patients reporting common AEs (greater than or equal to 2.0% in any group) by preferred term and treatment approach(SAF) Period: Treatment period (Periods 1, 2 and 3)

Preferred term	Vilda 50mg bid + metformin N=998 n (%)	Placebo + metformin N=1001 n (%)
Back pain	105 (10.5)	86 (8.6)
Diarrhoea	105 (10.5)	104 (10.4)
Hypertension	105 (10.5)	128 (12.8)
Nasopharyngitis	104 (10.4)	108 (10.8)
Arthralgia	100 (10.0)	94 (9.4)
Influenza	93 (9.3)	64 (6.4)
Upper respiratory tract infection	83 (8.3)	69 (6.9)
Headache	82 (8.2)	73 (7.3)
Urinary tract infection	73 (7.3)	71 (7.1)
Dizziness	67 (6.7)	41 (4.1)
Pain in extremity	67 (6.7)	75 (7.5)
Bronchitis	59 (5.9)	59 (5.9)

Dyslipidaemia	58 (5.8)	71 (7.1)
Osteoarthritis	55 (5.5)	42 (4.2)
Gastritis	48 (4.8)	33 (3.3)
Musculoskeletal pain	40 (4.0)	29 (2.9)
Dyspepsia	38 (3.8)	27 (2.7)
Pharyngitis	38 (3.8)	40 (4.0)
Abdominal pain	37 (3.7)	31 (3.1)
Cough	35 (3.5)	33 (3.3)
Viral infection	35 (3.5)	26 (2.6)
Asthenia	34 (3.4)	15 (1.5)
Depression	34 (3.4)	31 (3.1)
Gastroenteritis	33 (3.3)	41 (4.1)
Hepatic steatosis	31 (3.1)	35 (3.5)
Cataract	30 (3.0)	33 (3.3)
Diabetic neuropathy	30 (3.0)	30 (3.0)
Nausea	30 (3.0)	20 (2.0)
Anaemia	29 (2.9)	26 (2.6)
Gastrooesophageal reflux disease	29 (2.9)	20 (2.0)
Pneumonia	27 (2.7)	21 (2.1)
Hypertriglyceridaemia	26 (2.6)	15 (1.5)
Anxiety	25 (2.5)	41 (4.1)
Pyrexia	24 (2.4)	11 (1.1)
Hyperhidrosis	23 (2.3)	16 (1.6)
Tonsillitis	23 (2.3)	17 (1.7)
Abdominal pain upper	22 (2.2)	23 (2.3)
Vertigo	22 (2.2)	16 (1.6)
Sciatica	21 (2.1)	9 (0.9)
Tremor	21 (2.1)	13 (1.3)
Insomnia	20 (2.0)	12 (1.2)
Rhinitis	20 (2.0)	13 (1.3)
Spinal pain	20 (2.0)	10 (1.0)
Sinusitis	19 (1.9)	22 (2.2)
Limb injury	17 (1.7)	25 (2.5)

Most events were either assessed as mild or moderate. Severe events were reported in 10.5% of patients in the early combination group and 10.6% of patients in the monotherapy group.

Overall, no major difference between treatment groups was seen for any severe AEs. Severe AEs within the SOC Cardiac disorders were slightly less frequent in the early combination group (0.9%, 9 patients) than in the monotherapy group (2.3%, 23 patients); the difference was not driven by any particular events, e.g., the largest difference in this SOC was seen for severe myocardial infarction (0% vs 0.3%, corresponding to 0 and 3 patients). Severe AEs within the SOC Nervous system disorders were slightly more frequent in the early combination group (1.9%, 19 patients) than in the monotherapy group (1.2%, 12 patients) and severe events within the SOC Gastrointestinal disorders were slightly less frequent in the early combination group (0.6%, 6 patients) than in the monotherapy group (1.3%, 13 patients).

Overview of adverse events during period 1

During the study period 1 (when comparing a two-drug combination with monotherapy); however, the incidence of adverse events was slightly increased for the early combination group compared with the monotherapy group: AEs 74% vs 68% and SAEs 14% vs 12%; SOC Infections and infestations (42% vs. 34%), SOC Musculoskeletal and connective tissue disorders (28% vs. 24%), SOC Gastrointestinal disorders (23% vs. 20%) and SOC Nervous system disorders (20% vs. 16%). The number of hypoglycaemic events was 12 (1.2%) in the combination group and 7 patients (0.7%) in the monotherapy group.

Serious adverse event/deaths/other significant events

Deaths

Twenty-two deaths were reported during this study (13 in the early combination group vs. 9 in the monotherapy group). None of the deaths were considered related to the study drugs. Most of the AEs related to the main reason of death were reported in single or very few patients, and no noteworthy difference between treatment groups were observed for any preferred terms.

Serious adverse events

SAEs over the entire study period were numerically less frequently reported in the early combination group (16.6%, 166 patients) compared to the monotherapy group (18.3%, 183 patients). Differences between treatment groups were generally small for any SAEs. The largest difference was observed for pneumonia (1.4% of patients in the early combination therapy group vs. 0.5% in the monotherapy group, corresponding to 14 vs. 5 patients). Most SAEs were reported in single patients only.

Adverse events of special interest

Hypoglycaemic events

The incidence of hypoglycaemic events during the entire study period was low and similar between treatment groups (13 in the early combination therapy group vs. 9 in the monotherapy group, see **Table 14**). The events were mostly mild in nature, and all of them were of grade 1. Most events were not suspected to be related to the study drug(s). Also, for other features related to hypoglycaemic events (e.g. precipitating events, time of the event in relation to last meal, dose and daytime) an overall comparable pattern was noted in both treatment groups. Most of the hypoglycaemic events occurred in Period 1 (12 in the early combination group and 7 in the monotherapy group). During Period 2, only one hypoglycaemic event was reported which occurred in the monotherapy group and the remaining events occurred during Period 3 when insulin was introduced.

Table 14 Number of hypoglycaemic events during the treatment period by event profile and treatment approach (SAF) Period: Treatment period (Periods 1, 2 and 3)

	Vilda 50mg bid + metformin N=998 n (%)	Placebo + metformin N=1001 n (%)
Total number of hypoglycemic events	13	9
Fasting plasma glucose value (mmol/L)		
<=2.2	0	0
>2.2-2.8	6 (46.2)	6 (66.7)
>2.8-<3.1	7 (53.8)	3 (33.3)
Not recorded	0	0
Grade		
Grade 1	13 (100)	9 (100)
Grade 2	0	0
Suspected Grade 2	0	0
Severity		
Mild	12 (92.3)	9 (100)
Moderate	0	0
Severe	1 (7.7)	0

Most of the patients reporting hypoglycaemic events during the entire treatment period (11 in the early combination therapy group vs. 6 in the monotherapy group) experienced one event only (9 patients in the early combination therapy group and 4 patients in the monotherapy group, see **Table 15**). There were no discontinuations due to hypoglycaemic events, and no grade 2 or suspected grade 2 events were reported.

During Period 1, 12 hypoglycaemic events were reported in 10 patients in the early combination group and 7 events in 4 patients in the monotherapy group. During Period 2, only one patient in the monotherapy group experienced a hypoglycaemic event.

Table 15 Number of patients experiencing hypoglycaemic events during the treatment period by event profile and treatment approach (SAF) Period: Treatment period (Periods 1, 2 and 3)

	Vilda 50mg bid + metformin N=998 n (%)	Placebo + metformin N=1001 n (%)
Number (%) of patients with at least one hypoglycemic event	11 (1.1)	6 (0.6)
Number (%) of patients with		
one hypoglycemic event	9 (0.9)	4 (0.4)
two hypoglycemic events	2 (0.2)	1 (0.1)
>2 hypoglycemic events	0	1 (0.1)
Number (%) of patients who discontinued due to hypoglycemic events	0	0
Number (%) of patients with grade 2 hypoglycemic events	0	0
Number (%) of patients with suspected grade 2 hypoglycemic events	0	0

Severe hypoglycaemic events in Period 1 were reported in one patient in the early combination group.

In the early combination group 27 asymptomatic low blood glucose occurrences were reported, and 10 in the monotherapy group. For most events no action was taken (for 81.5% and 90.0% of low blood glucose occurrences in the early combination and the monotherapy groups, respectively) and no relationship to study drug was suspected (85.2% and 100% of low blood glucose occurrences in the early combination and the monotherapy groups, respectively).

Asymptomatic low blood glucose occurrences were reported in 6 patients in the early combination group and in 3 patients in the monotherapy group during the entire study period, corresponding to 0.6% and 0.3% of patients, respectively. No patients discontinued study due to low blood glucose occurrences.

During Period 1, asymptomatic low blood glucose occurrences were reported in 4 patients in the early combination group and in 1 patient in the monotherapy, and in Period 2 in one patient in either treatment group.

Microvascular and macrovascular complications

Any microvascular or macrovascular complications during the treatment period by treatment approach were reported in a comparable proportion of patients in both treatment groups (30.5% of patients in the early combination group, and 33.1% of patients in the monotherapy group **Table 16**). Most frequently reported (in ≥ 2% of patients) were hypertension (10.5% in the early combination and 12.8% of patients in the monotherapy group), progression to renal insufficiency, defined as eGFR<60mL/min/1.73m2 (6.9% and 7.3%) and diabetic neuropathy (3.0% and 3.0%, respectively).

Over the 5-year study duration, a numerical reduction in the risk of time to first adjudicated macrovascular event was seen with the early combination treatment approach vs. initial monotherapy (hazard ratio 0.71; 95% CI [0.42, 1.19], statistical significance at the one-sided 2.5% level p=0.097) (**Figure 9**. The adjudicated first macrovascular events occurred in 2.4% vs. 3.3% of patients in the early combination treatment and monotherapy groups (post-hoc analyses, data on file).

Figure 9 KM plot for time to first macrovascular event (adjudicated) for overall study (Safety set)

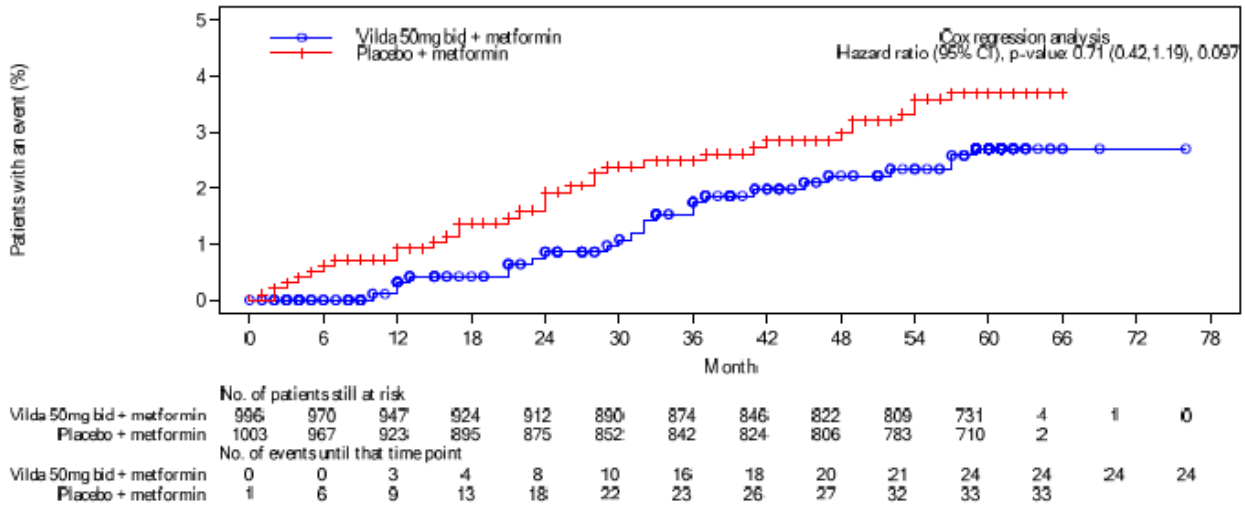


Table 16 Number of patients experiencing microvascular or macrovascular complications during the treatment period by treatment approach (SAF)

Complication	Vilda 50mg bid + metformin N=998 n (%)	Placebo + metformin N=1001 n (%)
Any microvascular/macrovascular complication	304 (30.5)	331 (33.1)
New or progression of existing microvascular/macrovascular complications or new onset microalbuminuria	267 (26.8)	291 (29.1)
Acute coronary syndrome	0	3 (0.3)
Acute myocardial infarction	3 (0.3)	4 (0.4)
Albuminuria	1 (0.1)	0
Angina pectoris	7 (0.7)	14 (1.4)
Angina unstable	2 (0.2)	1 (0.1)
Aortic aneurysm	3 (0.3)	1 (0.1)
Aortic dissection	1 (0.1)	0
Aortic stenosis	2 (0.2)	0
Aortic valve incompetence	1 (0.1)	1 (0.1)
Arrhythmia	3 (0.3)	2 (0.2)
Arteriosclerosis	4 (0.4)	3 (0.3)
Arteriosclerosis coronary artery	2 (0.2)	0
Arteriosclerotic retinopathy	1 (0.1)	0
Atrial fibrillation	14 (1.4)	19 (1.9)
Atrioventricular block first degree	5 (0.5)	6 (0.6)
Atrioventricular block second degree	0	1 (0.1)
Blood pressure fluctuation	0	1 (0.1)
Bradycardia	3 (0.3)	2 (0.2)
Bundle branch block right	5 (0.5)	4 (0.4)
Cardiac failure	4 (0.4)	6 (0.6)
Cardiac failure chronic	4 (0.4)	1 (0.1)
Cardiac failure congestive	3 (0.3)	0
Cardiomyopathy	1 (0.1)	0
Cardiovascular insufficiency	1 (0.1)	0
Cerebral haemorrhage	2 (0.2)	1 (0.1)
Cerebral infarction	1 (0.1)	3 (0.3)
Cerebral ischaemia	1 (0.1)	4 (0.4)
Cerebrovascular accident	2 (0.2)	3 (0.3)
Cerebrovascular disorder	3 (0.3)	1 (0.1)
Cerebrovascular insufficiency	0	2 (0.2)
Conduction disorder	0	3 (0.3)
Coronary artery disease	6 (0.6)	5 (0.5)
Coronary artery stenosis	2 (0.2)	3 (0.3)
Deep vein thrombosis	3 (0.3)	0
Diabetic microangiopathy	0	1 (0.1)
Diabetic nephropathy	6 (0.6)	6 (0.6)

Diabetic neuropathy	30 (3.0)	30 (3.0)
Diabetic retinopathy	14 (1.4)	6 (0.6)
Diabetic vascular disorder	1 (0.1)	1 (0.1)
Essential hypertension	3 (0.3)	1 (0.1)
Extrasystoles	2 (0.2)	1 (0.1)
Eye pain	2 (0.2)	4 (0.4)
Haemorrhagic stroke	0	1 (0.1)
Hypertension	105 (10.5)	128 (12.8)
Hypertensive angiopathy	1 (0.1)	3 (0.3)
Hypertensive cardiomyopathy	1 (0.1)	1 (0.1)
Hypertensive crisis	1 (0.1)	3 (0.3)
Hypertensive heart disease	1 (0.1)	2 (0.2)
Hypotension	7 (0.7)	4 (0.4)
Ischaemic stroke	2 (0.2)	5 (0.5)
Left atrial dilatation	1 (0.1)	0
Left ventricular dysfunction	2 (0.2)	1 (0.1)
Left ventricular hypertrophy	1 (0.1)	3 (0.3)
Microalbuminuria	12 (1.2)	18 (1.8)
Mitral valve disease	0	1 (0.1)
Mitral valve incompetence	2 (0.2)	0
Myocardial infarction	5 (0.5)	8 (0.8)
Myocardial ischaemia	8 (0.8)	8 (0.8)
Nephropathy	3 (0.3)	2 (0.2)
Orthostatic hypotension	0	1 (0.1)
Palpitations	14 (1.4)	3 (0.3)
Pericardial effusion	0	1 (0.1)
Pericarditis	1 (0.1)	0
Peripheral arterial occlusive disease	3 (0.3)	9 (0.9)
Peripheral venous disease	13 (1.3)	6 (0.6)
Prinzmetal angina	1 (0.1)	0
Retinopathy	0	2 (0.2)
Retinopathy hypertensive	1 (0.1)	4 (0.4)
Sinus bradycardia	2 (0.2)	1 (0.1)
Sinus tachycardia	6 (0.6)	5 (0.5)
Supraventricular extrasystoles	4 (0.4)	4 (0.4)
Tachycardia	7 (0.7)	8 (0.8)
Transient ischaemic attack	1 (0.1)	1 (0.1)
Tricuspid valve incompetence	1 (0.1)	1 (0.1)
Vascular encephalopathy	1 (0.1)	1 (0.1)
Ventricular arrhythmia	0	1 (0.1)
Ventricular extrasystoles	7 (0.7)	6 (0.6)
Ventricular fibrillation	0	2 (0.2)
Vertebrobasilar insufficiency	1 (0.1)	3 (0.3)
Vision blurred	8 (0.8)	5 (0.5)
Progression to renal insufficiency (eGFR < 60ml/min/1.73m**2)	69 (6.9)	73 (7.3)
Doubling of baseline serum creatinine to at least 200µM (2.26mg/dL)	1 (0.1)	5 (0.5)
All-cause mortality	13 (1.3)	9 (0.9)

As part of safety surveillance, cardiovascular events were monitored and adjudicated in the VERIFY study; however, the study was not powered to assess differences in cardiovascular events. A reduction in the risk of time to first adjudicated macrovascular event was seen with the early combination treatment approach vs. monotherapy (HR 0.71; 95% CI [0.42, 1.19]). Adjudicated first macrovascular events was numerically lower in the early combination vs the monotherapy groups [2.4% vs. 3.3% of patients]; however, the low cumulative number of recurrent events must be considered, and no firm conclusions can be made from these results.

Laboratory findings

No major or consistent changes or clinically relevant differences between treatment groups were reported for any haematology, clinical chemistry including liver enzymes, urinalysis, vital signs, body weight and ECG findings.

Safety in special populations

The overall incidence of AEs was comparable between the early combination and the monotherapy group for all age subgroups (<48 years: 83.6% vs. 80.5%, respectively; 48 to <62 years: 82.1% vs. 84.1%; ≥ 62 years: 86.0% vs. 83.7%).

AEs within the SOC Cardiac disorders were more frequently reported in older patients, as to be expected, and were comparable between the early combination and the monotherapy group within each age category (<48 years: (5.0% vs. 5.9%, respectively; 48 to <62 years: 11.3% vs. 10.8%; ≥ 62 years: 13.6% vs. 14.7%). For other SOC or specific PTs no consistent age-related trend was observed, and differences between treatment groups were overall comparable within age category.

Discontinuation due to adverse events

Also, AEs leading to study drug discontinuation over the entire study period were slightly less frequently reported in the early combination group (4.1%, 41 patients) compared to the monotherapy group (5.3%, 53 patients). Differences between treatment groups were small for any preferred terms, and most AEs leading to discontinuation were reported in single patients only.

Table 17 Number (%) of patients (at least 0.2% of patients in any group) with AEs leading to discontinuation by preferred term and treatment approach (SAF) Period: Treatment period (Periods 1, 2 and 3)

Preferred term	Vilda 50mg bid + metformin N=998 n (%)	Placebo + metformin N=1001 n (%)
Any preferred term	41 (4.1)	53 (5.3)
Pancreatic carcinoma	3 (0.3)	1 (0.1)
Abdominal distension	2 (0.2)	0
Gastritis	2 (0.2)	1 (0.1)
Abdominal pain upper	1 (0.1)	2 (0.2)
Invasive ductal breast carcinoma	1 (0.1)	2 (0.2)
Pregnancy	1 (0.1)	2 (0.2)
Diarrhoea	0	4 (0.4)
Renal failure	0	2 (0.2)
Transaminases increased	0	3 (0.3)

Adverse events leading to dose adjustment and/or interruption

The incidence of adverse events requiring dose adjustment or study drug interruption during the entire treatment was balanced between the early combination group (13.9%) and the monotherapy group (13.1%). Differences between treatment groups were generally small for any preferred terms, and most were reported in single or few patients only. Differences of 0.5% or more were observed for myocardial infarction (0% vs. 0.5% in the early combination and monotherapy group, 0 and 5 patients, respectively) gastritis (0.9% vs. 0.4%, 9 and 4 patients), asthenia (0.7% vs. 0.2%, 7 and 2 patients), dizziness (0.7% vs. 0.1%, 7 and 1 patients).

2.5.1. Discussion on clinical safety

Overall (including study period 1-3), the safety outcome for the early combination group versus the monotherapy group was similar with regards to AEs (84% vs 83%) and SAEs (16% vs 18%). Most frequently reported AEs were within the SOC Infections and infestations (49% vs. 46%), SOC Musculoskeletal and connective tissue disorders (33% vs. 34%), SOC Gastrointestinal disorders (32% vs. 31%) and SOC Nervous system disorders (26% vs. 22%) for the early combination treatment therapy versus the monotherapy group. The number of hypoglycaemic events was 13 (1.3%) in the early

combination group and 9 patients (0.9%) in the monotherapy group. All hypoglycaemic evens were mild (grade 1).

The incidence of subjects experiencing any microvascular or macrovascular complications was 30% and 33% for early combination and monotherapy group, respectively. Most frequently reported (in ≥ 2% of patients) were hypertension (10.5% in the early combination and 12.8% of patients in the monotherapy group), progression to renal insufficiency, defined as eGFR<60mL/min/1.73m2 (6.9% and 7.3%) and diabetic neuropathy (3.0% and 3.0%, respectively). The study was not powered to assess differences in cardiovascular events. Post-hoc analyses of showed a numerical reduction in the risk of time to first adjudicated macrovascular event for the early combination treatment approach vs. initial monotherapy (HR 0.71; 95% CI [0.42, 1.19]; however, the low cumulative number recurrent events must be considered, and no firm conclusions can be made from these results.

During the study period 1 (when comparing a two-drug combination with monotherapy); however, the incidence of adverse events was slightly increased for the early combination group compared with the monotherapy group: AEs 74% vs 68% and SAEs 14% vs 12%; SOC Infections and infestations (42% vs. 34%), SOC Musculoskeletal and connective tissue disorders (28% vs. 24%), SOC Gastrointestinal disorders (23% vs. 20%) and SOC Nervous system disorders (20% vs. 16%). The number of hypoglycaemic events was 12 (1.2%) in the combination group and 7 patients (0.7%) in the monotherapy group.

2.5.2. Conclusions on clinical safety

The safety profile for the entire study period was similar for the early metformin/vildagliptin combination treatment group and for the metformin monotherapy group (followed by sequential addition of vildagliptin). No new or unexpected signal was identified. However, during period 1, the incidences of adverse events were, as expected, slightly increased in the combination group compared with the metformin monotherapy group since a two-drug combination, as opposed to monotherapy, will normally result in additional adverse events. The incidence of microvascular or macrovascular complications was balanced between the groups. Most frequently reported were hypertension, progression to renal insufficiency (<60mL/min/1.73m2) and diabetic neuropathy. The study was not powered to assess differences in cardiovascular events.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA did not submit an updated RMP version with this application. It was considered based on the data submitted in the application there is no need for an update of the RMP.

2.7. Update of the Product information

As a consequence of this new indication wording, sections 4.1, 4.4, 4.5, 5.1 and 6.6 of the SmPC have been updated. Particularly, VERIFY study data (on initial combination of vildagliptin with metformin) and a warning with regard to drugs that inhibit renal transporter (OCT2/MATE inhibitors) and corresponding update in drug interactions has been added. The Package Leaflet has been updated accordingly, and

changes made to bring the PI it in line with the QRD v10.1 template.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Due to the pathophysiology of the disease, the majority of T2DM patients require more treatment as the disease progresses and beta-cell function declines over time. The guidelines for management of hyperglycaemia in type II diabetes recommends metformin as first-line choice of therapy with sequential addition of other oral antidiabetic drugs. The VERIFY study submitted in the current variation, has been performed with the aim to show that the risk of initial treatment failure is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy in a patient population with newly diagnosed type 2 diabetes. Based on the results of this study, the MAH has proposed to extend the indication for vildagliptin containing products to include "initial combination of vildagliptin and metformin, when diabetes is not adequately controlled by diet and exercise alone".

3.1.2. Main clinical studies

The VERIFY study was designed to investigate early combination therapy of vildagliptin and metformin with metformin monotherapy, and subsequent, sequential addition of vildagliptin, in treatment-naïve patients with type 2 diabetes mellitus, aged 18-70 year. The primary objective was to demonstrate the superiority of early combination of vildagliptin 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% at two consecutive measurements) was lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy.

The study was a multi-centre, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period. The study was split into 3 periods. After a 3-week run-in period, patients were randomised 1:1 to metformin and vildagliptin (n=998) or metformin and placebo (n=1,003) and entered the study period 1. The duration of period 1 could differ between patients depending on the time when the second of two HbA1c measurements, taken at two consecutive visits after randomization, confirmed HbA1c ≥ 7.0%, i.e. when primary goal was met. At that point, patients entered period 2 of the study. In period 2, patients who were randomized to placebo and metformin in period 1 received vildagliptin and continued with metformin. Patients who were randomized to the early combination vildagliptin and metformin in period 1 continued with this treatment. If a second treatment failure was documented in period 2, patients entered period 3, in which patients were initiated to open-label insulin.

3.2. Favourable effects

A significant reduction in the RR for time to initial treatment failure was observed in the early combination treatment group compared with the monotherapy group (HR 0.51 [95% CI 0.45–0.58]; p<0.001). The median observed time to treatment failure in the monotherapy group was 36.1 months, while the median treatment failure time for those receiving early combination therapy could only be estimated to be beyond the study duration at 61.9 months.

The second treatment failure, during the second phase of study, was also significantly reduced in the early combination group compared with metformin and sequentially added vildagliptin (HR 0.74 [95% CI 0.63, 0.86; p<0.001).

Glycaemic control, assessed by the annualized slope of HbA1c over time from week 26 to end of period 1 deteriorated slightly more slowly in the early combination treatment group than in the monotherapy group, although not statistically significant (−0.02, 95% CI [−0.05, 0.00]; one-sided p=0.042). Descriptive analysis demonstrated that HbA1C, up to the end of period 1, was consistently lower with the early combination treatment approach versus monotherapy. At end of study, the difference in HbA1c between the groups was small.

The preliminary results of all the exploratory efficacy analyses provided some indicative support of maintained beta-cell function and delayed loss of insulin sensitivity with early combination intervention.

3.3. Uncertainties and limitations about favourable effects

The clinical relevance of reaching glycaemic control faster (ie the results of the primary endpoint) is not fully supported by available data.

The analysis of time to 2nd treatment failure, compared the strategy of metformin monotherapy and sequentially added vildagliptin with an early combination therapy strategy. This analysis was added a post-hoc analysis a but could still be to some extent be considered as supportive.

The MAH has provided an acceptable rationale for the change of the primary endpoints and has confirmed that the decision was not data driven.

3.4. Unfavourable effects

Overall (including study period 1-3), the safety outcome for the early combination group versus the monotherapy group was similar with regards to AEs (84% vs 83%) and SAEs (16% vs 18%). Most frequently reported AEs were within the SOC Infections and infestations (49% vs. 46%), SOC Musculoskeletal and connective tissue disorders (33% vs. 34%), SOC Gastrointestinal disorders (32% vs. 31%) and SOC Nervous system disorders (26% vs. 22%) for the early combination treatment therapy versus the monotherapy group. The number of hypoglycaemic events was 13 (1.3%) in the early combination group and 9 patients (0.9%) in the monotherapy group. All hypoglycaemic evens were mild (grade 1).

The incidence of subjects experiencing any microvascular or macrovascular complications was 30% and 33% for early combination and monotherapy group, respectively. Most frequently reported (in ≥ 2% of patients) were hypertension (10.5% in the early combination and 12.8% of patients in the monotherapy group), progression to renal insufficiency, defined as eGFR<60mL/min/1.73m2 (6.9% and 7.3%) and diabetic neuropathy (3.0% and 3.0%, respectively). The study was not powered to assess differences in cardiovascular events. Post-hoc analyses of showed a numerical reduction in the risk of time to first adjudicated macrovascular event for the early combination treatment approach vs. initial monotherapy

(HR 0.71; 95% CI [0.42, 1.19]; however, the low cumulative number recurrent events must be considered, and no firm conclusions can be made from these results.

During the study period 1 (when comparing a two-drug combination with monotherapy) the incidence of adverse events was slightly increased for the early combination group compared with the monotherapy group: AEs 74% vs 68% and SAEs 14% vs 12%; SOC Infections and infestations (42% vs. 34%), SOC Musculoskeletal and connective tissue disorders (28% vs. 24%), SOC Gastrointestinal disorders (23% vs. 20%) and SOC Nervous system disorders (20% vs. 16%). The number of hypoglycaemic events was 12 (1.2%) in the combination group and 7 patients (0.7%) in the monotherapy group.

3.5. Uncertainties and limitations about unfavourable effects

Safety profile was in line with the known safety profile.

3.6. Effects Table

Table 2. Effects Table for vildagliptin/metformin in treatment-naïve patients with T2DM

Effect	Short descri-ption	Unit	Metformin + vildagliptin as initial combination	Metformin monotherapy (+ vildagliptin sequentially added in the 2nd period of the study)	Uncertainties / Strength of evidence	References
Favourable Effects						
HbA1c	Time to initial treatment failure	%	429/998 (43%)	614/1003 (62%)	HR (CI): 0.51 (0.45, 0.58) p<0.001	VERIFY
HbA1c	Time to second treatment failure	%			HR (CI): 0.74 (0.63, 0.86) p<0.001	VERIFY
Unfavourable Effects						
During the entire study (period 1-3)						
AEs	Incidence		84%	83%		
SAEs	Incidence		16%	18%		
SOC Inf.*)	Incidence		49%	46%		
SOC Ner. *)	Incidence		26%	22%		
SOC Gas. *)	Incidence		32%	31%		
SOC Mus. *)	Incidence		33%	34%		
Period 1 of the study						
AEs	Incidence		74%	68%		
SAEs	Incidence		14%	12%		
SOC Inf.*)	Incidence		42%	34%		
SOC Ner. *)	Incidence		20%	16%		
SOC Gas. *)	Incidence		23%	20%		
SOC Mus. *)	Incidence		28%	24%		

Abbreviations: *) SOC Infections and infestations, SOC Musculoskeletal and connective tissue disorders, SOC Gastrointestinal disorders and SOC Nervous system disorders.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The guidelines for management of hyperglycaemia in type II diabetes recommends metformin as first-line choice of therapy with sequential addition of other oral antidiabetic drugs.

In this variation, the results from the VERIFY study has been submitted. This study had the aim to investigate if there is a benefit of initiating treatment with two drugs simultaneously compared to metformin monotherapy in patients with newly diagnosed type 2 diabetes. The study met its primary objective, to demonstrate the superiority of early combination of vildagliptin 50mg bid and metformin over metformin monotherapy by testing the hypothesis that the risk of confirmed initial treatment failure (defined as HbA1c ≥ 7.0% at two consecutive measurements) is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy.

However, the clinical relevance of this result can be questioned considering that as soon as a patient fails on metformin monotherapy, several other treatment options are readily available. The benefit of a longer time to failure, as was seen in the combination group is not obvious, and in fact, at the end of study (month 60), HbA1c was very similar in the two study groups. Even it its acknowledged that the study may not have had the power to show differences in diabetic complications, the incidences of these events did not differ between study groups.

To further assess the benefit of initial combination compared to sequentially added vildagliptin, an analysis of a second treatment failure was performed in period 2 of the study. The RR for time to second treatment failure during period 2 of the study was significantly reduced in the combination treatment group compared with the sequential metformin treatment. Thus, even if both groups now were receiving the same treatment, patients in the initial combination group had a longer time to treatment failure. However, also in this situation, additional treatments are available which was also reflected in the study with the introduction of insulin treatment in patients with second treatment failure.

It is acknowledged that the clinical relevance of the results of the VERIFY study cannot be further justified based on data from the study itself; potential support must be derived from published literature. The results of the follow up of the UPKDS study are considered as the strongest support for long term benefit of early intensive treatment of patients with type 2 diabetes indicating a reduced risk of both micro-and macrovascular complications. It could also be considered that it makes a lot of sense that early intensive treatment of patients who have not yet developed complications could be of higher benefit compared to patients who have already developed e.g. diabetic retinopathy.

However, the UKPDS data are rather old and the relevance of the result in the context of current treatment recommendations can be questioned. In addition, the long term importance of optimizing glycaemic control in patients with type 2 diabetes for the reduction of risk of macrovascular complications has been debated both in the context of older, large prospective trials (the ADVANCE and ACCORD trials) as well as in the context of more recent (positive) cardiovascular outcome trials for which it has often been put forward that the benefit is not only based the lowering of blood glucose.

Thus, it is considered that current knowledge cannot undisputedly support the clinical relevance of reducing blood glucose as fast as possible in newly diagnosed patients with type 2 diabetes, even though the hypothesis that this could reduce at least the risk of microvascular complications seem plausible.

Current EU regulatory therapeutic indications for products for the treatment of type 2 diabetes largely follow the treatment algorithms recommended by learned societies. The results of the VERIFY study has been acknowledged by the European Association of Study of Diabetes (EASD) (*Buse JB, Diabetologia, 2019*) and it is suggested that "providers should engage in shared decision making around initial

combination therapy in new onset cases of type 2 diabetes". However, early combination is not recommended as first line therapy until more knowledge is available.

The safety profile for the entire study period was similar for the early metformin/vildagliptin combination treatment group and for the metformin monotherapy group (followed by sequential addition of vildagliptin). No new or unexpected signal was identified. However, during period 1, the incidences of adverse events were, as expected, slightly increased in the combination group compared with the metformin monotherapy group since a two-drug combination, as opposed to monotherapy, will normally result in additional adverse events. The incidence of microvascular or macrovascular complications was balanced between the groups. Most frequently reported were hypertension, progression to renal insufficiency (<60mL/min/1.73m2) and diabetic neuropathy. The study was not powered to assess differences in cardiovascular events.

3.7.2. Balance of benefits and risks

Current knowledge cannot undisputedly support the clinical relevance of using initial combination treatment and reducing blood glucose as fast as possible in newly diagnosed patients with type 2 diabetes, and initial combination treatment is currently not recommended in the treatment algorithms from learned societies. Therefore, proposed inclusion of study results from the finalised VERIFY study in section 5.1 is accepted while further change proposed in section 4.1 to extend the indication to include "initial combination of vildagliptin and metformin, when diabetes is not adequately controlled by diet and exercise alone" is not recommended. The MAH agreed.

The MAH also applied to change the wording in section 4.1. of the SmPC with regards to the use of vildagliptin in combination with other glucose lowering agents i.e. to make a general cross-reference to section 5.1. of combination use instead of reflecting specific combinations in section 4.1. This is in line with the wording of other oral anti-diabetic drugs and has been agreed by the CHMP. The final agreed wording for section 4.1. was as follows;

Eucreas is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:

- *in patients who are inadequately controlled with metformin hydrochloride alone.*
- *in patients who are already being treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.*

in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

3.8. Conclusions

The overall B/R of Eucreas, Icandra, Zomarist is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and II
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.4, 4.5, 5.1 and 6.6 of the SmPC for Eucreas, Icandra and Zomarist to change the existing indication with regards to the use in combination with other diabetes medicines, to reflect the VERIFY study data (on initial combination of vildagliptin with metformin) and expand existing warning on drugs that may affect renal function or metformin disposition by including drugs that inhibit renal transporter (OCT2/MATE inhibitors) and corresponding update in drug interactions. PI update to QRD v10.1. The Package Leaflet and Annex II are updated in accordance.

The grouped worksharing procedure leads to amendments to the Summary of Product Characteristics, Package Leaflet and Annex II.

Amendments to the marketing authorisation

In view of the data submitted with the grouped worksharing procedure, amendments to Annex(es) I, IIIB and II are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Worksharing applicant (WSA) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Eucreas_Icandra_Zomarist-H-C-WS-1937-G'