20 September 2012
EMA/CHMP/568007/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Galvus	vildagliptin
Eucreas	vildagliptin / metformin hydrochloride
Jalra	vildagliptin
Zomarist	vildagliptin / metformin hydrochloride
Icandra	vildagliptin / metformin hydrochloride
Xiliarx	vildagliptin

Procedure No. EMEA/H/C/xxxx/WS/0272

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd. submitted to the European Medicines Agency on 12 April 2012 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

Medicinal product:	International non-proprietary name:	Presentations:
Galvus, EMEA/H/C/000771/WS/0272	vildagliptin	See Annex A
Eucreas, EMEA/H/C/000807/WS/0272	vildagliptin / metformin hydrochloride	See Annex A
Icandra, EMEA/H/C/001050/WS/0272	vildagliptin / metformin hydrochloride	See Annex A
Jalra, EMEA/H/C/001048/WS/0272	vildagliptin	See Annex A
Xiliarx, EMEA/H/C/001051/WS/0272	vildagliptin	See Annex A
Zomarist, EMEA/H/C/001049/WS/0272	vildagliptin / metformin hydrochloride	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of indication for the use of vildagliptin and vildagliptin/metformin in triple therapy with a sulphonylurea and metformin affecting sections 4.1, 4.2, 4.8 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested worksharing procedure proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Kristina Dunder

Appointed Rapporteur for the WS procedure: Kristina Dunder

Steps taken for the assessment

Submission date:	12 April 2012
Start of procedure:	22 April 2012
Rapporteur's preliminary assessment report circulated on:	15 June 2012
Rapporteur's updated assessment report circulated on:	11 July 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 July 2012
MAH's responses submitted to the CHMP on:	17 August 2012

Rapporteur's assessment report on the MAH's responses circulated on:	30 August 2012
CHMP opinion:	20 September 2012

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/177/2011 (for vildagliptin) and P/169/2010 (for vildagliptin/metformin) on the granting of a product-specific waiver.

2. Scientific discussion

2.1. Introduction

Metformin is an established initial therapeutic agent for diabetes, acting by reducing primarily the hepatic glucose output (Davidson and Peters 1997; Consoli, et al. 2004). Sulfonylureas are also common anti-diabetics that improve blood glucose levels by stimulating insulin secretion from pancreatic β-cells in a non-glucose-dependent manner (Krentz and Bailey 2005). The combination of metformin plus a SU is a broadly used dual therapy for the treatment of T2DM. However, many patients on dual-combination therapy with metformin and a SU agent do not achieve or maintain glycaemic control. In this setting, use of insulin is often the next therapeutic step, although the need of parenteral administration makes this option undesirable by many patients.

Triple oral anti-diabetic (OAD) combinations are an alternative option suggested by guidelines (ADA-EASD Consensus Algorithm). There are a limited number of therapeutic options to add to metformin+SU therapy, in particular drugs that do not increase the risk of hypoglycemia or result in weight gain. Hence, there is a need for new anti-diabetic agents to complement the commonly used combination of sulfonylurea and metformin in patients with T2DM inadequately controlled on dual OAD therapy.

Complementing the pharmacological effect of metformin and SU on glycemic control, vildagliptin enhances the glucose-dependent insulin secretion. It is a potent and selective DPP-4 inhibitor that prevents the rapid degradation of endogenous glucagon-like peptide-1 and glucose-dependent insulinotropic peptide that in turn enhances glucose-dependent insulin secretion and suppresses glucagon release thereby providing glycemic control in type 2 diabetes mellitus (T2DM) patients. Vildagliptin is weight neutral and is associated with low risk of hypoglycemia either as monotherapy or in dual combination with metformin, SU, or TZD.

Vildagliptin is an oral antidiabetic agent which belongs to the dipeptidyl peptidase 4 (DPP-4) inhibitors class used for the treatment of T2DM. It was approved in the EU under the name Galvus in September 2007. Two additional marketing authorisations were granted in EU for duplicate licenses in November 2008 (Jalra and Xiliarx). The fixed dose combination with metformin was approved in November 2007 as Eucreas and duplicate licenses in December 2008 (Icandra and Zomarist).

2.2. Non-clinical aspects

Updated versions of the ERAs for vildagliptin and vildagliptin/metformin were submitted, as requested by CHMP.

Overall, the updated assessments suggest that the placement of the foreseen amounts of vildagliptin and vildagliptin/metformin fixed dose combination on the EU market does not constitute any significant risk to the environment.

The updated ERA is acceptable. It should be pointed out, that while this application concerns a new indication, the disease population is the same as for previous approvals and the original conclusions on the ERA for vildagliptin and vildagliptin/metformin are unchanged.

2.3. Clinical Efficacy aspects

One pivotal study was submitted in support of the current application.

Table 1 Overview of controlled efficacy studies

Study No.	Study objective, population	Randomized patients	Treatment duration	Treatment arms	Protocol-specified efficacy
23152	Efficacy and safety of vildagliptin 50 mg bid as add-on therapy in T2DM patients with inadequate glycemic control (HbA_{1c} ≥7.5 and ≤11%) with dual combination of metformin (≥ 1500 mg) and glimepiride (≥ 4 mg).	318	24 weeks	Vilda 50 mg bid + stable dose of metformin (≥1500 mg) + glimepiride (≥4 mg) (N=158 patients) Placebo + stable dose of metformin (≥1500 mg) + glimepiride (≥4 mg) (N=160 patients)	Change in HbA_{1c} (vs. placebo)

T2DM = type 2 diabetes; vilda = vildagliptin

2.3.1. Methods – analysis of data submitted

Main clinical study

Dose selection rationale

No dose response studies were provided with the current application. The selected vildagliptin 50 mg bid dose reflects the recommended dosage in the label as add-on therapy to metformin for patients with T2DM. In add-on therapy to metformin for patients with T2DM, vildagliptin at 50 mg bid was clinically significant in reducing HbA1c by -1.1%, as compared to placebo, after 24 weeks of treatment in patients inadequately controlled with metformin (CLAF237A2303). Vildagliptin 50 mg bid was chosen for this study since patients on metformin-based therapy benefited more from the 50 mg bid regimen than the once daily regimen. This is likely due to an effect of the evening dose on overnight hepatic glucose production, and it also was presumed that patients with more advanced diabetes not controlled on dual OAD therapy would benefit from this overnight effect on hepatic glucose production of the evening dose.

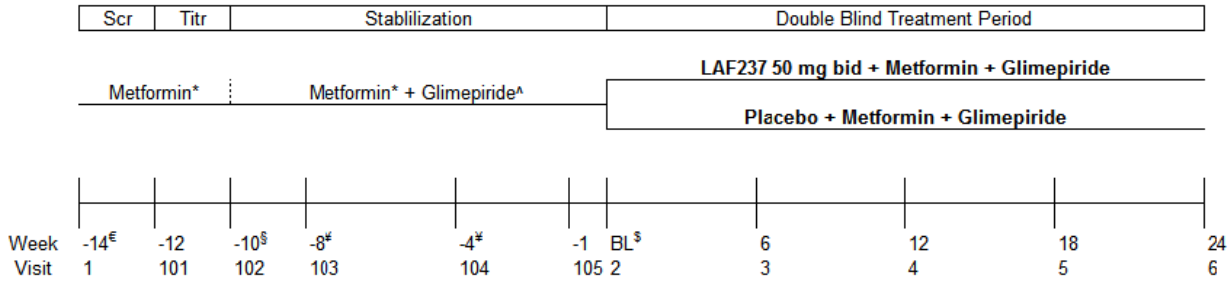
The rationale for the choice of vildagliptin dose is accepted. The dose approved for the combination of vildagliptin with metformin (50 mg BID) was applied in the study. It should be noted that the approved posology for vildagliptin in combination with SU is 50 mg OD as vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg OD. In this previous study, the incidence of hypoglycaemia was low in combination with SU, but there was more hypoglycaemia events observed with vildagliptin 100 mg/day (6 patients = 3.6% of patients) than with placebo (1 patient = 0.6% of patients).

Considering that patients already on bi-therapy (Metformin and SU) are more difficult to treat than patients on monotherapy (Metformin or SU) and that vildagliptin is used at 100 mg/day with metformin, the choice of a dose of 100 mg for a triple therapy makes sense. Nevertheless, hypoglycaemia and possibility to decrease the dose of SU should be carefully assessed.

Study design (CLAF237A23152)

This was a multi-center, double-blind, randomized, placebo-controlled study of vildagliptin as add-on therapy to metformin plus glimepiride in T2DM patients with inadequate glycemic control (HbA1c ≥7.5 and ≤11%) with dual combination of metformin (≥1500 mg) and glimepiride (≥4 mg). The study consisted of screening period, up to 12-week titration and/or stabilization period of the glimepiride dose and 24-week double blind treatment period (Figure 1).

Figure 1 Study design of study CLAF237A23152



Patients with T2DM not adequately controlled on a stable dose of OADs for at least 12 weeks prior to screening visit were included in the clinical study. Acceptable background therapy prior to enrollment included metformin ≥1500 mg as monotherapy (HbA1c ≥ 8.5% and ≤11%) or dual combination of metformin ≥1500 mg plus sulfonylurea (SU), metformin ≥1500 mg plus thiazolidinedione (TZD), or metformin ≥1500 mg plus glinide (HbA1c ≥7.5% and ≤11%) stable for at least 12 weeks prior to the screening visit. Eligible patients continued their current metformin treatment ≥1500 mg throughout the study. Patients on background therapy with OADs other than glimepiride had to agree to switch to glimepiride to be included in the clinical trial. Patients with a history of intolerance to SU were not eligible for this trial.

Screening period

Patients attended a screening Visit 1 where the inclusion/exclusion criteria were assessed. Based on background OAD therapy, patients who met all inclusion/exclusion criteria could either proceed to randomization or enter into the titration and/or stabilization period with glimepiride as described below. Screening period was to be not longer than 1-2 weeks.

Titration period

After screening visit eligible patients taking stable dose of metformin ≥1500 mg + glimepiride ≥4 mg for at least 12 weeks proceeded directly to Visit 2 and were randomized to the 24 week treatment period.

After screening eligible patients on dual therapy of metformin (≥1500 mg) plus more than half-of maximum daily dose of SU labeled for the region (or glimepiride ≥2 mg or <4 mg) proceeded directly to Visit 102 (Week -10), discontinued their current SU therapy and were switched to 4 mg glimepiride at that visit to enter 10 week run-in stabilization period.

After screening, eligible patients on dual therapy with metformin ≥1500 mg plus less than half-dose of maximum daily dose of SU labeled for the region or on dual therapy with metformin ≥1500 mg plus <2 mg glimepiride or on dual therapy with metformin ≥1500 mg plus TZD or glinide discontinued their current SU, TZD or glinide therapy were switched to glimepiride 2 mg at visit 101 (Week -12), up-titrated to 4 mg in 2 weeks at Visit 102 (Week - 10) and then continued in a 10-week stabilization period. Eligible patients on monotherapy metformin ≥1500 mg entered a titration period for glimepiride at Visit 101 (Week -12) as described for TZD or glinide therapy.

At Visit 102 (Week -10), prior to up titration to 4 mg glimepiride, a finger stick capillary glucose measurement was performed at the investigator site using a glucometer. Patients with fasting plasma glucose >7 mmol/L (126 mg/dL) or blood glucose >6.3 mmol/L (113 mg/dL) were up-titrated to 4 mg glimepiride if the titration was not contraindicated in the investigator's opinion due to the risk of hypoglycemia. Patients who up-titrated were eligible to continue in the study.

Stabilization period

During the stabilization period each patient received two phone calls from investigator site (Visit 103 and Visit 104) to monitor AEs and patient compliance with background metformin plus glimepiride therapy. When warranted for safety reasons patients were to attend unscheduled visits during any time of titration and stabilization periods. Patients who could not tolerate metformin ≥1500 mg plus glimepiride ≥4 mg therapy during stabilization run-in period were discontinued from the study. At the end of the stabilization period, patients attended Visit 105 (Week -1) to assess eligibility for HbA1c ≥7.5 and ≤11% and other inclusion/exclusion criteria.

Patients proceeded to randomization as soon as HbA1c eligibility was confirmed by central lab results.

The overall design is acceptable. The titration and stabilisation periods ensured that patients included in the study were on adequate doses of both metformin and glimepiride.

Study Participants

The population in this study consisted of male and female (non-fertile or of childbearing potential using a medically approved birth control method) with T2DM, 18-80 years old and with Body Mass Index (BMI) ≥22 to ≤45 kg/m2 at Visit 1.

Patients were to be inadequately controlled (HbA1c ≥8.5% and ≤11.0%) with metformin (≥1500 mg) monotherapy, or patients inadequately controlled (HbA1c ≥7.5 and ≤11.0%) with a combination of metformin (≥1500 mg) plus an SU, glinide or TZD.

Eligible patients on background therapy with OAD other than glimepiride were switched to glimepiride and underwent titration and stabilization period as described in above.

At the end of stabilization period only patients with HbA1c levels of ≥7.5 and ≤11% at Week - 1 (Visit 105) were eligible for randomization at Visit 2 (BL). The dose of metformin was maintained unchanged throughout the study.

Patients were excluded if treated with weight control products, DPP-4 inhibitors, GLP-1 analogues/mimetics or insulin within the previous 6 months, growth hormone within the previous 6 months and any oral anti-diabetic therapy other than metformin, SU, TZD and glinide within 12 weeks of Visit 1.

Patients with a history or evidence of serious medical conditions, including current diagnosis of congestive heart failure (NYHA III or IV), myocardial infarction (MI) within the past 6 months, coronary artery bypass surgery or percutaneous coronary intervention within the past 6 months, stroke or transient ischemic attack (TIA) within the past 3 months or

sustained and clinically relevant ventricular arrhythmia were also excluded as were patients with second or third degree AV block without a pace maker or long QT syndrome or QTc > 500ms.

Inclusion and exclusion criteria were adequate. Of note, patients with significant CV disease were excluded. This is acceptable. Current experience regarding CV safety with vildagliptin and use in patients with CHF has been assessed both in procedures EMEA/H/C/771/WS/06/G and EMEA/H/771/WS/187. It was concluded that there was no indication of an increased risk of CV events with vildagliptin in a population which included 16-18 % high risk patients. Furthermore, analysis of data in patients with documented CHF did not indicate an increased incidence of overall AEs or cardiac (i.e. arrhythmic, heart failure-related or ischaemic) AEs with vildagliptin relative to all comparators. Although there are limitations to the available data, there are currently no safety signals with regards to cardiac safety.

Treatments

Permitted dose adjustments and interruptions of study treatment

Vildagliptin/placebo

Study drug dose adjustments were not permitted.

Metformin

The dose of metformin (≥ 1500 mg) used at Visit 1 was to be maintained unchanged throughout the study. A patient whose dose of metformin was changed was to be discontinued from the trial.

Glimepiride (blister pack 2 mg/ 4 mg): guidelines for dose reduction

The dose of glimepiride (blister pack 2 mg/4 mg) could be adjusted downward to a maximum tolerated dose at the investigators discretion after Visit 2 for the following reasons:

- hypoglycemic event requiring the assistance of another person to treat
- 3 hypoglycemic events per week
- 3 asymptomatic low glucose values (i.e. plasma glucose values <3.1 mmol/L (56 mg/dL) or blood glucose values <2.8 mmol/L (50 mg/dL)) per week

If the dose was reduced, the patient remained on that dose of glimepiride for the remainder of the trial. Patients who could not tolerate the minimal dose of glimepiride 2 mg were discontinued.

Study treatment could be temporarily interrupted for documented reasons such as AEs. However, treatment was restarted as soon as possible.

Rescue medication

Rescue medication (per investigator discretion, insulin or pioglitazone) could be used in addition to ongoing study medication at or after Visit 3 (Week 6) for those patients who were not achieving a satisfactory therapeutic effect and whose elevated glucose was not due to illness, or other incidental circumstance potentially causing deterioration of glucose control.

Rescue medication was to be prescribed according to clinical judgment and the corresponding package insert.

Unsatisfactory therapeutic effect (UTE) was defined as follows:

- Starting from Visit 3 (Week 6) up to Visit 4 (Week 12): FPG >240 mg/dL* (13.3 mmol/L), confirmed by a repeat measure within 3 working days in the absence of an intercurrent illness

- Starting from Visit 4 (Week 12) up to Visit 6 (Week 24): FPG >200 mg/dL* (11.1 mmol/L), confirmed by a repeat measure within 3 working days in the absence of an intercurrent illness
- Symptoms of worsening hyperglycemia (i.e. polyuria, polydipsia, weight loss) regardless of visit, in the absence of any intercurrent illness or other incidental circumstances potentially causing deterioration of glucose control.

* Two elevated FPG levels within 3 days, at least one of which was completed by the central laboratory, in the absence of any intercurrent illness or other incidental circumstances potentially causing deterioration of glucose control.

Use of rescue medication was to be recorded on the eCRF with an indication of whether the rescue treatment was administered for ≥5 consecutive days or ≥7 days over a 30 day period.

Concomitant treatment

Treatment with GLP-1 analogues or mimetics, other DPP-4 inhibitors, any oral anti-diabetic therapy other than study medication, chronic corticosteroid treatment or growth hormone analogs was prohibited.

All other prior and concomitant non-study medications (not specifically contraindicated in the exclusion criteria) were allowed.

Treatments given during the study were adequate. Instructions for when to introduce rescue medication were in place and it should be noted that the criteria were strengthened over time.

Objectives and endpoints

The primary efficacy objective was to demonstrate the efficacy of add-on therapy with vildagliptin 50 mg bid to metformin and glimepiride in patients with T2DM by testing the hypothesis that the HbA1c reduction with vildagliptin 50 mg bid is superior to that with placebo added to metformin and glimepiride after 24 weeks of treatment. Primary efficacy parameter was the change in HbA1c from baseline to study endpoint in the FAS.

Secondary efficacy objectives were:

- To demonstrate the efficacy of add-on therapy with vildagliptin 50 mg bid to metformin and glimepiride in patients with T2DM by testing the hypothesis that the FPG reduction with vildagliptin 50 mg bid was superior to that with placebo after 24 weeks of treatment.
- To evaluate the safety and tolerability of vildagliptin as add-on therapy to metformin and glimepiride in patients with type 2 diabetes inadequately controlled with combination of metformin and glimepiride as compared to placebo after 24-week treatment.
- To evaluate the responder rate of vildagliptin 50 mg bid as add-on therapy to metformin and glimepiride in patients with type 2 diabetes, as compared to placebo after 24-week treatment.

The chosen objectives and endpoints were adequate. The primary objective is in line with the recently adopted “Guideline on clinical investigation of medicinal products in the treatment of diabetes” (CPMP/EWP/1080 Rev.1).

Sample size

A sample size of 246 completed patients (123 per arm) was targeted. Assuming a drop-out rate of 15%, about 290 patients (145 patients per arm) were to be randomized with an equal randomization ratio 1:1 to the two treatment groups. This sample size would generally ensure 90% power with a one-

sided significance level of 2.5% to declare superiority of vildagliptin 50mg bid over placebo in HbA1c reduction (%) from baseline after 24weeks of treatment, assuming a clinically relevant difference of 0.5 absolute units to placebo and a standard deviation of 1.2 %, which was consistent with the results of the study LAF237A2305 and LAF237A2303, which had similar designs.

The sample size calculations were adequate.

Randomisation and blinding

Eligible patients were randomized at Visit 2 via Interactive Response Technology (IRT) to receive either vildagliptin 50 mg bid or placebo in a ratio of 1:1 in addition to their continued metformin ≥1500 mg plus glimepiride ≥4 mg treatment.

Patients, investigator staff, persons performing the assessments, and data analysts remained blind to the identity of the treatment from the time of randomization until database lock.

Unblinding only occurred in the cases of patient emergencies and at the conclusion of the study. Once the patient was unblinded during the study, he/she was to be discontinued.

Only after the trial was completed, the data file verified, and protocol violations determined, were the remaining drug codes broken and used for data analysis.

The randomisation and blinding procedures were adequate.

Statistical methods

Analysis sets

The following analysis data sets were defined:

The Randomized Set (RAN) consisted of all randomized patients.

The Full analysis set (FAS) consisted of all randomized patients who received at least one dose of study medication and had at least one post-randomization efficacy parameter measurement. Following the intent-to-treat principle, subjects were analyzed according to the treatment they are assigned to at randomization.

The Safety Set (SAF) consisted of all patients that received at least one dose of study drug. Patients were analyzed according to the treatment received. Note that the safety set allowed the inclusion of non-randomized patients who received the study drug in error.

The Per Protocol set (PP) included patients in one of the following three categories:

- FAS patients who did not take rescue medication and completed at least 22 weeks of treatment with no major protocol deviations and had a valid assessment of the primary efficacy variable HbA1c within 7 days after the last dose of study drug.
- FAS patients who took rescue medication according to criteria mentioned in the protocol, and had no major protocol deviations prior to taking rescue medication, and had a valid assessment of the primary efficacy variable HbA1c prior to or at initiation of rescue medication.
- FAS patients that discontinued from study drug due to unsatisfactory therapeutic response as per protocol, had a valid assessment of the primary efficacy variable HbA1c within 7 days after the last dose of study drug, and had no major protocol deviations prior to discontinuation.

Major protocol deviations were pre-specified prior to unblinding treatment analysis. Patients who added rescue medication and then discontinued for unsatisfactory therapeutic response were considered in

the second category. Major protocol deviations were pre-specified prior to unblinding treatment codes for analyses.

Statistical hypothesis, model, and method of analysis

The primary efficacy variable was change from baseline in HbA1c at study endpoint, assessed in the Full analysis set. The test for the superiority of vildagliptin 50 mg bid to placebo as add-on therapy to metformin plus glimepiride for the effect of reducing HbA1c after 24 weeks of treatment, was based on the following null hypotheses and one-sided alternative hypotheses at an alpha level of 2.5%:

$H_0: \delta_{\text{Vilda 50 mg bid}} = \delta_{\text{Placebo}}$ versus $H_a: \delta_{\text{Vilda 50 mg bid}} < \delta_{\text{Placebo}}$,

Where δs are the mean change from baseline at Week 24 endpoint in HbA1c in the treatment group indicated.

An analysis of covariance (ANCOVA) model including terms for treatment, baseline HbA1c (centered by subtracting the overall mean baseline HbA1c of all treatment groups and pooled center was used to compare the treatment effect. The possibility of a treatment by pooled center interaction or a treatment by baseline HbA1c interaction was examined, although the interaction terms were not included in the primary analysis model. The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (vildagliptin – placebo), and the two-sided adjusted 95% confidence interval along with the p-value for the difference was obtained from the primary analysis model. The analysis of the primary efficacy variable using the FAS was the primary basis of conclusion. The analysis based on the Per Protocol Set was performed to assess the robustness of the conclusion. The same testing procedure as for the FAS analysis was used.

For the secondary efficacy variable, the percentage of patients meeting predefined responder criteria based on HbA1c targets at study endpoint as well as the percentage of patients meeting was computed and compared using a Chi-square test in the FAS. Three definitions of responders were defined:

1. HbA1c endpoint < 7%
2. HbA1c endpoint <7% in patients with baseline HbA1c ≤ 8%
3. HbA1c endpoint ≤ 6.5%

The change from baseline in FPG at study endpoint was analyzed using ANCOVA model in the same way as the primary efficacy variable.

Subgroup analysis

The primary efficacy variable change from baseline in HbA1c was assessed in the FAS by descriptive statistics across subpopulations of patients defined by baseline HbA1c category (≤ 8% and >8%, and ≤ 9% and > 9%), BMI (< 30 kg/m2, ≥ 30 kg/m2, at Visit 1), age (< 65 years, ≥ 65 years at Visit 1), gender and race.

Within each subgroup, summaries of absolute values and changes from baseline in HbA1c by visit were presented. The analysis and summaries used the FAS.

Sensitivity analysis with regard to handling rescue medication

As sensitivity analysis to the method of handing rescue medication related data (censored at the start of rescue medication), a similar ANCOVA model as for the primary variable change from baseline at Week 24 in HbA1c was performed in FAS with all data collected up to and including Week 24. For this sensitivity analysis, the Week 24 endpoint was defined as the measurement obtained at the last post-

baseline study visit prior to or at scheduled Visit 6 (Week 24), regardless of whether it is obtained at a scheduled or unscheduled visit, and regardless of whether patients take rescue medication or not.

Repeated measures analysis

As a sensitivity analysis to the LOCF approach, the change from baseline in HbA1c at all available time points from all patients in the FAS was analyzed using a restricted maximum likelihood (REML)-based repeated measure approach. The treatment effects at the end of study visit were estimated from the model and compared.

Handling on missing values/discontinuations

Data after discontinuations for any reason were imputed by carrying the last on-treatment measurement (scheduled or unscheduled) forward (LOCF) through the end of trial.

Patients who started rescue medication were considered as censored from the start date of the rescue medication onward. Data after the start of rescue medication were imputed by the last on-treatment measurement before or at the start of rescue medication, carried forward (LOCF) through the final schedule study visit.

Patients without a baseline or without a post-baseline measurement were excluded from the primary efficacy analysis.

Safety and demographic data

The number and percentage of patients with treatment emergent adverse events was summarized by primary system organ class, preferred term, maximum severity and relationship to study drug. The number and percentage of patients who died, had serious adverse events (SAEs), adverse events leading to discontinuation and adverse events requiring temporarily study drug interruption were tabulated separately. The incidence rates of AEs confirmed by various adjudication committees, AEs of predefined risk and hypoglycemic events were also summarized.

Hematology and biochemistry data were summarized for absolute values, changes from baseline, and treatment emergent notable abnormalities. Vital signs, body weight ECG findings and urinalysis by category were evaluated descriptively.

Patient disposition, Demographic and baseline background characteristics data were summarized by treatment.

The statistical methods were adequate.

2.3.2. Results

Disposition of patients

A total of 564 patients were enrolled out of which 246 patients were discontinued during the screening period. The randomization scheme in study CLAF237A23152 resulted in 1:1 allocation for vildagliptin 50 mg bid + metformin + glimepiride (hereunder referred to as “vildagliptin”) and placebo + metformin + glimepiride (hereunder referred to as “placebo”); 158 and 160 patients respectively enrolled in the trial. There from, 144 and 155 patients respectively completed the study. The percentage of patients who discontinued was higher in the vildagliptin group (8.9%) than in the placebo group (3.1%) mainly due to a greater percentage of patients who withdrew consent (4.4% vs. 1.3%). Discontinuations due to AEs were infrequent and similar in both treatment groups (one patient, 0.6%, in each group) (**Table 2**).

Table 2 Patient disposition (Randomized Set)

Disposition Reason	Vilda 50 mg bid +Met + Glim N=158 n (%)	Placebo + Met + Glim N=160 n (%)	Total N=318 n (%)
Completed	144 (91.1)	155 (96.9)	299 (94.0)
Discontinued	14 (8.9)	5 (3.1)	19 (6.0)
Abnormal laboratory value(s)	1 (0.6)	0 (0.0)	1 (0.3)
Administrative problems	1 (0.6)	0 (0.0)	1 (0.3)
Adverse event(s)	1 (0.6)	1 (0.6)	2 (0.6)
Death	0 (0.0)	1 (0.6)	1 (0.3)
Lost to follow-up	2 (1.3)	1 (0.6)	3 (0.9)
Patient withdrew consent	7 (4.4)	2 (1.3)	9 (2.8)
Protocol deviation	2 (1.3)	0 (0.0)	2 (0.6)

Discontinuations were more common in the vildagliptin treated group compared to placebo, mainly due to more withdrawals of consent and administrative problems. Although withdrawal of consent may include patients who are not satisfied with the treatment, the overall discontinuation rates were low and balanced between groups, especially with regards to AEs (only two patients discontinued for this reason, one in each group).

Recruitment

A total of 40 centers in 11 countries enrolled at least one patient (number of centers in brackets): Australia (3), Germany (3), Hungary (2), India (10), Italy (2), Korea (5), Mexico (4), Philippines (2), Romania (4), Taiwan (4) and United Kingdom (1). Fifteen out of 40 centers were located in Europe.

Study initiation date: 12-Oct-2010 (first patient first visit)

Study completion date: 21-Nov-2011 (last patient last visit)

Conduct of the study

There were no amendments to the protocol.

There were no changes from the protocol in study conduct.

Some changes and clarifications to the planned analyses were made.

Protocol deviations

The most frequent major protocol deviation that led to an exclusion from the PP set was “less than 22 weeks of randomized double-blind treatment and patient discontinued due to reasons other than unsatisfactory therapeutic response”. This deviation was reported in 8.2% patients in the vildagliptin group and 3.1% of patients in the placebo group, which is consistent with the higher discontinuation rate in the vildagliptin group as shown in Table 2. These patients were included in the full analysis set. All other protocol deviations leading to exclusion from any analysis population were infrequent and with no major differences between treatment groups.

No major differences between treatment groups were observed for other protocol deviations not leading to exclusion from any analysis population except “FPG ≥200 mg/dL at weeks 12- 24 and no repeat or study drug not stopped”. This deviation was more frequently reported in the placebo group (11.3% of patients) compared to the vildagliptin group (4.4%).

The changes and clarifications made to the planned analyses are not considered to affect the outcome or the interpretation of the study. Protocol deviations were rather few and do not evoke any concerns regarding the conduct of the study.

Baseline data

In pivotal study CLAF237A23152, both treatment groups were well-balanced for all patient demographic characteristics at baseline (Table 3). Mean age was 55 years in both groups, and approximately 20% of patients were ≥65 years of age.

The proportion of male/female patients was almost balanced in both treatment groups. Approximately 73% of the patients were Asian (mostly Indians: 49.7%, and Chinese: 10.4%), followed by Caucasian (22.6%), with a balanced distribution between treatment groups. Mean BMI was 28 kg/m2 for both treatment groups. Most patients (72.6%) were non-obese (BMI < 30 kg/m2). Overall, there were no major differences between the treatment groups.

Table 3 Patient baseline demographic characteristics (Randomized set)

	Vilda 50 mg bid + Met + Glim		Placebo + Met + Glim		Total	
	N=158		N= 160		N=318	
Age						
n	158		160		318	
Mean	55.3		55.0		55.1	
Min, Max	24.0	80.0	26.0	79.0	24.0	80.0
Age categorisation, n (%)						
<65	129	(81.6%)	122	(76.3%)	251	(78.9%)
≥65	29	(18.4%)	38	(23.8%)	67	(21.1%))
< 75	153	(96.8%)	153	(95.6%)	306	(96.2%)
≥75	5	(3.2%)	7	(4.4%)	12	(3.8%)
Gender, n (%)						
Male	80	(50.6%)	72	(45.0%)	152	(47.8%)
Female	78	(49.4%)	88	(55.0%)	166	(52.2%)
Race, n (%)						
Caucasian	34	(21.5%)	38	(23.8%)	72	(22.6%)
Asian	116	(73.4%)	116	(72.5%)	232	(73.0%)
Native american	3	(1.9%)	2	(1.3%)	5	(1.6%)
Other	5	(3.2%)	4	(2.5%)	9	(2.8%)
Weight (kg)						
n	158		160		318	
Mean	73.2		72.4		72.8	
Min, Max	47.8	133.0	46.0	136.0	46.0	136.0
Body Mass Index (kg/m^2)						
n	158		160		318	
Mean	27.9		28.0		28.0	
Min, Max	22.0	44.9	22.0	42.0	22.0	44.9

Demography information is collected on the day of the screening measurement (Week -14, Visit 1).

The groups were well balanced with regards to demographic characteristics. About 20 % of patients were elderly although only about 4 % were older than 75 years. The majority of patients were Asian (73 %) and only 23 % were Caucasian, consequently the BMI was rather low. This is acceptable since no clinically relevant differences in the effect of vildagliptin have been observed between Asians and Caucasians.

Patient baseline background characteristics in study CLAF237A23152 were comparable between both treatment groups (Table 4). Mean HbA1c values was 8.7% and mean FPG value was 9.3 mmol/L for the vildagliptin group, while the mean HbA1c was 8.8% and mean FPG was 9.5 mmol/L for the placebo group. The vildagliptin group had a few more patients with HbA1c less or equal to 8% (30.4% vs. 22.5% in the placebo group). Mean duration of type 2 diabetes was similar between the two treatment groups (vildagliptin: 7.1 and placebo: 7.5 years). Also renal function, as measured by GFR (MDRD), was similarly distributed between treatment groups. Overall, there were no major differences between the treatment groups.

Most patients (122 vildagliptin patients and 132 placebo patients) received metformin ≥1500 mg/day + glimepiride at study entry. The mean duration of metformin use (vildagliptin group: 43.8 months and placebo group: 41.3 months) and mean metformin daily dose (1790 mg/day vs. 1769 mg/day, respectively) in these patients was comparable for both treatment groups.

The mean duration of glimepiride use (26.5 vs. 25.7 months, respectively) and mean daily dose (4.4 vs. 4.5 mg/day, respectively) in these patients was also comparable for both treatment groups.

Table 4 Patient baseline background characteristics (Randomized set)

	Vilda 50 mg bid + Met + Glim N=158		**Placebo + Met + Glim** N=160		**Total** N=318	
Duration of Type 2 Diabetes (years)						
n	158		160		318	
Mean	7.1		7.5		7.3	
Min, Max	0.2	30.9	0.3	30.0	0.2	30.9
Baseline HA1c (percent)						
N	228		221		449	
Mean	8.7		8.8		8.8	
Min, Max	7.2	10.8	7.0	11.0	7.0	11.0
Categorised Baseline A1c (%) n (%)						
< 8	48	(30.4)	36	(22.5)	84	(26.4)
> 8	110	(69.6)	124	(77.5)	234	(73.6)
≤ 9	99	(62.7)	102	(63.8)	201	(63.2)
≥ 9	59	(37.3)	58	(36.3)	117	(36.8)
Fasting plasma glucose (mmol/L)						
N	158		160		318	
Mean	9.3		9.5		9.4	
Min, Max	3.9	18.3	4.8	16.3	3.9	18.3
GFR (MDRD) (mL/min/1.73 m2)						
Normal (>80)	99 (62.7%)		104 (65.0%)		203 (63.8%)	
Mild (>50 - <80)	55 (34.8%)		50 (31.3%)		105 (33.0%)	
Moderate (>30 - <50)	4 (2.5%)		6 (3.8%)		10 (3.1%)	

Notably some patients with HbA1c below the inclusion criterion of 7.5 % were included in both treatment groups. Overall, 36 % of patients had mild to moderate renal impairment. According to the SmPC, patients with moderate renal impairment should be treated with vildagliptin 50 mg rather 100 mg. Exclusion criteria includes: "Clinically significant renal dysfunction as indicated by serum creatinine levels at Visit 1 and Visit 105: serum creatinine ≥ 1.5 mg/dL (132 µmol/L) for males and ≥ 1.4 mg/dL (123 µmol/L) for females". Thus, ten patients are outside the inclusion criteria.

Concomitant medication

The majority of the patients were taking concomitant medications during the randomized double-blind period as well as significant non-drug therapies (vildagliptin group: 90.5% and placebo group: 80.6%).

Most commonly taken concomitant medications during the study period were antihypertensive medications (vildagliptin group: 53.8% vs. placebo group: 57.5%) and lipid lowering medications (vildagliptin group: 36.7% vs. placebo group: 37.5%). The main classes of the antihypertensive medication were plain ACE inhibitors (vildagliptin group: 19.6% vs. placebo group: 17.5%), plain angiotensin II antagonists (vildagliptin group: 13.3% vs. placebo group: 18.1%) and dihydropyridine derivatives (vildagliptin group: 17.1% vs. placebo group: 21.3%). The main lipid-lowering medications were statins (vildagliptin group: 29.7% vs. placebo group: 30.6%).

The baseline background characteristics were balanced between groups and are as expected for the target population.

Numbers analysed

Populations for analyses are summarized in **Table 5**. Almost all patients were included in the Full analysis set and the Safety set, and more than 90% of patients in both treatment groups were included in the Per protocol set.

Table 5 Number (%) of patients in the analysis sets (Randomized Set)

Sets	Vilda 50mg bid + Met + Glim N=158 n (%)	Placebo + Met + Glim N=160 n (%)	Total N=318 n (%)
Randomized Set	158 (100)	160 (100)	318 (100)
Full Analysis Set	152 (96.2)	160 (100)	312 (98.1)
Safety Set	157 (99.4)	160 (100)	317 (99.7)
Per Protocol Set	144 (91.1)	155 (96.9)	299 (94.0)

More patients in the vildagliptin group than in the placebo group were excluded from the FAS and the PP sets, however, exclusion rates were low.

Outcomes and estimation

In the pivotal study [Study CLAF237A23152], the primary efficacy endpoint was the change in HbA1c from baseline to study endpoint, censored by rescue medication, in the FAS. The ANCOVA results for the change in HbA1c from baseline to endpoint for both FAS and Per protocol set are summarized in Table 6.

Baseline HbA1c values were comparable between both treatment groups. Vildagliptin 50 mg bid as add-on to metformin and glimepiride therapy demonstrated a clinically significant reduction in HbA1c from baseline to study endpoint of -1.01% compared to -0.25% with placebo, and the difference to placebo of -0.76% was statistically significant ($p<0.001$).

Results in the Per Protocol set were similar as observed for the FAS.

Table 6 ANCOVA results for change in HbA1c (%) from baseline to endpoint by treatment (Full Analysis Set and Per Protocol Set)

				Difference in adjusted mean change (Vilda-Placebo)		
Treatment	**n**	**Baseline mean (SE)**	**Adjusted mean change (SE)**	**mean (SE)**	**(95% CI)**	**P-Value**
Full analysis Set						
Vilda 50mg bid + Met + Glim	152	8.75 (0.07)	-1.01 (0.09)	-0.76 (0.12)	(-0.98 , -0.53)	<0.001*
Placebo + Met + Glim	160	8.80 (0.07)	-0.25 (0.09)			
Per protocol Set						
Vilda 50mg bid + Met + Glim	144	8.78 (0.07)	-1.05 (0.09)	-0.80 (0.12)	(-1.03 , -0.57)	<0.001*
Placebo + Met + Glim	155	8.79 (0.07)	-0.25 (0.09)			

Baseline is measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement is missing. Endpoint is defined as the final available post-baseline assessment obtained at any visit (scheduled or unscheduled), prior to or at the start of rescue medication use, up to final scheduled study visit.
n is the number of patients with observations at both baseline and endpoint.
Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p values were from an ANCOVA model containing terms for treatment, baseline and pooled centers.
* indicates statistical significance at one-sided 2.5% level. Primary analysis is based on Full analysis set.

A clinically relevant reduction of HbA1c was observed when vildagliptin was added to dual therapy with metformin and glimepiride, compared to placebo. Similar results were observed for both the FAS and the PP populations.

Secondary efficacy variables in study CLAF237A23152 were responder rates based on the proportion of patients reaching predefined HbA1c and change in FPG.

Responder rates based on HbA1c reduction were distinctly higher in the vildagliptin group than in the placebo group for all defined categories, and differences between treatment groups were statistically significant for all responder categories (Table 7). Almost 30% of vildagliptin-treated patients reached HbA1c < 7% target compared to 6% of placebo-treated patients and 13.2% patients in the vildagliptin group achieved HbA1c ≤ 6.5% vs. 1.3% in the placebo group.

Table 7 Number of patients who responded at endpoint (Full analysis set)

	Vilda 50mg bid + Met + Glim N=152 n (%)	Placebo + Met + Glim N=160 n (%)	p-value*
N'[1]	152 (100)	160 (100)	
Responder Criterion			
At least one criterion met	43 (28.3)	9 (5.6)	<0.001
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≥ 7%[2]	43/152 (28.3)	9/160 (5.6)	<0.001
HbA_{1c} < 7% in patients with 7% ≥ baseline HbA_{1c} ≥ 8%[3]	17/ 44 (38.6)	5/ 36 (13.9)	0.014
HbA_{1c} ≤ 6.5% in patients with baseline HbA_{1c} > 6.5%[2]	20/152 (13.2)	2/160 (1.3)	<0.001

Baseline is the measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement is missing. Endpoint is defined as the final available post-baseline assessment obtained at any visit (scheduled or unscheduled), prior to or at the start of rescue medication use, up to final scheduled study visit. In the case of a missing scheduled visit sample, the closest unscheduled visit within 7 days of scheduled visit is used.
* Chi-square test for Vilda 50 mg bid + Met + Glim vs. Placebo + Met + Glim.
[1] Number of patients with both baseline and endpoint HbA_{1c} measurements, which is used as denominator unless specified otherwise.
[2] Denominator includes only patients with baseline HbA_{1c} ≥ 7% (> 6.5%) and endpoint HbA_{1c} measurement.
[3] Denominator includes only patients with 7% ≤ baseline HbA_{1c} ≥ 8% and endpoint HbA_{1c} measurement.

ANCOVA results for the change from baseline to endpoint in fasting plasma glucose (FPG) are summarized in Table 8.

Baseline FPG values were comparable between both treatment groups. Consistent with the results for HbA1c, the addition of vildagliptin to treatment with metformin and glimepiride resulted in a clinically relevant reduction in FPG of -1.11 mmol/L compared to nearly no change in the placebo group (+0.02 mmol/L). The difference to placebo of -1.13 mmol/L was clinically and statistically significant (p<0.001). Results for the Per Protocol set were similar as observed for the Full analysis set.

Table 8 ANCOVA results for change in FPG (mmol/L) from baseline to endpoint by treatment (Full analysis set)

				Difference in adjusted mean change (Vilda-Placebo)		
Treatment	**n**	**Baseline mean (SE)**	**Adjusted mean change (SE)**	**mean (SE)**	**(95% CI)**	**P-Value**
Full analysis Set						
Vilda 50mg bid + Met + Glim	152	9.34 (0.20)	-1.11 (0.21)	-1.13 (0.27)	(-1.65 , -0.60)	<0.001*
Placebo + Met + Glim	160	9.52 (0.17)	0.02 (0.20)			
Per protocol Set						
Vilda 50mg bid + Met + Glim	144	9.40 (0.20)	-1.22 (0.21)	-1.24 (0.26)	(-1.76 , -0.72)	<0.001*
Placebo + Met + Glim	155	9.51 (0.17)	0.02 (0.20)			

Baseline is measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement is missing. Endpoint is defined as the final available post-baseline assessment obtained at any visit (scheduled or unscheduled), prior to or at the start of rescue medication use, up to final scheduled study visit.
n is the number of patients with observations at both baseline and endpoint.
Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p values were from an ANCOVA model containing terms for treatment, baseline and pooled centers.
* indicates statistical significance at one-sided 2.5% level. Primary analysis is based on Full analysis set.

The outcomes of the secondary endpoints both support the primary endpoint. A relevant responder rate would remain if the entire randomized set was taken into account (43/158 = 27.2 %).

Ancillary analyses

In study CLAF237A23152, mean changes in HbA1c were summarized for the subgroups by HbA1c baseline category, baseline BMI, age, gender and race.

Change in HbA1c by HbA1c baseline category

Consistent with previous studies in the vildagliptin program, patients with a higher baseline value (HbA1c > 8%) showed a greater mean reduction in HbA1c from baseline to study endpoint (vildagliptin group: -1.10% and placebo group -0.38%) compared to patients with HbA1c ≤ 8% (vildagliptin group: -0.67% and placebo group: +0.23%).

Similar results were obtained for baseline categories HbA1c > 9% and ≤ 9%. Change from baseline to study endpoint in patients with HbA1c >9% were -1.38% in the vildagliptin group and -0.76% in the placebo group and in patients with baseline HbA1c ≤ 9% mean changes were -0.72% for vildagliptin and +0.05% for placebo.

Change in HbA1c by BMI category at baseline

No effect of baseline BMI on changes in HbA1c was observed. Patients with a BMI <30 kg/m2 showed a mean change in HbA1c from baseline at study endpoint of -0.98% in the vildagliptin and -0.25% in the placebo groups; patients with a BMI ≥ 30 kg/m2 had a mean change of - 0.96% in the vildagliptin and -0.22% in the placebo group.

Change in HbA1c by age category

No age-related effect on the difference between vildagliptin and placebo for the endpoint change in HbA1c was determined. Mean change in HbA1c from baseline at study endpoint in patients < 65 years were -0.92% for the vildagliptin group and -0.21% for the placebo group; the corresponding changes in patients ≥ 65 years were -1.20 % for the vildagliptin group and - 0.34% for the placebo group.

Change in HbA1c by gender

There were no differences between genders with regard to the difference between vildagliptin and placebo for the changes from baseline in HbA1c. The mean changes in HbA1c from baseline at study endpoint in male patients were -1.03% for the vildagliptin group and -0.38% for the placebo group; and the corresponding changes in females were -0.92% for the vildagliptin group and -0.12% for the placebo group.

Change in HbA1c by race

Vildagliptin demonstrated similar glucose-lowering efficacy in sub-groups by race category. Asian patients (73% of all study population, including mostly Indians, see Table 3) showed a mean change in HbA1c from baseline to study endpoint of -0.96% in the vildagliptin group and -0.23% in the placebo group (baseline HbA1c 8.80% for the vildagliptin group and 8.92% for the placebo group); for Caucasian patients (23% of all study population) the mean changes in HbA1c were -1.05% for the vildagliptin group and -0.21% for the placebo group (baseline HbA1c 8.58% for the vildagliptin group and 8.47% for the placebo group). The HbA1c reduction in these sub-groups was clinically relevant and similar to HbA1c reduction in the overall study population. The number of patients in the other race categories were too small to draw meaningful conclusions.

The subgroups analysis did not reveal any new findings. A greater effect was observed for patients with higher HbA1c at baseline, which is in line with previous findings. No change in effect by age, BMI, gender or race was observed.

Clinical studies in special populations

No studies in special population were performed. It should be noted that 21 % of patients were older than 65 (29 on vildagliptin and 38 on placebo) and overall 33 % of patients had mild renal impairment and 3 % had moderate renal impairment.

2.3.3. Discussion

The scope of the current type II variation is to add a new indication for both vildagliptin and the fixed vildagliptin/metformin combination for use of vildagliptin in triple combination with metformin and SU.

Data from one clinical study has been provided. No dose finding study was performed. The vildagliptin dose selected corresponds to the already approved dosing regimen for the combination of vildagliptin with metformin (50 mg BID). It should be noted that the approved posology for vildagliptin in combination with SU is 50 mg OD as the additional effect of vildagliptin 100 mg daily was not considered to outweigh the observed increase in hypoglycaemia.

Design and conduct of clinical studies

The study was generally well designed and conducted as reflected by relatively few protocol deviations. The inclusion and exclusion criteria were adequate and would identify a representative population. Of note, patients with significant CV disease were excluded. However, current experience regarding CV safety with vildagliptin and use in patients with CHF has been assessed both in procedures EMEA/H/C/771/WS/06/G and EMEA/H/771/WS/187. Although there are limitations to the available data, there are currently no safety signals with regards to cardiac safety. The exclusion of these patients can be accepted since the study is not sized to detect rare events.

The study included titration and stabilisation periods of sufficient duration to ensure that patients included in the study were on adequate doses of both metformin and glimepiride. Instructions for when to introduce rescue medication were in place and it should be noted that the criteria were strengthened over time.

The primary objective, HbA1c change from baseline, is in line with the recently adopted “Guideline on clinical investigation of medicinal products in the treatment of diabetes” (CPMP/EWP/1080 Rev.1). The secondary endpoints (FPG change from baseline and responder rates) are relevant. Statistical methods were adequate.

Efficacy data and additional analyses

The baseline demographic and background characteristics were balanced between groups and the population recruited is considered representative for the target population. The mean baseline HbA1c was 8.7 and 8.8 % for vildagliptin and placebo respectively. About 20 % of patients were elderly although only about 4 % were older than 75 years. The majority of patients were Asian (73 %) and only 23 % were Caucasian. This is acceptable since no clinically relevant differences in the effect of vildagliptin have been observed between Asians and Caucasians. Overall, 36 % of patients had mild to moderate renal impairment.

Discontinuations were few but slightly more common in the vildagliptin treated group compared to placebo, mainly due to more withdrawals of consent and administrative problems. Slightly more

patients in the vildagliptin group than in the placebo group were excluded from the FAS and the PP sets, however, exclusion rates were low.

A clinically relevant reduction of HbA1c was observed when vildagliptin was added to dual therapy with metformin and glimepiride, compared to placebo (-0.76 %, placebo-adjusted). Similar results were observed for both the FAS and the PP populations.

The outcomes of the secondary endpoints both support the primary endpoint. Responder rates (at least one criterion met) were significantly higher for the vildagliptin group (28.3 % vs 5.6 % for vildagliptin and placebo respectively). A relevant responder rate would remain if the entire randomized set was taken into account (43/158 = 27.2 %). A significant difference with regards to lowering of FPG was also observed.

Subgroups analysis showed a greater effect for patients with higher HbA1c at baseline, which is in line with previous findings. No change in effect by age, BMI, gender or race was observed.

Long-term data on the efficacy of vildagliptin 50 mg bid add-on therapy in patients with T2DM inadequately controlled by dual combination of metformin (≥1500 mg) and glimepiride (≥4 mg) beyond the 24 week treatment period in study CLAF237A23152 are not available. However, the long term efficacy of vildagliptin has been established in earlier clinical studies in other indications.

Conclusions on clinical efficacy

The efficacy of vildagliptin 50 mg BID in combination with metformin and SU has been adequately shown.

2.4. Clinical Safety aspects

2.4.1. Patient exposure

The mean duration of overall exposure to study medication was similar in both treatment groups (23.1 weeks for vildagliptin and 24.0 weeks for the placebo group). Also rescue medication free exposure was comparable between both treatment groups (Table 9).

Table 9 Duration of exposure to study drug during the randomized double-blind period by treatment (Randomized Set)

Duration of Exposure in weeks	Vilda 50mg bid + Met + Glim N=158	Placebo + Met + Glim N=160
Exposure		
n	158	160
Mean (SD)	23.1 (4.35)	24.0 (2.21)
Min-Max	0.0-27.3	5.1-32.6
Median	24.0	24.0
Exposure categories		
0 - <4	3 (1.9%)	0 (0.0%)
4 - <8	2 (1.3%)	1 (0.6%)
8 - <12	3 (1.9%)	1 (0.6%)
12 - <16	1 (0.6%)	1 (0.6%)
16 - <20	2 (1.3%)	2 (1.3%)
20 - <24	32 (20.3%)	32 (20.0%)
≥24	115 (72.8%)	123 (76.9%)
Rescue medication free exposure		
n	158	160
Mean (SD)	22.7 (4.76)	22.5 (4.40)
Min- Max	0.0-27.3	5.1-32.6
Median	24.0	24.0
Rescue medication free exposure categories		
0 - <4	3 (1.9%)	0 (0.0%)
4 - <8	4 (2.5%)	5 (3.1%)
8 - <12	3 (1.9%)	2 (1.3%)
12 - <16	2 (1.3%)	12 (7.5%)
16 - <20	4 (2.5%)	5 (3.1%)
20 - <24	32 (20.3%)	31 (19.4%)
≥24	110 (69.6%)	105 (65.6%)

A patient is counted in only one duration range, per treatment.
Duration of exposure (weeks) disregarding any treatment interruptions: (last known date of drug intake – treatment start date + 1)/7, or if date of last study drug intake was not known: (last visit date – treatment start date)/7.
Duration of rescue medication free exposure (weeks) disregarding any treatment interruptions: (last study drug date without rescue medication – Visit 2 date+ 1)/7, or if the subject never took rescue medication rescue-free duration is set to the corresponding overall duration of exposure.

Rescue medication use

Rescue medication was used by fewer patients in the vildagliptin group (n= 6/158, 3.8%) compared to the placebo group (n= 22/160, 13.8%). The mean exposure to rescue medication for patients who used rescue medication was 8.9 weeks in the vildagliptin group and 10.4 weeks in the placebo group. Most frequently used was insulin, with distinctly more patients in the placebo group taking insulin rescue medication (n=13) compared to one patient in the vildagliptin group. Pioglitazone alone was used by 5 patients in the vildagliptin group and by 4 patients in the placebo group. Also 5 patients in the placebo group and none in the vildagliptin group took insulin together with pioglitazone as rescue medication.

Glimepiride dose reductions during the study

Glimepiride dose reductions at any point during the study were reported for 3 patients in the vildagliptin and 1 patient in the placebo group.

Duration of exposure was slightly lower in the vildagliptin treated group due to more early discontinuations. However, a higher proportion of patients in the vildagliptin group completed the study without the need for rescue. Dose reductions of glimepiride were more common in the vildagliptin treated group; however, numbers were very low (3 vs 1 patients).

Adverse events

The percentage of patients with any AEs was comparable in the vildagliptin and the placebo group (50.3% vs. 47.5%). The System Organ Class (SOC) with the highest number of events was the Infections and infestations SOC, with slightly lower incidence rates in vildagliptin patients compared to placebo (19.1% vs. 21.3%) (Table 10).

Overall the incidences of AEs in the following SOCs were more frequent (5% or more difference) in the vildagliptin group than in the placebo group: Nervous system disorders (15.9% vs. 8.1%), and Skin and subcutaneous tissue disorders (11.5% vs. 3.1%). The overall difference in the incidences of AEs by the Nervous system disorders SOC was driven by more dizziness and tremor events in vildagliptin (7.0% vs. 1.9% in the placebo group and 4.5% vs. 1.3% in the placebo group, respectively). The overall difference in the Skin and subcutaneous tissue disorders was driven by more hyperhidrosis events on vildagliptin (6.4% vs. 0.6% in the placebo group). The majority of these events was mild and might be a reflection of mild hypoglycemia in light of better glycaemic control in the vildagliptin group. None of these events led to study discontinuation.

Table 10 Number (%) of patients with AEs by primary system organ class (Safety set)

Primary system organ class	Vilda 50mg bid + Met + Glim N=157 n (%)	Placebo + Met + Glim N=160 n (%)
Any primary system organ class	79 (50.3)	76 (47.5)
Blood and lymphatic system disorders	6 (3.8)	3 (1.9)
Cardiac disorders	3 (1.9)	2 (1.3)
Ear and labyrinth disorders	0 (0.0)	1 (0.6)
Eye disorders	1 (0.6)	2 (1.3)
Gastrointestinal disorders	16 (10.2)	9 (5.6)
General disorders and administration site conditions	17 (10.8)	10 (6.3)
Hepatobiliary disorders	2 (1.3)	5 (3.1)
Infections and infestations	30 (19.1)	34 (21.3)
Injury, poisoning and procedural complications	2 (1.3)	4 (2.5)
Investigations	3 (1.9)	1 (0.6)
Metabolism and nutrition disorders	15 (9.6)	9 (5.6)
Musculoskeletal and connective tissue disorder	10 (6.4)	18 (11.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0 (0.0)	1 (0.6)
Nervous system disorders	25 (15.9)	13 (8.1)
Psychiatric disorders	4 (2.5)	4 (2.5)
Renal and urinary disorders	1 (0.6)	4 (2.5)
Reproductive system and breast disorders	0 (0.0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	5 (3.2)	5 (3.1)
Skin and subcutaneous tissue disorders	18 (11.5)	5 (3.1)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
Coded using MedDRA version 14.1.

The reporting rates were only slightly higher for the vildagliptin group. Apart from Nervous system disorders and Skin and subcutaneous tissue disorders discussed above, a slightly higher reporting of GI events was observed. This is in line with previous submissions. Of note, no malignancies were observed in the vildagliptin treated group.

Most frequently occurring adverse events

Overall the most frequent AEs (reported in ≥ 2% of patients in either treatment group) were comparable between treatments (**Table 11**). The event with the highest reporting rate was urinary tract infections, with similar incidence rates in both groups (vildagliptin group: 6.4% and placebo group: 8.1%). AEs that were more frequently reported in the vildagliptin group than in the placebo group were hypoglycemia-like events, i.e. dizziness and hyperhidrosis. Hypoglycemia was slightly more frequent in the vildagliptin than in the placebo groups (5.1% vs. 1.9%).

Five patients (3.2%) in the vildagliptin group reported anemia events. Four of them presented decreased hemoglobin levels at baseline and the anemia events were considered mild and not suspected to be related to the study drug. One patient, with a history of uterine haemorrhages, reported an anemia AE after planned surgery, which was not suspected to be related to the study drug

by the investigator. None of these 5 anemia cases were reported as SAEs or led to study drug discontinuation.

Table 11 Number (%) of patients reporting common AEs (greater or equal to 2% in any group) by preferred term (Safety set)

Preferred term	Vilda 50mg bid + Met + Glim N=157 n (%)	Placebo + Met + Glim N=160 n (%)
-Any preferred term	79 (50.3)	76 (47.5)
Dizziness	11 (7.0)	3 (1.9)
Hyperhidrosis	10 (6.4)	1 (0.6)
Urinary tract infection	10 (6.4)	13 (8.1)
Headache	8 (5.1)	6 (3.8)
Hypoglycaemia	8 (5.1)	3 (1.9)
Upper respiratory tract infection	8 (5.1)	3 (1.9)
Asthenia	7 (4.5)	3 (1.9)
Tremor	7 (4.5)	2 (1.3)
Pain	6 (3.8)	4 (2.5)
Anaemia	5 (3.2)	0 (0.0)
Fatigue	4 (2.5)	0 (0.0)
Gastritis	4 (2.5)	2 (1.3)
Pharyngitis	2 (1.3)	4 (2.5)
Back pain	1 (0.6)	5 (3.1)
Pain in extremity	1 (0.6)	6 (3.8)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category.
Preferred terms are sorted by descending order of incidence in the Vildagliptin 50 mg group.
Coded using MedDRA version 14.1.

The MAH provided a review of all anaemia events across the study program for vildagliptin showing that there is no relevant imbalance in the reporting when compared to placebo or active comparators. The overall reporting rates were 1.7 % for vildagliptin, 0.7 % for placebo and 1.8 % for comparators.

Drug-related adverse events

The overall incidence rate of AEs that were suspected to be drug-related was higher in the vildagliptin treatment group (12.7%) compared with the placebo group (4.4%). The difference was mainly driven by dizziness (vildagliptin: 3.8% vs. placebo: 0%) and tremor (vildagliptin: 3.2% vs. placebo 0%) observed in nervous system disorders SOC.

More drug-related AEs were reported in the vildagliptin group. These AES are mainly dizziness, tremor, but also hypoglycaemia (vildagliptin: 2.5% vs. placebo: 0.6%) and skin and subcutaneous tissue disorders (vildagliptin: 3.8% versus placebo: 0.6%, including hyperhidrosis and 2 events of pruritus generalised in the vildagliptin group).

Severity of adverse events

Most events were assessed as mild (vildagliptin: 39.5% vs. placebo: 35.0%) or moderate (vildagliptin: 10.2% vs. placebo: 10.6%). Severe AEs were reported in 1 patient in the vildagliptin group (severe hypoglycemia) and in 3 patients in the placebo group (severe acute cholecystitis, severe headache, severe asphyxia and suicide).

Serious adverse events and deaths

An overview of death, serious or other clinically significant AEs is presented in Table 12.

One patient in the placebo group died during the study due to suicide. The overall incidence of SAEs was very low and similar in both groups.

Table 12 Number (%) of patients with serious or clinically significant AEs during the double-blind period (Safety set)

Event category	Vilda 50mg bid + Met + Glim N=157 n (%)	Placebo + Met + Glim N=160 n (%)
Deaths	**0 (0.0)**	**1 (0.6)**
SAEs	**3 (1.9)**	**2 (1.3)**
Angina pectoris	1 (0.6)	0
Angina unstable	0	1 (0.6)
Asphyxia	0	1 (0.6)
Cholelithiasis	1 (0.6)	0
Completed suicide	0	1 (0.6)
Duodenitis	1 (0.6)	0
Dyspnoea	1 (0.6)	0
Gastritis	1 (0.6)	0
Hiatus hernia	1 (0.6)	0
Hypoglycaemia	1 (0.6)	0
Hyponatraemia	0	1 (0.6)
Myocardial ischaemia	0	1 (0.6)
Nausea	1 (0.6)	0
Thrombocytopenia	0	1 (0.6)
Viral infection	0	1 (0.6)

The incidence of SAEs was very low (3 patients (1.9%) in the vildagliptin and 2 patients (1.3%) in the placebo group). All SAEs were singular events and reported in not more than one patient, and no particular trends were noted for any type of events. One hypoglycemia SAE was reported in a vildagliptin-treated patient as a result of decrease in food intake during postsurgical period, which was not suspected be drug-related by the investigator.

SAEs were few without trends were observed.

Adverse events of predefined risk

A comprehensive Risk Management Plan (RMP) is in place for vildagliptin since its original approval. It defines the following identified and potential risks: hepatic, muscle, skin and/or vascular, neuropsychiatric-related events, acute pancreatitis, breast cancer, serious infections, hypoglycemia and angioedema. The RMP for the fixed dose combination of vildagliptin and metformin includes lactic acidosis as an additional identified risk due to the metformin component.

There were no relevant differences in the incidence rates of predefined risk AEs of hepatic, muscle, skin and/or vascular, neuropsychiatric-related events, and infections between vildagliptin and placebo groups. The incidence rates of these events are summarized in**Table 13**. In addition, there were no acute pancreatitis and lactic acidosis AEs reported in this study and no breast cancer or angioedema

cases confirmed by the adjudication committees. None of the infection events on vildagliptin were serious.

Table 13 Incidence of adverse events by predefined risk and treatment (Safety set)

Predefined Risk Category Preferred term Maximum severity	Vilda 50 mg bid + metformin + glimepiride N=157 n (%)	Placebo + metformin + glimepiride N=160 n (%)	Total N=317 n (%)
Predefined Risk Category			
Total	34 (21.7)	37 (23.1)	71 (22.4)
Mild	27 (17.2)	28 (17.5)	55 (17.4)
Moderate	7 (4.5)	8 (5.0)	15 (4.7)
Severe	0	1 (0.6)	1 (0.3)
Hepatic disorder AEs			
Total	2 (1.3)	3 (1.9)	5 (1.6)
Mild	2 (1.3)	3 (1.9)	5 (1.6)
Infections AEs			
Total	30 (19.1)	34 (21.3)	64 (20.2)
Mild	24 (15.3)	26 (16.3)	50 (15.8)
Moderate	6 (3.8)	8 (5.0)	14 (4.4)
Muscle event-related terms			
Total	3 (1.9)	3 (1.9)	6 (1.9)
Mild	3 (1.9)	3 (1.9)	6 (1.9)
Neuropsychiatric-related AEs			
Total	1 (0.6)	1 (0.6)	2 (0.6)
Moderate	1 (0.6)	0	1 (0.3)
Severe	0	1 (0.6)	1 (0.3)
Skin and/or vascular-related AEs			
Total	1 (0.6)	1 (0.6)	2 (0.6)
Moderate	1 (0.6)	1 (0.6)	2 (0.6)

Risk categories are presented alphabetically; preferred terms are sorted within event category alphabetically. A patient with multiple AEs within a SMQ is counted only once in the SMQ category for that treatment.
Coded using MedDRA version 14.1.
Vilda = vildagliptin

The reporting of AEs of special interest was balanced between treatment groups.

Hypoglycaemic events

The proportion of patients who experienced hypoglycaemic events was low in both treatment groups, but was slightly higher in the vildagliptin than in the placebo group (n=8, 5.1% vs. n=3, 1.9%), (**Table 14**). Most of these patients had a single episode of hypoglycaemic event; multiple hypoglycaemic events (two or more) were only reported for one patient in each treatment group. None of these hypoglycaemic events led to study discontinuation and only one of these events was considered grade 2 as a result of reduced food intake after planned surgery, which was not suspected by the investigator to be drug-related.

Table 14 Number of patients experiencing hypoglycemic events during the randomized double-blind period by event profile and treatment (Safety Set)

	Vilda 50mg bid + Met + Glim N=157 n (%)	Placebo + Met + Glim N=160 n (%)
Number (%) of patients with at least one hypoglycemic event	8 (5.1)	3 (1.9)
Number (%) of patients with		
one hypoglycemic event	7 (4.5)	2 (1.3)
two hypoglycemic events	0 (0.0)	1 (0.6)
>2 hypoglycemic events	1 (0.6)	0 (0.0)
Number (%) of patients who discontinued due to hypoglycemic events	0 (0.0)	0 (0.0)
Number (%) of patients with grade 2 hypoglycemic events	1 (0.6)	0 (0.0)
Number (%) of patients with suspected grade 2 hypoglycemic events	0 (0.0)	0 (0.0)

Hypoglycemic events are defined as: a) symptoms suggestive of hypoglycemia, where the patient is able to initiate self-treatment and plasma glucose measurement is <3.1 mmol/L (grade 1), b) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and plasma glucose measurement is <3.1 mmol/L (grade 2), c) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and no plasma glucose measurement is available (suspected grade 2).hypoglycemic events.

The total number of hypoglycaemic events was higher in the vildagliptin group (n=11) than in the placebo group (n=4) (**Table 15**). Most of hypoglycaemic events were assessed as mild (9 out of 11 events in the vildagliptin and 4 out of 4 events in the placebo group).

Table 15 Number of hypoglycaemic events during the randomized double-blind period by event profile and treatment (Safety Set)

	Vilda 50mg bid + Met + Glim N=157 n (%)	Placebo + Met + Glim N=160 n (%)
Total number of hypoglycemic events	**11**	**4**
Plasma glucose value (mmol/L)		
≤2.2	1 (9.1)	0 (0.0)
>2.2-2.8	8 (72.7)	1 (25.0)
>2.8-<3.1	2 (18.2)	3 (75.0)
Grade		
Grade 1	10 (90.9)	4 (100)
Grade 2	1 (9.1)	0 (0.0)
Severity		
Mild	9 (81.8)	4 (100)
Moderate	1 (9.1)	0 (0.0)
Severe	1 (9.1)	0 (0.0)
Relationship to study drug		
Not suspected	7 (63.6)	2 (50.0)
Suspected	4 (36.4)	2 (50.0)

More than one action could be taken per event and a symptomatic event may have more than one symptom.

Hypoglycaemic event was taken into account when patients have symptoms of hypoglycaemia and a plasma glucose < 3.1 mmol/L.

Hypoglycaemias were more common in the vildagliptin treated group as could have been expected considering the lowering in HbA1c observed in this group. However, events were mostly mild. As discussed above, the only severe hypoglycaemic episode occurred in the post-surgical period and was due to inadequate food intake. In addition, three reductions of doses of glimepiride were needed during the study. A statement recommending that a lower dose of SU may be considered to reduce the risk of hypoglycaemia and a special warnings and precautions for use is included in the SmPC. The higher dose of 50 mg BID in combination with SU used in this study, however, appears safe and tolerable.

Laboratory findings

Changes from baseline to endpoint were small for all clinical chemistry, hematology and urinalysis variables and no major differences between both treatment groups were observed.

Persistent hepatic enzyme elevations (ALT or AST) were not reported in the vildagliptin group. Two patients in the vildagliptin group had CPK elevations >10 x ULN at the last study visit. Both cases were from Korea. The patients were clinically asymptomatic and the events were not considered to be AEs by the investigators. One case was associated with excessive alcohol use; the other was confounded by omeprazole therapy, known to be associated with myopathies including rhabdomyolysis (Clark and Strandell, 2006). Both events resolved after treatment discontinuation. Muscle events are being continuously monitored by the MAH and in the recent renewal procedure it was decided that in the next PSUR, the MAH should perform a cumulative review of all cases of myalgia, and discuss whether or not this adverse event should be added to section 4.8 of the SmPC.

ECGs, vital signs, body weight and physical examinations

There were no clinically significant changes in ECG findings at study endpoint reported in the vildagliptin group. There were no major changes in vital signs over time and mean values at Week 24 were similar for both treatment groups. Mean body weight slightly increased by 0.6 kg in the vildagliptin group from 73.1 kg at baseline to 73.7 kg at study end and remained almost unchanged in the placebo group 72.4 kg at baseline vs. 72.3 kg at study end.

Thus, no relevant weight increase was observed when vildagliptin was used in triple combination.

Adverse drug reactions

Safety data from Study CLAF237A23152 were analyzed according to a pre-defined algorithm used to define ADRs for previously approved indications. The following set of criteria was used to assess if an AE was an ADR:

- A difference of AE ≥2% in the vildagliptin group than in placebo group, and
- For suspected drug-related events, a difference of AE >0.2% in the incidence rate and difference in incidence of AEs >1 event

For events meeting the above two criteria and therefore qualifying as ADRs, the Council for International Organizations of Medical Sciences (CIOMS) frequency category was determined based on the incidence of suspected drug-related AEs (**Table 17**).

Based on the criteria for ADR determination, the following events were classified as ADRs: dizziness (common), hyperhidrosis (common), hypoglycemia (common), asthenia (common) and tremor (common) (**Table 16** and **Table 17**).

Table 16 Number (%) of patients reporting AEs in vildagliptin 50 mg bid group with incidence rate >= 2% compared to placebo group by preferred term in the Primary safety population - Study CLAF237A23152 (safety population)

Preferred term	Vilda 50 mg bid + metformin + glimepiride N=157 n (%)	Placebo + metformin + glimepiride N=160 n (%)
Dizziness	11 (7.01)	3 (1.88)
Hyperhidrosis	10 (6.37)	1 (0.63)
Hypoglycaemia	8 (5.1)	3 (1.88)
Upper respiratory tract infection	8 (5.1)	3 (1.88)
Asthenia	7 (4.46)	3 (1.88)
Tremor	7 (4.46)	2 (1.25)
Anaemia	5 (3.18)	0
Fatigue	4 (2.55)	0

Preferred terms are sorted by descending order of incidence in the Vilda 50 mg bid group

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment

Events classified as ADRs are shown in bold

Vilda = vildagliptin

Table 17 Number (%) of patients reporting suspected drug-related AEs in vildagliptin 50 mg bid group with incidence rate >0.2% and incidence >1 event compared to placebo group by preferred term in the Primary safety population – Study CLAF237A23152 (safety population)

Preferred term	Vilda 50 mg bid + metformin + glimepiride N=157 n (%)	Placebo + metformin + glimepiride N=160 n (%)
Dizziness	6 (3.82)	0
Tremor	5 (3.18)	0
Asthenia	4 (2.55)	1 (0.63)
Hyperhidrosis	4 (2.55)	1 (0.63)
Hypoglycaemia	4 (2.55)	1 (0.63)
Hypoaesthesia	3 (1.91)	0
Pain	3 (1.91)	1 (0.63)
Nausea	2 (1.27)	0
Pruritus generalised	2 (1.27)	0

Preferred terms are sorted by descending order of incidence in the Vilda 50 mg bid group

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment

Events classified as ADRs are shown in bold

Vilda = vildagliptin

The following ADRs were identified and proposed to be included in the SmPC:

Nervous system disorders	
Common	Dizziness, tremor
General disorders and administration site condition	
Common	Asthenia
Metabolism and nutritional disorders	
Common	Hypoglycaemia
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis

There were no withdrawals reported due to adverse reactions in the vildagliptin + metformin + glimepiride treatment group vs. 0.6% in the placebo + metformin + glimepiride treatment group.

The incidence of hypoglycemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride vs. 1.9 % for the placebo + metformin + glimepiride group). One severe hypoglycaemic event was reported in the vildagliptin group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg in the vildagliptin group and -0.1 kg in the placebo group). Considering the improvement in HbA1c (which usually would result in some weight gain) with vildagliptin, the MAH's conclusion that the effect on body weight was neutral is endorsed.

This ADR list for the indication will be included in the appropriate section of the product information.

Safety in special populations

Patients in the Primary safety population (CLAF237A23152) were evaluated for AEs and hypoglycaemic events by age categories <65 and ≥65 years of age.

Adverse events

In Study CLAF237A23152, the overall incidence of AEs for patients <65 years was 51.6% in the vildagliptin group and 41.0% in the placebo group. For patients ≥65 years, the overall incidence of AEs was 44.8% in the vildagliptin group and 68.4% in the placebo group.

The most frequent AEs for patients <65 years were infections (incidence of AEs was 22.7% in the vildagliptin group and 16.4% in the placebo group). This was driven mainly by more upper respiratory tract infection events in the vildagliptin group (5.5%) compared with the placebo group (1.6%).

For patients ≥65 years, the most frequent AEs were also infections, with substantially more patients in the placebo group (36.8%) reporting infection AEs compared with the vildagliptin group (3.4%). However, the number of patients ≥65 years was relatively low (29 vildagliptin patients and 38 placebo patients).

Notwithstanding the small subgroup size, the analysis by age did not indicate an increased risk of AEs in the older population. The analyses with regards to age do not evoke any safety concerns.

Hypoglycaemia

In Study CLAF237A23152, 8 patients in the vildagliptin group experienced hypoglycaemic events, of which 6 patients, were <65 years of age, and 2 patients were ≥65 years of age.

Three patients in the placebo group experienced hypoglycaemic events, of which 2 patients were <65 years and 1 patient was ≥65 years.

Overall, there were no differences between age subgroups with respect to percentages of patients reporting hypoglycaemic events in either treatment group.

The subgroup analyses with regards to age do not evoke any safety concerns. No conclusion could be drawn from the analysis of hypoglycaemic events in elderly patients, given the low number of elderly patients including in the study.

Discontinuation due to AES

In Study CLAF237A23152, AEs resulting in discontinuation were reported by 1 patient in the vildagliptin group (pruritus) and by 2 patients in the placebo group (one patient with tinnitus, tremor and dizziness, and one patient who committed suicide by asphyxia) (Table 18).

One patient in the vildagliptin group presented with generalized pruritus of moderate severity from Day 1 to Day 27, leading to study discontinuation. The event (pruritus generalized) resolved after study drug discontinuation. The investigator suspected a relationship between the event and the study medication.

Overall, the incidence of AEs leading to discontinuation was very low in both treatment groups. However, given the low number of elderly patients including in the study, no conclusions can be drawn.

Table 18 Discontinuations due to adverse events by preferred term regardless of relationship to treatment in the Primary safety population – Study CLAF237A23152 (safety population)

Event category	Vilda 50mg bid + Met + Glim N=157 n (%)	Placebo + Met + Glim N=160 n (%)
Discontinuation due to AEs	**1 (0.6)**	**2 (1.3)**
Asphyxia	0	1 (0.6)
Completed suicide	0	1 (0.6)
Dizziness	0	1 (0.6)
Pruritus generalised	1 (0.6)	0
Tinnitus	0	1 (0.6)
Tremor	0	1 (0.6)

Post marketing experience

Vildagliptin is approved in more than 95 countries worldwide. On the basis of sales data, the cumulative patient exposure for vildagliptin and the fixed dose combination of vildagliptin/metformin (Eucreas) since the first launch of the product through Dec-2011 is estimated to be approximately 993,969 patient treatment years (PTY) and 1,651,940 PTY, respectively. The combined (vildagliptin and vildagliptin/metformin) total exposure as of Dec-2011 is estimated to be 2,645,910 PTY.

Vildagliptin is not marketed for the triple combination therapy with metformin and glimepiride in any country.

The safety profile of vildagliptin is well established in its present indications and combinations with regular safety updates being provided to Heath Authorities. The safety data from study

CLAF237A23152 in the present application are consistent with the safety data obtained through marketed use of vildagliptin in the approved indications.

2.4.2. Discussion

In support of the current application for the new indication "*Vildagliptin is indicated in the treatment of type 2 diabetes mellitus in triple combination with a SU and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.*" safety data from the 24-week clinical study CLAF237A23152 has been provided.

The duration of exposure was slightly lower in the vildagliptin treated group due to more early discontinuations. However, a higher proportion of patients in the vildagliptin group completed the study without the need for rescue medication. Dose reductions of glimepiride were more common in the vildagliptin treated group; however, numbers were very low (3 vs 1 patient).

The AE reporting rates were only slightly higher for the vildagliptin group than for placebo (50.3 % vs 47.5 %). The imbalance was driven by a higher reporting within the SOCs "Nervous system disorders" (vildagliptin: 15.9% vs. placebo: 8.1%) and "Skin and subcutaneous tissue disorders" (vildagliptin: 11.5% vs. placebo: 3.1%). This could be explained by a higher reporting of hypoglycaemia and possibly hypoglycaemia events such as dizziness, hyperhidrosis and tremor within these groups. Further to this, a slightly higher reporting of GI events was observed. This is in line with previous submissions. Of note, no malignancies were observed in the vildagliptin treated group.

A higher reporting of anaemia events (5 vs 0 events) was observed in the vildagliptin treated group. These events have been classified as "not suspected to be related to the study drug". A review of anaemia events across the vildagliptin study program have been provided, showing no over-reporting of such events in the large safety data base.

SAEs were reported in few patients in the vildagliptin (n=3) and the placebo group (n=2). 2 events of pruritus generalised have been observed in the vildagliptin group, pruritus being a well-known side effect of vildagliptin.

The reporting of AEs of special interest related to the identified and potential risks in the RMP was low and balanced between treatment groups.

Hypoglycaemias were more common in the vildagliptin treated group (11 vs 4 events) as could have been expected considering the lowering in HbA1c observed in this group. However, events were mostly mild. The only severe hypoglycaemic episode occurred in the post-surgical period and was due to inadequate food intake. More reductions of doses of glimepiride were need in the vildagliptin group versus placebo group (3 versus 1). A statement recommending that a lower dose of SU may be considered to reduce the risk of hypoglycaemia has been amended to the SmPC. The dose of vildagliptin 50 mg BID in combination with SU used in this study, however, appears safe and tolerable.

There were no significant findings with regards to laboratory findings and vital signs apart from two cases with CPK elevations. Muscle events are being continuously monitored by the MAH and in the recent renewal procedure it was decided that in the next PSUR, the MAH should perform a cumulative review of all cases of myalgia, and discuss whether or not this adverse event should be added to section 4.8 of the SmPC. The two new cases observed do not call for any changes to this commitment.

Adverse events that met both the criteria for adverse drug reactions set out by the MAH were selected for presentation in the SmPC. This is acceptable and the SmPC is amended with this information. No withdrawals due to listed adverse events were reported in the vildagliptin treated group. One patient in each treatment groups discontinued due to AEs. The event (generalized pruritus) that led to

discontinuation of the vildagliptin treated patient was suspected to be treatment related. One additional patient in the placebo group discontinued due to death.

Taking the improvement in HbA1c into consideration (which usually would result in some weight gain) t can be concluded that the effect of vildagliptin on body weight is neutral, when used in triple combination with metformin and SU.

The subgroup analyses with regards to age do not evoke any safety concerns.

Conclusions on clinical safety

The safety data provided with this application indicates that the use of vildagliptin in triple combination with metformin and SU is well tolerated. No new safety concerns are evoked and the safety profile for vildagliptin appears unchanged.

2.5. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure

Summary of the risk management plan (including the changes related to the application presented highlighted)

GALVUS

Drug-induced liver injury (DILI)	activities Targeted follow-up using a questionnaire/ checklist. European post-marketing long-term observational study (Study LAF237A2401) Drug utilization study (Study LAF237A2402) Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403)	in patients with hepatic impairment including patients with a pre-treatment ALT or AST >3X the upper limit of normal (ULN). (SmPC Section 4.2 and Section 4.4) Prescribing information includes precautions and liver enzyme monitoring. (SmPC Section 4.4, Special warnings and precautions for use) The SmPC "Undesirable effects" section describes the frequency and severity of hepatic dysfunction observed with vildagliptin. (SmPC Section 4.8, Undesirable effects)
Angioedema	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. European post-marketing long-term observational study (Study LAF237A2401) Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403)	Prescribing information includes angioedema as an adverse reaction. (SmPC section 4.8, Undesirable effects)
Acute pancreatitis	Routine pharmacovigilance activities European post-marketing long-term observational study (Study LAF237A2401) Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403)	Listing pancreatitis as a post-marketing adverse event in (SmPC section 4.8, Undesirable effects)
Skin lesions	Routine pharmacovigilance activities Targeted follow-up of serious events using a questionnaire/ checklist. European post-marketing long-term observational study (Study LAF237A2401)	Skin lesions found in monkeys are described under SmPC Section 4.4 warnings and precautions, 4.8 post-marketing experience and Section 5.3, Preclinical Safety data
Hypoglycemia	Routine pharmacovigilance activities	Listing as an adverse event in SmPC section 4.8, Undesirable

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	Targeted follow-up using a questionnaire/ checklist. All reports of hypoglycemia of greater severity (defined as hypoglycemic episodes assessed as life-threatening by the reporting physician or Novartis, or which result in coma) will be assessed as unlisted. All other episodes of hypoglycemia will be considered as listed Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403) France only : LAF237AFR01	effects
Important potential risks		
Serious infections	Routine pharmacovigilance activities European post-marketing long-term observational study (Study LAF237A2401)	None
Compromised Cardiac Function	Routine pharmacovigilance activities Clinical study in patients with congestive heart failure, LAF237A23118	Cardiac failure: There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients. (SmPC section 4.4)
Muscle events/ myopathy with and without concurrent statin use	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/checklist for all serious events from spontaneous reports, post-marketing surveillance study reports and clinical trial reports regardless of suspectedness. Detailed analysis in PSUR	None
~~Hypoglycemia~~	~~Routine pharmacovigilance activities~~ ~~Targeted follow-up using a questionnaire/ checklist.~~ ~~All reports of hypoglycemia of greater severity (defined as~~	~~Listing as an adverse event in SmPC section 4.8, Undesirable effects~~

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	~~hypoglycemic episodes assessed as life threatening by the reporting physician or Novartis, or which result in coma) will be assessed as unlisted.~~ ~~All other episodes of hypoglycemia will be considered as listed~~ ~~Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403)~~ ~~France only : LAF237AFR01~~	
Neuropsychiatric events	Routine pharmacovigilance activities	None
Breast cancer	Routine pharmacovigilance activities European post-marketing long-term observational study (LAF237A2401)	None
Important missing information		
Gender incidence/ frequency differences	Routine pharmacovigilance activities Gender stratification of data in PSUR	None
Patients with severe hepatic impairment	Routine pharmacovigilance activities	The SmPC states that vildagliptin therapy "is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >3X the upper limit of normal. (SmPC section 4.2 Posology and method of administration)
Patients with compromised cardiac function (*NYHA functional class III-IV)*	Routine pharmacovigilance activities Clinical study in patients with congestive heart failure, LAF237A23118	Cardiac failure: There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients. (SmPC section 4.4)
Pregnancy	Routine pharmacovigilance activities	Vildagliptin should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the fetus. (SmPC Section 4.6 Pregnancy and lactation)

EUCREAS

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Transaminase elevation and Drug-induced liver injury (DILI)	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. European post-marketing long-term observational study (Study LAF237A2401) Drug utilization study (Study LAF237A2402) Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403)	Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >3X the upper limit of normal (ULN). (SmPC Section 4.2 and Section 4.4) Prescribing information includes precautions and liver enzyme monitoring. (Section 4.4, Special warnings and precautions for use) The SmPC "Undesirable effects" section describes the frequency and severity of hepatic dysfunction observed with vildagliptin. (SmPC Section 4.8, Undesirable effects)
Angioedema	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. European post-marketing long-term observational study (Study LAF237A2401) Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403)	Prescribing information includes angioedema as an adverse reaction. (SmPC section 4.8, Undesirable effects)
Acute pancreatitis	Routine pharmacovigilance activities European post-marketing long-term observational study (Study LAF237A2401) Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403)	Listing pancreatitis as a post-marketing adverse event in (SmPC section 4.8, Undesirable effects
Lactic acidosis	Routine pharmacovigilance activities Startified analyses for age and renal function status European post-marketing long-term observational study (LAF237A2401)	Prescribing information includes lactic acidosis in SmPC.
Skin lesions	Routine pharmacovigilance activities Targeted follow-up of serious events using a questionnaire/ checklist. European post-marketing long-term observational study (Study LAF237A2401)	Skin lesions found in monkeys are described under SmPC Section 4.4 warnings and precautions, 4.8 post-marketing experience and Section 5.3, Preclinical Safety data
Hypoglycemia	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist.	Listing as an adverse event in SmPC section 4.8, Undesirable effects

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	All reports of hypoglycemia of greater severity (defined as hypoglycemic episodes assessed as life-threatening by the reporting physician or Novartis, or which result in coma) will be assessed as unlisted. All other episodes of hypoglycemia will be considered as listed Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403) France only : LAF237AFR01	
Important potential risks		
Serious infections	Routine pharmacovigilance activities European post-marketing long-term observational study (Study LAF237A2401)	None
Compromised Cardiac Function	Routine pharmacovigilance activities Clinical study in patients with congestive heart failure, LAF237A23118	Cardiac failure: There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients. (SmPC section 4.4)
Muscle events/ myopathy with and without concurrent statin use	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/checklist for all serious events from spontaneous reports, post-marketing surveillance study reports and clinical trial reports regardless of suspectedness. Detailed analysis in PSUR	None
~~Hypoglycemia~~	~~Routine pharmacovigilance activities~~ ~~Targeted follow-up using a questionnaire/ checklist.~~ ~~All reports of hypoglycemia of greater severity (defined as hypoglycemic episodes assessed as life-threatening by~~	~~Listing as an adverse event in SmPC section 4.8, Undesirable effects~~

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	~~the reporting physician or Novartis, or which result in coma) will be assessed as unlisted.~~ ~~All other episodes of hypoglycemia will be considered as listed~~ ~~Multinational, multicenter, post-authorization, prospective observational cohort study (Study LAF237A2403)~~ ~~France only : LAF237AFR01~~	
Neuropsychiatric events	Routine pharmacovigilance activities	None
Breast cancer	Routine pharmacovigilance activities European post-marketing long-term observational study (LAF237A2401)	None
Important missing information		
Gender incidence/ frequency differences	Routine pharmacovigilance activities Gender stratification of data in PSUR	None
Patients with severe hepatic impairment	Routine pharmacovigilance activities	The SmPC states that vildagliptin therapy "is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >3X the upper limit of normal. (SmPC Section 4.2 Posology and method of administration)
Patients with compromised cardiac function (*NYHA functional class III-IV)*	Routine pharmacovigilance activities Clinical study in patients with congestive heart failure, LAF237A23118	Cardiac failure: There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients. (SmPC section 4.4)
Pregnancy	Routine pharmacovigilance activities	Vildagliptin should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the fetus. (SmPC Section 4.6 Pregnancy and lactation)

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.6. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

4.1 Therapeutic indications

Vildagliptin is indicated in the treatment of type 2 diabetes mellitus in adults:

As monotherapy
- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

As dual oral therapy in combination with
- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

As triple oral therapy in combination with
- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

4.2 Posology and method of administration

Posology
Adults
When used as monotherapy, ~~or~~ in ~~dual~~ combination with metformin or a thiazolidinedione, or in combination with metformin and a sulphonylurea, the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.

When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Doses higher than 100 mg are not recommended.

If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione ~~or with metformin and a sulphonylurea~~ hasve not been established.

[…]

4.4 Special warnings and precautions for use

[…]

Hypoglycaemia
Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

[…]

4.8 Undesirable effects

[…]

Combination with metformin and a sulphonylurea

Table 5 Adverse reactions reported in patients who received Galvus 50 mg twice daily in combination with metformin and a sulphonylurea (N=157)

Metabolism and nutritional disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Dizziness, tremor
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
General disorders and administration site condition	
Common	Asthenia

Description of selected adverse reactions

There were no withdrawals due to adverse reactions reported in the vildagliptin + metformin + glimepiride treatment group versus 0.6% in the placebo + metformin + glimepiride treatment group.

The incidence of hypoglycaemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride group versus 1.9% for the placebo + metformin + glimepiride group). One severe hypoglycaemic event was reported in the vildagliptin group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg in the vildagliptin group and -0.1 kg in the placebo group).

[…]

5.1 Pharmacodynamic properties

[…]

A 24-week randomised, double-blind, placebo-controlled trial was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (≥1500 mg daily) and glimepiride (≥4 mg daily). Vildagliptin in combination with metformin and glimepiride significantly decreased HbA_{1c} compared with placebo. The placebo-adjusted mean reduction from a mean baseline HbA_{1c} of 8.8% was -0.76%.

Table ~~6~~7 Key efficacy results of vildagliptin in placebo-controlled monotherapy trials and in add-on combination therapy trials (primary efficacy ITT population)

Monotherapy placebo controlled studies	**Mean baseline HbA_{1c} (%)**	**Mean change from baseline in HbA_{1c} (%) at week 24**	**Placebo-corrected mean change in HbA_{1c} (%) at week 24 (95%CI)**
Study 2301: Vildagliptin 50 mg twice daily (N=90)	8.6	-0.8	-0.5* (-0.8, -0.1)
Study 2384: Vildagliptin 50 mg twice daily (N=79)	8.4	-0.7	-0.7* (-1.1, -0.4)
		* p< 0.05 for comparison versus placebo	
Add-on / Combination studies			
Vildagliptin 50 mg twice daily +	8.4	-0.9	-1.1* (-1.4, -0.8)

metformin (N=143)			
Vildagliptin 50 mg daily + glimepiride (N=132)	8.5	-0.6	-0.6* (-0.9, -0.4)
Vildagliptin 50 mg twice daily + pioglitazone (N=136)	8.7	-1.0	-0.7* (-0.9, -0.4)
Vildagliptin 50 mg twice daily + metformin + glimepiride (N=152)	8.8	-1.0	-0.8* (-1.0, -0.5)
		* p< 0.05 for comparison versus placebo + comparator	

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Malta.

3. Overall conclusion and impact on the benefit/risk balance

Vildagliptin was approved in the EU in September 2007. Vildagliptin is currently approved as monotherapy (when metformin is inappropriate) and in combination with metformin, SU and thiazolidinedione. The fixed dose combination with metformin was approved in November 2007.

The current type II variation is an application for a new indication: "*Vildagliptin is indicated in triple combination with a SU and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.*" for Galvus/Jalra/Xiliarx (vildagliptin) and to include the triple combination with metformin in the indication for Eucreas/Icandra/Zomarist (vildagliptin and metformin).

Benefits

Beneficial effects

With the currently submitted study the MAH has adequately shown that the addition of vildagliptin to dual therapy with metformin and SU results in further HbA1c lowering. The observed placebo-adjusted reduction of 0.76 % is considered clinically relevant and was further supported by the secondary endpoints with significantly higher responder rates for vildagliptin (28 % vs 6 %, vildagliptin and placebo respectively) as well as a significant effect on FPG. These results were obtained with vildagliptin dose already approved for the combination of vildagliptin with metformin (50 mg bid). It should be noted that the approved posology for vildagliptin in combination with SU is 50 mg once daily as the additional effect of vildagliptin 100 mg daily was not considered to outweigh the observed increase in hypoglycaemia at the time of approval of this combination.

Uncertainty in the knowledge about the beneficial effects

Long-term data on the efficacy of vildagliptin 50 mg bid add-on therapy in patients with T2DM, inadequately controlled by a combination of metformin and SU, beyond 24 weeks are not available. However, studies with longer duration were included in the MAA for vildagliptin, which is considered sufficient.

Risks

Unfavourable effects

With this application 24-week safety data in 318 patients (158 in the vildagliptin treated group) has been provided. The AE reporting rates were only slightly higher for the vildagliptin treated group than for placebo (50.3 % vs 47.5 %). The imbalance was driven by a higher reporting of hypoglycaemia and possibly hypoglycaemia related events such as dizziness, hyperhidrosis and tremor. Further to this, a slightly higher reporting of GI events was observed. This is in line with previous submissions. Of note, no malignancies were observed in the vildagliptin treated group. SAEs were few with 3 patients in the vildagliptin treated group and 2 patients in the placebo group reporting events. Due to the low numbers, no trends could be observed.

With regards to the identified and potential risks: hepatic, muscle, skin and/or vascular, neuropsychiatric-related events, acute pancreatitis and infections, the reporting was low and balanced between treatment groups. No cases of acute pancreatitis were observed.

Hypoglycaemias were more common in the vildagliptin treated group (11 vs 4 events) as could have been expected considering the lowering in HbA1c observed in this group. However, events were few and mostly mild. Only one severe hypoglycaemic episode occurred in the vildagliptin treated group vs none in the placebo group. More reductions of doses of glimepiride were observed in the vildagliptin group versus placebo group (3 versus 1).

During the MAA, it has been shown in a previous study 2305 that vildagliptin 100 mg is no more effective than vildagliptin 50 mg once daily in combination with a SU. In this study, the incidence of hypoglycaemia was low in combination with SU, but there was more hypoglycaemia events observed with vildagliptin 100 mg/day (6 patients = 3.6% of patients) than with placebo (2 patients = 0.6% of patients).

The increase in hypoglycaemia risk was in the same range in study 23152 (5.1% of patients versus 1.9%) with 50 mg bid as was observed for the 100 mg daily dose in the dual therapy study, but a lower dose was not investigated in study 23152. However, in this setting, the dose of vildagliptin 50 mg bid in combination with SU appears safe and tolerable with regards to hypoglycaemias. Thus, based on the new data available with study 23152 the higher dose of vildagliptin for the triple combination is acceptable provided that the proposed recommendations for lowering the SU dose in case of hypoglycaemia are included in the SmPC, sections 4.2 and 4.4, as a safety measure.

There were no significant findings with regards to laboratory findings and vital signs apart from two cases with CPK elevations (further discussed below).

Adverse events that met both the criteria for adverse drug reactions set out by the MAH were selected for presentation in the SmPC. This is acceptable and the SmPC have been amended with this information.

Taking the improvement in HbA1c (which usually would result in some weight gain) with vildagliptin into account, it can be concluded that the effect of vildagliptin on body weight was neutral when used in triple combination with metformin and SU.

Neither the safety data from the overall population nor the subgroup analyses with regards to age evoke any new safety concerns.

Uncertainty in the knowledge about the unfavourable effects

The patients of the study are rather young and with few co-morbidities and co-medications. The risks of the triple combination, notably regarding hypoglycaemic events, are unknown in a more vulnerable population.

Two cases with CPK elevations were observed in the study. None of these CPK elevations were considered an AE or study drug suspected by the investigators. Muscle events are being continuously monitored by the MAH and in the recent renewal procedure it was decided that in the next PSUR, the MAH should perform a cumulative review of all cases of myalgia, and discuss whether or not this adverse event should be added to section 4.8 of the SmPC. The two new cases observed do not call for any changes to this commitment.

Balance

Importance of favourable and unfavourable effects

The data provided has adequately shown that adding vildagliptin to the combinations therapy with metformin and SU results in a clinically relevant lowering of HbA1c.

This effect was achieved without an unacceptable increase in hypoglycaemic events or weight gain. The safety profile remained unchanged and no new safety issues emerged with this new combination. The risk of hypoglycaemia could be managed in clinical practice but the prescribers should be informed on this risk. Section 4.2 in the SmPC has been amended to include information to consider a reduction of the dose of SU to avoid hypoglycaemic event, in line with the texts of other DPP-4 inhibitors and a warning regarding hypoglycaemia in section 4.4 has also been amended.

Benefit-risk balance

Discussion on the benefit-risk assessment

The combination of metformin plus a SU is a broadly used dual therapy for the treatment of T2DM. However, many patients on dual-combination therapy with metformin and a SU agent do not achieve or maintain glycaemic control. The data presented show that adding a third drug with a different mechanism of action, vildagliptin, to a dual combination with metformin and SU is efficient and that the combination has an acceptable safety profile.

4. Recommendations

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

Variation accepted		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication for the use of vildagliptin and vildagliptin/metformin in triple therapy with a sulphonylurea and metformin affecting sections 4.1, 4.2, 4.8 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in Vildagliptin version 10.1 and Vildagluiptin/metformin version 8.1 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA