20 September 2012
EMA/CHMP/565928/2012
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/0257

Note

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

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
CPK	Creatine phosphokinase
CV	Cardiovascular
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
FAS	Full analysis set
FPG	Fasting plasma glucose
HbA_{1c}	Glycosylated hemoglobin A_{1c}
n	number of patients in study/treatment group
OAD	Oral anti-diabetic
PP	Per protocol
RMP	Risk management plan
SAE	Serious adverse event
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Standard deviation
SE	Standard error
Scr	Screening
SOC	System organ class
SYE	Subject-year exposure
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
Titr	Titration
TZD	Thiazolidinedione
ULN	Upper limit of normal
Vilda	Vildagliptin (LAF237)

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 15 March 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/0257	vildagliptin	See Annex A
Eucreas, EMEA/H/C/000807/WS/0257	vildagliptin / metformin hydrochloride	See Annex A
Icandra, EMEA/H/C/001050/WS/0257	vildagliptin / metformin hydrochloride	See Annex A
Jalra, EMEA/H/C/001048/WS/0257	vildagliptin	See Annex A
Xiliarx, EMEA/H/C/001051/WS/0257	vildagliptin	See Annex A
Zomarist, EMEA/H/C/001049/WS/0257	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 combination with insulin affecting sections 4.1, 4.2, 4.8 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

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

Rapporteur: Kristina Dunder

Appointed Rapporteur for the WS procedure: Kristina Dunder

1.2. Steps taken for the assessment

Submission date:	15 March 2012
Start of procedure:	25 March 2012
Rapporteur's preliminary assessment report circulated on:	21 May 2012
Rapporteur's updated assessment report circulated on:	15 June 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 June 2012
MAH's responses submitted to the CHMP on:	16 July 2012

Rapporteur's assessment report on the MAH's responses circulated on:	28 August 2012
CHMP opinion:	20 September 2012

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included 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

Vildagliptin is an oral antidiabetic agent which belongs to the dipeptidyl peptidase 4 (DPP-4) inhibitors class. 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).

Despite the benefits patients have from combination treatment of insulin and oral anti-diabetic (OAD), the use certain OADs is associated with increased risk of hypoglycaemia and/or weight gain. Thus, there is currently an unmet medical need for patients with T2DM who would benefit from insulin-OAD combination treatment to add another effective drug with good tolerability to the armamentarium of oral agents available for combination with insulin.

The present submission provides safety and efficacy data in support of a new indication for vildagliptin in combination with insulin (with or without metformin).

The MAH proposes that a positive benefit-risk balance has been established to allow for usage of vildagliptin in combination with insulin (with or without metformin), as follows:

"Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control"

In addition, an update of Sections 4.2, 4.8 and 5.1 of the SmPC in accordance with the safety and efficacy data provided in this application is proposed.

2.2. Clinical Efficacy aspects

Table 1 Overview of controlled efficacy studies

Study No.	Study objective, population	Randomized patients	Treatment duration	Treatment arms	Protocol-specified efficacy
23135	Efficacy and safety of vildagliptin 50 mg bid add-on therapy in patients with T2DM inadequately controlled by insulin, with or without concomitant metformin treatment (HbA_{1c} 7.5 - 11%)	449	24 weeks	Vilda 50 mg bid + stable dose of insulin with or without stable metformin (N=228 patients) Placebo + stable dose of insulin with or without stable metformin (N=221 patients)	Change in HbA_{1c} (*vs.* placebo)

T2DM = type 2 diabetes; vilda = vildagliptin

Table 2 Overview of supportive studies

Study No.	Study objective, population	Randomized patients	Treatment duration	Treatment arms	Protocol-specified exploratory efficacy
2311	Efficacy and safety in T2DM patients (HbA_{1c} 7.5-11%) who had been treated for at least 3 months with insulin with at least 30 U/day	296	24 weeks	Vilda 50 mg bid + insulin Placebo + insulin	Change in HbA_{1c} (*vs.* placebo)
23137	Safety (primary) / efficacy (exploratory) in T2DM patients with moderate or severe renal impairment (HbA_{1c} 6.5-10.0%)	525[#]	24 weeks	Vilda 50 mg qd + antidiabetic background treatment Placebo + antidiabetic background treatment	Change in HbA_{1c} (*vs.* placebo)
23138	Safety (primary) / efficacy (exploratory) in T2DM patients with severe renal impairment (HbA_{1c} 6.5-10.0%)	148[##]	24 weeks	Vilda 50 mg qd + antidiabetic background treatment Sita 25 mg qd + antidiabetic background treatment	Change in HbA_{1c} (*vs.* sitagliptin)

includes 10 patients with mild renal impairment inadvertently randomized.

includes 1 patient with moderate renal impairment inadvertently randomized.

T2DM = type 2 diabetes; vilda = vildagliptin; sita = sitagliptin.

The MAH have conducted two randomized, double-blind, placebo-controlled trial with the objective to evaluate the efficacy and safety of vildagliptin in combination with insulin in insulin-treated patients with type 2 diabetes (T2DM) with insufficient glycaemic control. Study CLAF237A23135 included patient with T2DM treated with basal and premixed insulin, with or without metformin. This study is considered pivotal for the indication.

The second study, Study CLAF237A2311 (which was submitted with the original marketing authorization application), included patients on insulin treated with any insulin regimen resulting in

almost half of the patients being treated with 3 or more insulin injections and insulin doses of approximately 80 U/day. Moreover, concomitant metformin was not allowed. Therefore, the study is not considered fully representative of current clinical practice.

In addition, two 6 months studies in patients with moderate and severe renal impairment (CLAF237A23137 and CLAF237A23138) previously submitted and assessed within procedure EMEA/H/C/771/1048/1051/WS/149 are provided as supportive evidence given that the majority of patients in these two studies (68% to 82% across studies and degree of renal impairment) were treated with insulin.

2.2.1. Methods – analysis of data submitted

Study CLAF237A23135

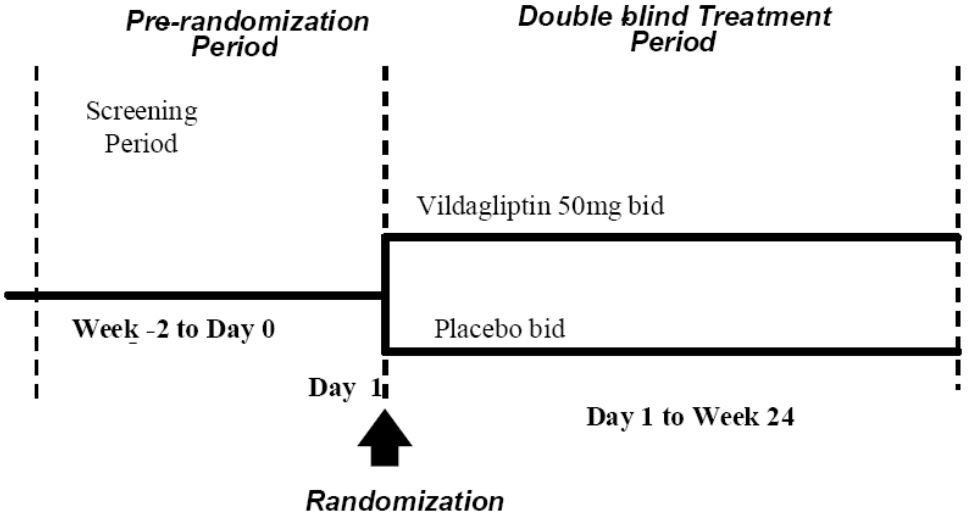
This was a multi-center, randomized, double-blind, placebo-controlled, parallel group study with a 24-week treatment period. Following a 2-week screening period, patients with T2DM receiving a stable dose of long-acting, intermediate-acting or pre-mixed insulin by one or two daily injection with or without stable metformin treatment were randomized 1:1 to treatment with vildagliptin 50 mg bid or placebo.

No dose finding study was performed. The vildagliptin dose selected corresponds to the already approved dosing regimen which is acceptable.

Patient enrolment was stratified by metformin use and conducted to achieve an approximately 60/40 ratio of patients receiving concomitant metformin treatment or no metformin treatment, respectively. Additionally, patients were stratified by the type of insulin (long-acting vs. intermediate-acting or pre-mixed insulin). Following screening, scheduled study visits were at Week 0 (start of study treatment), then at 4-week intervals: 4, 8, 12, 16, 20 and 24 (end of study treatment) weeks, as depicted in **Figure 1** below.

Patients continued on a stable dose of long or intermediate-acting or pre-mixed insulin and metformin, if applicable, throughout the study.

Figure 1 Design of study CLAF237A23135



The overall study design is acceptable. Both patients with metformin treatment and without such treatment were included and patients were stratified by metformin use, allowing assessment of both combinations.

Main inclusion and exclusion criteria

The study population consisted of male and female patients with T2DM, who had to be 18 to 80 years old, with HbA1c between ≥7.5 and ≤11% and FPG <270 mg/dL (15 mmol/L) at screening visit. Patients had to be treated with a stable dose (≤1 unit/kg/day) of long-acting, intermediate-acting or pre-mixed insulin for at least 12 weeks prior to screening visit. Patients could also be treated with a stable dose of metformin (≥1500 mg qd or a maximally tolerated dose) for at least 12 weeks prior to Visit 1. Body mass index had to be 22-40 kg/m2.

Patients were excluded if treated with other OAD than metformin. Other important exclusion criteria were significant cardiovascular (CV) disease (e.g. congestive heart failure NYHA III or IV, recent myocardial infarction (MI) or stroke).

The inclusion and exclusion criteria are adequate and would identify a representative population on a stable background therapy. 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 adverse events (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.

Objectives and endpoints

The primary efficacy objective was to demonstrate superiority of vildagliptin vs. placebo for the change in HbA1c from baseline to study endpoint in the overall population.

The primary efficacy endpoint was the change in HbA1c from baseline to study endpoint in the full analysis set (FAS).

Key secondary efficacy objective was to demonstrate superiority of vildagliptin vs. placebo in the subgroups using insulin alone or insulin + metformin.

Other secondary objectives included evaluation of fasting plasma glucose (FPG) and responder rates defined as proportion of patients reaching predefined HbA1c target.

The chosen objectives and outcomes are 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). The key secondary endpoint is relevant for the evaluation of the subgroups of patients treated with or without metformin. In addition an exploratory endpoint, investigating measures of insulin resistance and sensitivity as well as pancreatic β-cell function, was included. This will however not be further discussed in this report.

Treatments

Patients were instructed to take one tablet (vildagliptin 50 mg or vildagliptin 50 mg matching placebo) before the breakfast meal every day and one tablet (vildagliptin 50 mg or vildagliptin 50 mg matching placebo) before the evening meal every day except the day of the study visit.

Adjustments to the dose of study medication or metformin were not allowed.

Insulin

The dose of insulin had to remain stable or within a 10% increase of the baseline dose throughout the trial (with no change in frequency or insulin type) unless dose adjustments were required for safety reasons at the investigator's discretion. This could include insulin dose decreases for safety reasons at anytime without specific dose limits.

The addition of rapid or short-acting insulin and/or additional doses or amounts of the patient's usual insulin according to rescue medication criteria was allowed.

Rescue medication

Rescue medication included rapid or short acting insulin and/or additional doses or amounts of the patient's usual long-acting, intermediate-acting or pre-mixed insulin when administered according to prespecified criteria and when elevated glucose was not due to illness, or other incidental circumstance potentially causing deterioration of glucose control. No medications other than these specified insulin alterations were considered as rescue medication. Within the specified guidelines the insulin type, dose and dose frequency used for rescue were at the investigator's discretion.

Patients were to maintain stable metformin and insulin doses throughout the study. Instructions for allowed insulin dose adjustments (within a 10 % increase from baseline) as well as for rescue medication (insulin) were in place. This is of importance considering the study duration of 24 weeks with a placebo control in order not to jeopardise the wellbeing of the participants.

Statistical methods

The primary efficacy variable was the change from HbA1c (unit in %) measurement at baseline to the study endpoint, censored at the start of major change in insulin background therapy. The superiority of vildagliptin 50mg bid over placebo was evaluated by testing the following hypothesis:

$H0: \delta_{\text{vilda 50mg bid + insulin}} = \delta_{\text{placebo + insulin}}$ versus $Ha: \delta_{\text{vilda 50mg bid + insulin}} < \delta_{\text{placebo + insulin}}$

where δ are the change from baseline to study endpoint in HbA1c in the treatment group indicated.

The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment, pooled center, metformin use stratum and type of insulin stratum as the classification variable and baseline HbA1c as the covariate. A closed testing hierarchical methodology was used to maintain an overall 2.5% level for the primary one sided hypothesis and the two key secondary onesided hypotheses (namely the same variable assessed within the sub-populations of patients treated with insulin and concomitant metformin therapy, and patients treated with insulin only). The analysis of the primary efficacy variable using the Full analysis set was the primary basis of conclusion. A sensitivity analysis based on the PP set was also performed to assess the robustness of the conclusion.

The percentage of patients meeting each of the pre-defined responder criteria (categorical changes in HbA1c) was summarized in both the Full analysis and Per Protocol sets.

In addition to the two key secondary objectives, further secondary efficacy variables consisted of FPG and the exploratory efficacy variables (insulin resistance and sensitivity, beta-cell function parameters from oGTT). These variables were analyzed using the same ANCOVA model as specified for the primary efficacy variable.

All efficacy analyses were performed on data censored at the start of major changes in the insulin background therapy. Major change in insulin background therapy was defined as: a) rescue medication taken for ≥7 days in any 30-day period or ≥5 days consecutively, or b) any change (for reasons other than rescue) in insulin frequency and/or insulin type and/or ≥10% increase in dose for ≥7 days in any

30-day period or ≥5 days consecutively. In addition, changes in HbA1c were analyzed also using uncensored data.

Demographic and background data as well as safety data were summarized by treatment group.

Handling of missing data

Data after discontinuations for any reason (or if final schedule visit measurement is missing for any reason) were imputed by carrying the last on-treatment measurement (scheduled or unscheduled) forward (LOCF) through the final schedule visit (Week 24 visit).

Patients who started major changes in insulin background therapy were considered as censored from the start date of major changes in insulin onward. Data after the start of major changes in insulin were imputed by the last on-treatment measurement before or at the start of major insulin therapy changes, carried forward (LOCF) through the final schedule study visit (Week 24 visit).

Statistical methods were generally adequate.

The initiation of rescue medication should be seen as evidence of lack of efficacy. The use of censoring and LOCF should hence imply that subjects in need of a major change in insulin background therapy were treated as “failures” in the analyses. Of importance to support the primary analysis is however the sensitivity analysis without censoring of data. This may be considered a more conservative analysis under the assumption that it will be more subjects in the placebo arm that needed rescue/a major change in insulin background therapy.

Regarding the HbA1c responder analyses the same approach as in the primary analysis seems to have been used (i.e. LOCF). This should, analogous the primary analysis, imply a non-responder imputation in subjects who were censored due to a major change in insulin background therapy. However, the same, i.e. a non-responder imputation, is not necessarily true for patients who discontinued study treatment but is depending on the reason for discontinuation.

2.2.2. Results

Disposition of patients

A total of 717 patients were screened for eligibility and 268 failed screening. The most common reasons for screen failure were having not met diagnostic/severity criteria (49.6% of all screen failures) and unacceptable laboratory values (48.5%).

The randomization scheme resulted in an approximate 1:1 allocation for vildagliptin 50 mg bid and placebo, 228 and 221 patients respectively enrolled in the trial. The percentage of patients who discontinued was slightly higher in the placebo group mainly due to a higher percentage of patients that were lost to follow-up or who withdrew consent. Discontinuations due to AEs were infrequent, with a slightly higher incidence in the vildagliptin group than in the placebo group (**Table 3**). The largest imbalance was observed due to loss of follow-up (7 vs 0 in the placebo and vildagliptin groups respectively).

Table 3 Patient disposition (Randomized set)

Disposition Reason	Vilda 50mg bid N=228 n (%)	Placebo N=221 n (%)	Total N=449 n (%)
Completed	208 (91.2)	191 (86.4)	399 (88.9)
Discontinued	20 (8.8)	30 (13.6)	50 (11.1)
Administrative problems	1 (0.4)	1 (0.5)	2 (0.4)
Adverse event(s)	9 (3.9)	4 (1.8)	13 (2.9)
Death	0 (0.0)	1 (0.5)	1 (0.2)
Lost to follow-up	0 (0.0)	7 (3.2)	7 (1.6)
Patient withdrew consent	8 (3.5)	12 (5.4)	20 (4.5)
Protocol deviation	2 (0.9)	5 (2.3)	7 (1.6)

Table 4 Number (%) of patients in the analysis sets

Set	Vilda 50mg bid N=228	Placebo N=221	Total N=449
Randomized	228 (100%)	221 (100%)	449 (100%)
Safety	227 (99.6%)	221 (100%)	448 (99.8%)
FAS	224 (98.2%)	216 (97.7%)	440 (98.0%)
Per protocol	206 (90.4%)	196 (88.7%)	402 (89.5%)

Percentages are based on the number of patients in the Randomized set.

No major differences between treatment groups were observed for other protocol deviations not leading to exclusion from any analysis population. Most frequent was mis-stratification with regard of insulin type during randomization that occurred in 51.8% of patients in the vildagliptin group and 47.5% of patients in the placebo group, and oGTT test not performed at Visits 2, 5 and/or 8 (18.9% vs. 20.4%). The oGTT was made for exploratory purposes and the lack of data is therefore not crucial for the current assessment.

The high numbers of mis-stratification was due to incorrect choice of insulin type by the investigators in the IRT system. Sites were instructed to enter in the IRT system the type of insulin for a patient as long-acting or pre-mixed/intermediate. However, a number of investigators entered the incorrect insulin type and the patients were stratified by the IRT system by this designation. The mis-stratification did not result in unbalanced distribution of the three different types of insulin (long-acting, intermediate and premixed) in the two treatment groups. Given the inaccuracies within the IRT insulin category data, the insulin categories from the eCRF were considered for the primary or secondary analysis.

Conduct of the study

There were no amendments to the study protocol (released on 8-Jul-2010).

A total of 67 centers in 11 countries enrolled at least one patient (number of centers in brackets): Australia (5), Belgium (4), Czech Republic (6), Germany (13), Guatemala (5), Hong-Kong (2), Hungary (5), India (10), Romania (4), Slovakia (9), United Kingdom (4). Forty-five out of 67 sites were located in Europe.

First patient enrolled: 27-Sep-2010 (first patient first visit)

Last patient completed: 24-Oct-2011(last patient last visit)

Randomisation and blinding

At Visit 2 all eligible patients were randomized via IRT to one of the two treatment arms. Patients were stratified by:

- With or without concomitant metformin therapy;
- Type of insulin (long-acting vs. intermediate-acting/pre-mixed, regardless of rapid or short-acting insulin included in pre-mixed formulations).

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

Randomisation and blinding procedures were generally adequate, although mis-stratification occurred. As explained above, this was apparently due to difficulties in filling the form with regards to insulin treatment. Although the different types of insulin regimens (long-acting vs intermediate-acting/premixed) may be used in slightly different populations, the mis-stratification is not considered to affect the outcome.

Baseline demographics and background characteristics

Both treatment groups were well-balanced for most demographic and patient disease background characteristics at baseline.

Both treatment groups were well-balanced for all patient characteristics at baseline (Table 5- 2). Mean age was 59 years in both groups, and approximately 30% of patients were ≥65 years of age. The proportion of male/female patients was balanced (nearly 1:1) in both treatment groups. Most patients were Caucasian, followed by Asian (predominantly Indian ethnicity) and Other (predominantly Hispanic/Latino ethnicity). Mean BMI was 29 kg/m^2 in both treatment groups.

Table 5 Patient baseline demographic characteristics (Randomized set)

Demographic Variable	Vilda 50mg bid N=228	Placebo N=221	Total N=449
Age (Yrs)			
n	228	221	449
Mean	59.3	59.1	59.2
SD	9.85	10.08	9.95
Min	30.0	30.0	30.0
Median	60.0	60.0	60.0
Max	80.0	80.0	80.0
Age group			
< 65 yrs	160 (70.2%)	154 (69.7%)	314 (69.9%)
>=65 yrs	68 (29.8%)	67 (30.3%)	135 (30.1%)
< 75 yrs	210 (92.1%)	209 (94.6%)	419 (93.3%)
>=75 yrs	18 (7.9%)	12 (5.4%)	30 (6.7%)
Sex			
Female	119 (52.2%)	106 (48.0%)	225 (50.1%)
Male	109 (47.8%)	115 (52.0%)	224 (49.9%)
Race			
Asian	87 (38.2%)	86 (38.9%)	173 (38.5%)
Caucasian	116 (50.9%)	116 (52.5%)	232 (51.7%)
Other	25 (11.0%)	19 (8.6%)	44 (9.8%)
Ethnicity			
Hispanic/Latino	25 (11.0%)	24 (10.9%)	49 (10.9%)
Indian (Indian subcontinent)	62 (27.2%)	61 (27.6%)	123 (27.4%)
Chinese	24 (10.5%)	24 (10.9%)	48 (10.7%)
Other	117 (51.3%)	112 (50.7%)	229 (51.0%)
Height (cm)			
n	228	221	449
Mean	163.7	164.6	164.2
SD	9.91	10.32	10.12
Min	139.0	142.0	139.0
Median	164.5	165.0	165.0
Max	191.0	198.0	198.0
Body weight (kg)			
n	228	221	449
Mean	77.9	78.9	78.4
SD	16.24	16.69	16.45
Min	44.5	45.0	44.5
Median	75.3	76.1	76.0
Max	132.0	131.1	132.0
BMI (kg/m^2)			
n	228	221	449
Mean	28.9	29.0	28.9
SD	4.38	4.58	4.47
Min	21.1	22.0	21.1
Median	28.1	28.1	28.1
Max	40.1	39.8	40.1
BMI group			
<30 (kg/m^2)	138 (60.5%)	139 (62.9%)	277 (61.7%)
>=30(kg/m^2)	90 (39.5%)	82 (37.1%)	172 (38.3%)
>=35(kg/m^2)	23 (10.1%)	28 (12.7%)	51 (11.4%)

Similar baseline characteristics as for the overall RAN population were seen in the subset of the RAN patients with (139 vildagliptin and 137 placebo) and without (89 vildagliptin and 84 placebo) concomitant metformin use except for a slightly lower body weight in patients without concomitant metformin use (75.4 and 74.8 kg in the vildagliptin and placebo groups, respectively).

Most patient baseline background characteristics were comparable between both treatment groups. Mean HbA1c was 8.8% in both treatment groups, and distribution to BMI baseline categories was similar in both groups. FPG was slightly higher in the vildagliptin than in the placebo group (9.6 vs. 9.1 mmol/L). Mean duration of type 2 diabetes was 13 years in both groups.

Prior treatment with insulin was also comparable in both treatment groups. The proportion of patients using premixed insulin was higher than of intermediate or long-acting insulin, with comparable proportions of patients in both treatment groups. The number of insulin injections per day (1.8 in both treatment groups), duration of insulin use (4.4 years in both groups) and the mean total daily insulin dose (39.9 and 41.9 units in the vildagliptin and placebo groups, respectively) were also well balanced in both treatment groups. In spite of the mis-stratification, prior insulin treatment was balanced.

The mean metformin daily doses at screening were similar, with 1928 mg/day in the vildagliptin and 1948 mg/day in the placebo group. Mean metformin doses were adequate, indicating that the patients included were true treatment failures.

Overall similar baseline background characteristics as for the overall RAN population were seen in both subsets of the RAN patients with and without concomitant metformin. Higher proportion of patients (71.1%) was treated with premixed insulin in the insulin without concomitant metformin subgroup than in the insulin and metformin subgroup (54.0%).

Apart from the study indication, non insulin-dependent diabetes mellitus, most frequent medical conditions were vascular disorders (68.9% and 73.8% of patients in the vildagliptin and placebo groups, respectively, of these the most frequent was hypertension, 68.0% and 71.5% of patients, respectively). Also frequently reported were nervous system disorders (37.7% vs. 38.5%, most frequently peripheral neuropathy, 31.6% vs. 32.6%), surgical and medical procedures (29.4% vs. 24.4%), eye disorders (29.8% vs. 30.8%), and other metabolism disorders such as hyperlipidaemia (27.2% vs. 24.4%).

Thus, background medical conditions were as expected in a population of patients with type T2DM of long duration.

Primary efficacy results

The primary efficacy endpoint was the change in HbA1c from baseline to study endpoint in the full analysis set (FAS). The ANCOVA results for the change in HbA1c from baseline to endpoint for both Full analysis set and Per-protocol set are summarized in **Table 6**.

Vildagliptin 50 mg bid as add-on to stable insulin therapy regardless of metformin therapy demonstrated a reduction in HbA1c at study endpoint of -0.77% from a baseline of 8.80%, and the difference vs. placebo of -0.72% was statistically significant ($p<0.001$).

In the pivotal study CLAF237A23135, all efficacy data were censored at major change to the insulin background therapy. A total of 64 patients (14.3%), 27 (11.8%) in the vildagliptin group and 37 (16.7%) in the placebo group, had a major change to their insulin background therapy. Thus, the proportion of patients who were censored due to major changes in the insulin background therapy was higher in the placebo group.

The data of all 64 patients were censored for the analysis of the efficacy variables, including HbA1c. Efficacy data after the start of major changes in insulin were imputed by the last on-treatment

measurement before or at the start of major insulin therapy changes, carried forward (LOCF) through the final schedule study visit (Week 24 visit).

Results from the analysis using HbA1c data not censored at major change in insulin were similar as for censored data; the reduction in HbA1c at study endpoint in the vildagliptin group was -0.86% and the difference vs. placebo of -0.67% was statistically significant (p<0.001).

Similar results were also observed for the subsets of patients with or without concomitant metformin therapy. Differences between treatment with vildagliptin and placebo were slightly higher in patients not receiving concomitant metformin (-0.84%) than in those patients who received metformin (- 0.63%); differences vs. placebo were statistically significant (p<0.001) for both subsets of patients. Similar results for HbA1c reduction not censored at major change in insulin were shown in the insulin with metformin and insulin without metformin subgroups, the difference vs. placebo was -0.59% and -0.78%, respectively, both differences were statistically significant (p<0.001). Results in the Per protocol set were similar to the Full analysis set results.

Table 6 ANCOVA results for change in HbA1c (%) from baseline to study endpoint (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	221	8.80 (0.07)	-0.77 (0.08)	-0.72 (0.10)	(-0.92 , -0.52)	<0.001*
Placebo	215	8.84 (0.07)	-0.05 (0.08)			
Full-analysis set (Insulin + met)						
Vilda 50mg bid	133	8.78 (0.08)	-0.98 (0.09)	-0.63 (0.12)	(-0.86 , -0.39)	<0.001*
Placebo	134	8.80 (0.08)	-0.35 (0.09)			
Full-analysis set (Insulin)						
Vilda 50mg bid	88	8.84 (0.12)	-0.60 (0.19)	-0.84 (0.19)	(-1.21 , -0.47)	<0.001*
Placebo	81	8.90 (0.11)	0.24 (0.20)			
Per protocol set						
Vilda 50mg bid	206	8.82 (0.07)	-0.80 (0.09)	-0.75 (0.11)	(-0.96 , -0.54)	<0.001*
Placebo	196	8.82 (0.07)	-0.06 (0.09)			
Per protocol set (Insulin + met)						
Vilda 50mg bid	125	8.83 (0.08)	-1.02 (0.10)	-0.66 (0.13)	(-0.91 , -0.41)	<0.001*
Placebo	120	8.79 (0.09)	-0.36 (0.10)			
Per protocol set (Insulin)						
Vilda 50mg bid	81	8.81 (0.12)	-0.64 (0.20)	-0.89 (0.19)	(-1.28 , -0.51)	<0.001*
Placebo	76	8.86 (0.11)	0.26 (0.21)			

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. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24. 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, Hba1c at baseline, metformin use (not required for metformin use subgroups), insulin type and pooled centers.

Primary analysis is based on FAS.

* indicates statistical significance according to the hierarchical test procedure.

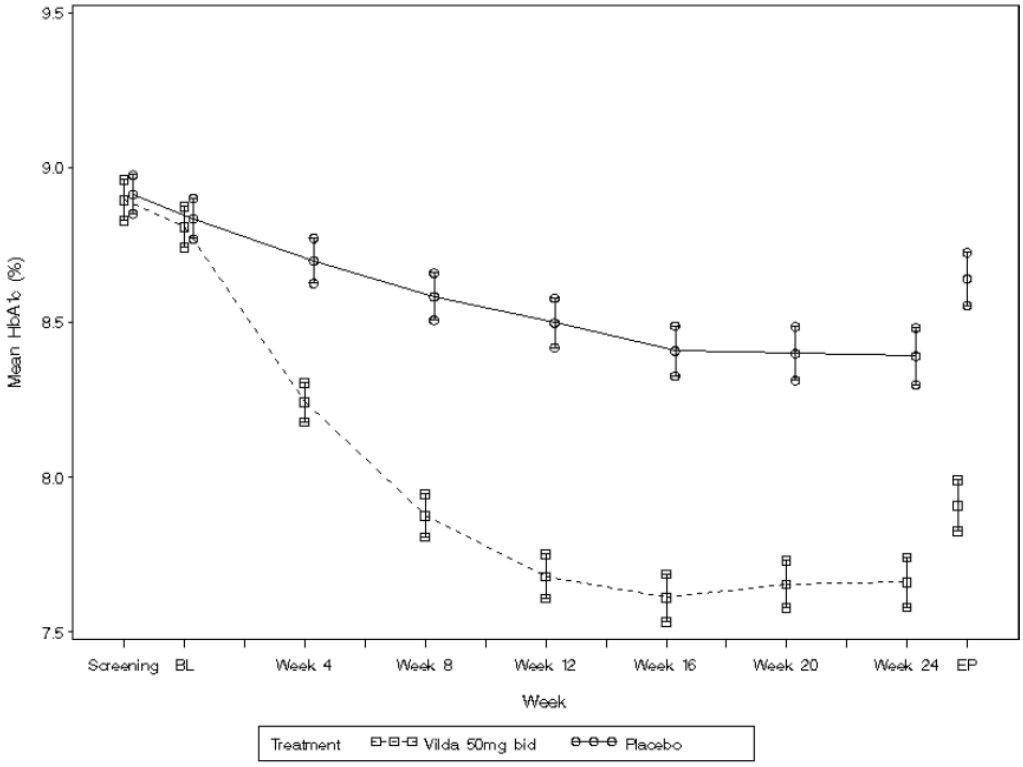
The primary endpoint was met for the study. The reduction of HbA1c from baseline was statistically significantly greater in the vildagliptin treated group. The reduction was clinically relevant. Also the secondary endpoints, i.e. to show superiority for vildagliptin compared to placebo in the two subgroups, were met.

The subgroup of patients on background metformin therapy consisted of 267 patients of which 133 were exposed to vildagliptin. Corresponding figures for patients no on metformin were 169 (88).

The sensitivity analyses of the primary endpoint without censoring of data supports the outcome in the primary analyses.

HbA1c values in the vildagliptin treatment group were consistently lower than in the placebo group at all post- baseline study visits as well as at study endpoint.

Figure 2 Mean HbA1c (%) by treatment and visit (Full analysis set)



Unadjusted means and standard errors (vertical bars) are given.
Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24.

The mean HbA1c time profiles for the subsets of patients receiving or not receiving concomitant metformin therapy resembled those of the overall FAS population; however, differences between the vildagliptin and the placebo groups were generally slightly larger in patients taking no concomitant metformin medication than in those patients taking metformin.

The curves separated after four weeks of treatment with a maximum effect was observed at week 16 where after the HbA1c reduction reached a plateau.

Additional sensitivity analyses for the HbA1c using BOCF

In the pivotal study CLAF237A23135, the primary efficacy endpoint was the change in HbA1c from baseline to study endpoint (HbA1c censored at major change in insulin) in the FAS population. Data after discontinuations for any reason (or if final schedule visit measurement is missing for any reason) and data after the start of major changes in insulin were imputed by carrying the last on-treatment measurement (scheduled or unscheduled) forward (LOCF) through the final schedule visit (Week 24 visit). Patients who had major changes in insulin background therapy were considered as censored from the start date of major changes in insulin onward (decreases in insulin dose were not considered major change in insulin). The HbA1c measurement taken at or before the start of major change in insulin reflects the lack of efficacy of the study treatment while maintaining a stable insulin dose.

The analysis of the primary endpoint showed that adding vildagliptin 50 mg bid to stable insulin therapy regardless of metformin therapy resulted in a robust reduction in HbA1c at study endpoint (- 0.77%) and the difference vs. placebo of -0.72% was statistically significant ($p<0.001$). In addition, an analysis of all available HbA1c data regardless of major changes in insulin background therapy for change in HbA1c at study endpoint from baseline in FAS was performed. The results were similar to the censored data; the reduction in HbA1c at study endpoint in the vildagliptin group was -0.86% and the difference vs. placebo of -0.67% was statistically significant ($p<0.001$).

An additional analysis using BOCF for patients with missing data at Week 24 and patients with major change in insulin background treatment was performed. The results were similar to the pre-planned analyses presented above confirming the efficacy of vildagliptin: The reduction in HbA1c at study endpoint in the vildagliptin group was -0.76%, and the difference vs. placebo of -0.62% was clinically relevant and statistically significant ($p<0.001$).

In conclusion, vildagliptin 50 mg bid in combination with a stable insulin therapy with or without metformin demonstrated a clinically relevant and statistically significant reduction in HbA_{1c} compared to placebo, irrespective of the method used for analysis of the change in HbA1c.

The requested analysis using BOCF, a theoretically more conservative approach, shows consistent results and, hence supports the primary analysis although, as might be expected, the difference between vildagliptin and placebo is somewhat smaller.

Key secondary efficacy outcomes

Treatment responders

Responder rates based on the proportion of patients reaching predefined HbA1c levels were distinctly higher in the vildagliptin group than in the placebo group for all defined categories, and differences between treatment with vildagliptin and placebo were statistically significant for all responder categories (**Table 7**).

Results for patients in the Per Protocol set were very similar. Similar results were observed for the subsets of FAS patients with and without concomitant metformin use, and differences between the vildagliptin and the placebo groups were statistically significant except for the two responder criteria "HbA1c < 7% in patients with baseline HbA1c ≤ 8%" and "HbA1c ≤ 6.5%" in patients without concomitant metformin use; however, the absolute number of patients in both treatment groups who met these two criteria appears to be low in both treatment groups.

Table 7 Number of patients who responded at study endpoint by treatment (Full Analysis Set and Full Analysis Set by concomitant metformin use)

Full Analysis Set	Vilda 50mg bid N=224 n (%)	Placebo N=216 n (%)	p-value*
N[1]	221 (100.0)	215 (100.0)	
Responder Criterion			
At least one criterion met	49 (22.2)	12 (5.6)	<0.001
HbA_{1c} < 7% [2]	49/221 (22.2)	11/214 (5.1)	<0.001
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	16/55 (29.1)	5/52 (9.6)	0.011
HbA_{1c} ≤ 6.5% [2]	17/221 (7.7)	5/215 (2.3)	0.010
Full Analysis Set Concomitant metformin use: yes	**Vilda 50mg bid N=136 n (%)**	**Placebo N=135 n (%)**	**p-value***
N[1]	133 (100.0)	134 (100.0)	
Responder Criterion			
At least one criterion met	28 (21.1)	7 (5.2)	<0.001
HbA_{1c} < 7% [2]	28/133 (21.1)	7/134 (5.2)	<0.001
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	8/30 (26.7)	2/34 (5.9)	0.036
HbA_{1c} ≤ 6.5% [2]	13/133 (9.8)	2/134 (1.5)	0.003
Full Analysis Set Concomitant metformin use: no	**Vilda 50mg bid N=88 n (%)**	**Placebo N=81 n (%)**	**p-value***
N[1]	88 (100.0)	81 (100.0)	
Responder Criterion			
At least one criterion met	21 (23.9)	5 (6.2)	0.001
HbA_{1c} < 7% [2]	21/88 (23.9)	4/80 (5.0)	<0.001
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	8/25 (32.0)	3/18 (16.7)	0.309
HbA_{1c} ≤ 6.5% [2]	4/88 (4.5)	3/81 (3.7)	>0.999

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. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24.

* Chi-square test for Vilda 50mg bid vs. Placebo.

1) Number of patients with both baseline and endpoint HbA1c measurements, which is used as denominator unless specified otherwise.

2) Denominator includes only patients with baseline HbA1c ≥ 7% (> 6.5%) and endpoint HbA1c measurement.

3) Denominator includes only patients with 7% ≤ baseline HbA1c ≤ 8% and endpoint HbA1c measurement.HbA1c ≤ 6.5% [2]

Thus, in the overall population, significantly higher proportions of patients reached the predefined targets. The overall responder rate was 22 %. Also in the subgroups with concomitant metformin or without metformin treatment all responder rates were in favour of vildagliptin treatment although numbers were small. The responder analysis appears to support the primary outcome.

Additional sensitivity analysis for responder rates

In the pivotal study CLAF237A23135, the responder rates analysis was carried out on data censored at major change to insulin therapy.

As requested by the reviewer, an additional analysis was performed where all subjects with missing HbA1c at Week 24 and patients who had major change in insulin background therapy were included as non-responders. The results of this analysis (**Table 8**) are consistent with the results from pre-planned analysis, and therefore support the efficacy of vildagliptin 50 mg bid used in combination with insulin.

Table 8 Number of patients who responded at study endpoint by treatment (Randomized set)

Randomized Set	**Vilda 50mg bid N=228 n (%)**	**Placebo N=221 n (%)**	**p-value***
N'[1]	228 (100.0)	221 (100.0)	
Responder Criterion			
At least one criterion met	49 (21.5)	12 (5.4)	<0.001
HbA_{1c} < 7% [2]	49/228 (21.5)	11/220 (5.0)	<0.001
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	16/57 (28.1)	5/55 (9.1)	0.010
HbA_{1c} ≤ 6.5% [2]	17/228 (7.5)	5/221 (2.3)	0.011

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. Study endpoint is defined as the assessment obtained at week 24 for patients who had a week 24 assessment and did not have a major change in insulin background therapy, or the baseline value for any other patients.

* Chi-square test for Vilda 50mg bid vs. Placebo.

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 HbA1c ≤ 8% and endpoint HbA1c measurement.

The number of patients classified as responders are the same although the percentage of patients are slightly different due to a different analysis population (here, including all randomised patients). The use of a failure approach seems hence to further confirm that using LOCF (as in the pre-planned analyses) implied that an assessment indicating lack of efficacy was carried forward.

Fasting plasma glucose

At baseline, adjusted mean FPG values in the vildagliptin treatment group compared to the placebo group were similar (9.84 vs. 9.50 mmol/L). ANCOVA results showed that the mean FPG decreased with vildagliptin by -0.77 mmol/L and by -0.18 mmol/L in the placebo group; the difference between treatment groups was -0.59 mmol/L (p=0.05) (Table 9).

Differences in changes in FPG between the vildagliptin and the placebo groups were larger in the subset of patients taking insulin without concomitant metformin (-1.07 mmol/L) than in patients taking insulin with concomitant metformin (-0.21 mmol/L), the differences between the vildagliptin and the placebo groups were not statistically significant for any subset of patients.

Similar differences in changes in FPG between the vildagliptin and the placebo groups were observed for the Per protocol set; however, statistical significance was not achieved for the overall PP set and for any subset of patients.

Table 9 ANCOVA results for change in FPG (mmol/L) from baseline to study 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	222	9.84 (0.20)	-0.77 (0.24)	-0.59 (0.30)	(-1.18 , 0.00)	0.050
Placebo	215	9.50 (0.20)	-0.18 (0.25)			
Full-analysis set (Insulin + met)						
Vilda 50mg bid	134	9.86 (0.24)	-0.98 (0.25)	-0.21 (0.33)	(-0.86 , 0.43)	0.521
Placebo	134	9.30 (0.24)	-0.77 (0.25)			
Full-analysis set (Insulin)						
Vilda 50mg bid	88	9.80 (0.36)	-0.75 (0.59)	-1.07 (0.57)	(-2.19 , 0.05)	0.060
Placebo	81	9.84 (0.35)	0.32 (0.62)			
Per Protocol set						
Vilda 50mg bid	206	9.82 (0.21)	-0.80 (0.25)	-0.53 (0.31)	(-1.13 , 0.07)	0.084
Placebo	196	9.56 (0.21)	-0.27 (0.25)			
Per protocol set (Insulin + met)						
Vilda 50mg bid	125	9.90 (0.25)	-1.07 (0.26)	-0.14 (0.34)	(-0.81 , 0.52)	0.670
Placebo	120	9.35 (0.25)	-0.92 (0.26)			
Per Protocol set (Insulin)						
Vilda 50mg bid	81	9.68 (0.39)	-0.76 (0.61)	-1.09 (0.58)	(-2.24 , 0.05)	0.061
Placebo	76	9.88 (0.36)	0.33 (0.63)			

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. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24. 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, FPG at baseline, metformin use (not required for metformin use subgroups) insulin type and pooled centers.

* indicates statistical significance at 5% level.

Consistent with the HbA1c results, FPG in the vildagliptin treatment group was consistently lower than in the placebo group at all post-baseline study visits as well as at study endpoint. However, the difference between treatment groups was largest in the first months of the study (i.e., Weeks 4, 8 and 12) and decreased towards the end of the study.

In patients taking insulin with metformin, differences in FPG between the vildagliptin and the placebo groups were generally smaller than in patients taking no concomitant metformin, and virtually no difference between treatments was observed at Week 24 and at study endpoint in both subsets of patients.

Although a less prominent effect was observed on FPG there was a trend in favour of vildagliptin treatment in all analyses. Considering the clinically relevant effect on HbA1c, this is acceptable and may reflect a more prominent effect of vildagliptin during daytime compared to night-time.

Comparison of results in subpopulations

In the pivotal study CLAF237A23135, mean changes in HbA1c were summarized for the subgroups HbA1c baseline category, BMI baseline category, age category, gender and race. Overall, the results for all subgroup categories were in line with the overall study results.

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 reduction in HbA1c from baseline to endpoint censored at major change in insulin (-1.10% and -0.31% in the vildagliptin 50 mg bid and in the placebo groups) compared to patients with HbA1c ≤ 8% (-0.28% and +0.15% in vildagliptin and placebo groups, respectively).

Similar results were seen for baseline categories HbA1c > 9% and ≤ 9%. Change from baseline to endpoint censored at major change in insulin in patients with HbA1c >9% were -1.40% and -0.56% in the vildagliptin 50 mg bid and the placebo groups, respectively, and in patients with baseline HbA1c ≤ 9% changes were -0.61% and +0.03%, respectively.

Change in HbA1c by BMI category at baseline

No consistent effect of BMI at baseline on changes in HbA1c was observed. Patients with a BMI <30 kg/m^2 showed a mean change in HbA1c from baseline at endpoint censored at major change in insulin of -0.96% and -0.13% in the vildagliptin 50 mg bid and the placebo group, respectively; patients with a BMI ≥ 30 kg had a mean change of -0.81% and -0.30% in the vildagliptin and placebo groups, respectively, and for those patients with a BMI ≥ 35 kg the changes were mean -0.28% (median -0.3%) and mean -0.62% (median -0.4%), respectively. The low number of patients with a BMI ≥ 35 kg at baseline (23 and 26 patients in the vildagliptin and the placebo group) limits the robustness of conclusions to be drawn for this BMI category.

Change in HbA1c by gender

No gender-related effect on change in HbA1c was observed. The mean changes in HbA1c from baseline at endpoint censored at major change in insulin in male patients were -0.90% and - 0.17% in the vildagliptin and the placebo treatment groups, respectively, and the corresponding changes in females were -0.90 and -0.23%, respectively.

Change in HbA1c by race

Caucasian patients (the majority of all patients) showed a mean change in HbA1c from baseline at endpoint censored at major change in insulin of -0.71% and -0.21% in the vildagliptin 50 mg bid and the placebo groups, respectively; for Asian patients a slightly higher mean change of -1.02% was observed in the vildagliptin group compared to Caucasian patients, and a similar change as for Caucasian patients in the placebo group (-0.25%). For “Other” patients a change in HbA1c of -1.32% and +0.13% was observed. The low number of patients in this subgroup (25 and 19 patients in the vildagliptin and the placebo group) does not allow valid conclusions to be drawn.

The subgroup analyses revealed (as expected) a greater reduction in HbA1c in patients with higher HbA1c at baseline. There was no relevant influence on HbA1c response by BMI, gender or race.

2.2.3. Supportive studies

The study design and results from supportive studies, relevant to the present application have previously been submitted. The studies are briefly summarized below.

Study CLAF237A2311

Study CLAF237A2311 was a 24-week randomized, double-blind, placebo-controlled study. Patients with type 2 diabetes (HbA1c 7.5-11%) who had been treated for at least 3 months with insulin were included in the trial. Eligible patients were randomized equally to vildagliptin 50 mg bid or placebo in addition to continuing their insulin therapy. The study included 296 patients of which 144 were randomised to vildagliptin and 152 to placebo.

In study CLAF237A2311, mean diabetes duration was about 15 years, with more than 6 years of insulin therapy, both longer than in CLAF237A23135 (about 13 and 4.4 years, respectively). Patients had mean BMI 33 kg/m^2 (more than 2/3 of patients were obese) and were receiving mean daily dose of insulin 82 U/day, which was twice as high as in pivotal study CLAF237A23135. The mean daily number of insulin injections was 2.8 and 45% of patients were receiving more than 3 injections per day, with one third requiring more than 4 injections per day. Generally, patient demographics, background characteristics and exposure to study drug were comparable for both the vildagliptin and placebo populations. Mean baseline HbA1c (8.53%) was similar to the baseline HbA1c (8.8%) in the pivotal Study CLAF237A23135.

The patients on vildagliptin treatment in study CLAF237A2311 showed a 0.51% mean decrease in HbA1c from a baseline of 8.52%. At study endpoint a statistically significant difference in change from baseline in HbA1c was observed with vildagliptin 50 mg bid combination treatment as compared to placebo (-0.27%, p=0.022).

The mean difference in HbA1c between the patients on vildagliptin treatment and was smaller than the difference in the pivotal study. Importantly, this slight improvement in glycemic control was accompanied by lower incidence and numbers of hypoglycemic events (incidence of events 22.9% vs. 29.6%; number of events 113 vs. 185, vildagliptin vs. placebo, respectively). A post-hoc subgroup analysis in the patient subgroup $\geq$ 65 years revealed a distinct difference (mean -0.6%, p=0.001) in favour of vildagliptin.

This study was assessed within the original MAA for vildagliptin. The addition of vildagliptin to insulin therapy resulted in a larger reduction in HbA1c compared to placebo (-0.27 %). At that time, the CHMP had concerns, whether a difference of 0.27% would be clinically meaningful. It should be noted that study CLAF237A2311 included patients with longer diabetes duration and a longer history of insulin treatment as well as higher insulin doses than study CLAF237A23135. The HbA1c outcome was markedly lower in this study compared to study CLAF237A23135. It could be speculated that this is due to lower endogenous insulin secretion in patients with longer duration and thus a diminished effect of vildagliptin. It is, however, noteworthy that although the effect on HbA1c was modest, the incidence of hypoglycaemias was lower in the vildagliptin treated group. The data from study CLAF237A2311, however, lend some additional support to the efficacy of vildagliptin in combination with insulin.

Studies CLAF237A23137 and CLAF237A23138

Both Study CLAF237A23137 and Study CLAF237A23138 were 24-week randomized, double-blind studies in patients with different degrees of renal impairment. The majority of patients (68% to 82% across the two studies and the degree of renal impairment) in these studies were treated with insulin at study entry, either as monotherapy or in combination with oral antidiabetics. Efficacy was an exploratory objective.

Study CLAF237A23137 included patients with moderate and severe renal impairment, and vildagliptin 50 mg qd was compared to placebo, either added to patient's background anti-diabetic therapy.

Study CLAF237A23138 included patients with severe renal impairment and vildagliptin 50 mg qd was compared to sitagliptin 25mg qd, either added to patient's background anti-diabetic therapy.

Overall, there were no major between-treatment differences in demographic or other baseline characteristics in studies CLAF237A23137 and CLAF237A23138. Mean HbA1c in the two studies (7.6% to 7.8%) was lower than the mean HbA1c in study CLAF237A23135 (8.8%). Patients enrolled in the two renal studies had a long-standing T2DM, with the duration ranging from 15 to 19 years, longer than the duration of T2DM in study CLAF237A23135.

In Study CLAF237A23137, 68.4% of randomized patients with moderate renal impairment were treated with insulin at study entry, and of the randomized patients with severe renal impairment in this study, 80.5% were on insulin background therapy at baseline.

In Study CLAF237A23138, 81.8% of randomized patients were on insulin background therapy at baseline.

A post-hoc analysis was performed in the subgroups of patients treated with insulin from studies CLAF237A23137 and CLAF237A23138. The results of this analysis showed clinically relevant reductions in HbA1c with vildagliptin 50 mg qd.

In the group of patients with moderate renal impairment in Study CLAF237A23137 (N=196), mean HbA1c was reduced by -0.61% from a baseline of 7.98% with vildagliptin and by -0.09% from a baseline of 7.88% with placebo (mean absolute changes from baseline).

In patients with severe renal impairment on insulin background therapy at baseline (N=175), mean HbA1c was reduced by - 0.74% from a baseline of 7.71% with vildagliptin and by -0.21% from a baseline of 7.75% with placebo.

In study CLAF237A23138, in patients on insulin background therapy at baseline (N=114), comparable efficacy was seen with vildagliptin 50 mg qd and sitagliptin 25 mg qd. Mean HbA1c was reduced by -0.50% from a baseline of 7.57% with vildagliptin and by -0.58% from a baseline of 7.83% with sitagliptin. These results were consistent with the data obtained from the Full analysis set in these studies. In both studies, insulin doses did not change significantly from baseline.

Studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149 with the aim of including a posology for patients with moderate to severe renal impairment. A majority of patients in both studies were on a background treatment with insulin in monotherapy or in combination with OADs. A reduced vildagliptin dose was used due to the increased exposure of vildagliptin in patients with renal impairment. Also in this population, a clinically relevant reduction of HbA1c was observed when vildagliptin was added to insulin.

Impact of BMI on efficacy

In Study CLAF237A23135 the highest BMI subgroup (BMI ≥ 35 kg/m²) had the smallest mean reduction from baseline in HbA1c (- 0.28%), compared with the BMI categories < 30 and ≥ 30 kg/m² (mean change from baseline -0.96% and -0.81%, respectively). However, the low number of patients with a BMI ≥ 35 kg at baseline (23 and 26 patients in the vildagliptin and the placebo group) limits the conclusions to be drawn for this BMI category.

It is noteworthy that in Study CLAF237A2311 the mean reduction in HbA1c from baseline was the same, -0.4%, irrespective of the BMI subgroup (<30, ≥ 30 or ≥ 35 kg/m²) [CSR CLAF237A2311, Table 9-3]. Data from two dedicated add-on to insulin studies do not suggest that vildagliptin efficacy is influenced by BMI.

Table 10 and Table 11 provide an overview of changes in HbA1c from baseline by BMI subgroups in key clinical studies where vildagliptin was used as monotherapy, or as add-on therapy, focusing on the approved doses. In most of the studies HbA1c improvements were similar across the different BMI subgroups (Studies 2301, 2310, 2327, 2327E1, 2303, 2308, 2338, 2354, 2304, 2305), while in some studies there was a trend towards a smaller HbA1c reduction in patients with higher BMI (Studies 2384, 2309,). Importantly, clinically relevant efficacy was maintained across all BMI categories.

This new analysis supports the conclusion in the CHMP Assessment Report that there is no relevant influence on HbA1c response by BMI, i.e. vildagliptin was efficacious irrespective of the BMI category. Importantly, vildagliptin has not been associated with weight gain (Foley et al, 2010), which is an important consideration for T2DM patients with high BMI.

Table 10 Effect of BMI on changes in HbA_{1c} (%) from baseline to study endpoint in key monotherapy studies (primary efficacy population)

		BMI at baseline (kg/m^2)		
		<30	**≥30**	**≥35**
Study 2301 (24 weeks)				
vilda 50 mg bid	n	26	64	31
	Baseline mean HbA_{1c}	8.63	8.53	8.63
	Mean change in HbA_{1c} (SE)	-0.94 (0.351)	-0.91 (0.194)	-0.92 (0.252)
placebo	n	33	61	31
	Baseline mean HbA_{1c}	8.52	8.34	8.35
	Mean change in HbA_{1c} (SE)	-0.47 (0.248)	-0.25 (0.186)	-0.45 (0.258)
Study 2384 (24 weeks)				
vilda 50 mg bid	n	32	47	27
	Baseline mean HbA_{1c}	8.64	8.21	8.07
	Mean change in HbA_{1c} (SE)	-1.01 (0.268)	-0.55 (0.178)	-0.42 (0.252)
placebo	n	37	51	28
	Baseline mean HbA_{1c}	8.48	8.44	8.53
	Mean change in HbA_{1c} (SE)	0.02 (0.244)	-0.08 (0.191)	-0.10 (0.255)
Study 2309 (52 weeks)				
vilda 50 mg bid	n	204	306	164
	Baseline mean HbA_{1c}	8.7	8.7	8.7
	Mean change in HbA_{1c} (SE)	-1.1 (0.09)	-0.8 (0.08)	-0.7 (0.11)
metformin 1000 mg bid	n	95	154	75
	Baseline mean HbA_{1c}	8.9	8.7	8.8
	Mean change in HbA_{1c} (SE)	-1.5 (0.15)	-1.4 (0.10)	-1.4 (0.15)
Study 2310 (104 weeks)				
vilda 50 mg bid	n	203	206	77
	Baseline mean HbA_{1c}	8.55	8.51	8.25
	Mean change in HbA_{1c} (SE)	-0.39 (0.10)	-0.36 (0.11)	-0.30 (0.18)
gliclazide (up to 320 mg/day)	n	203	206	93
	Baseline mean HbA_{1c}	8.75	8.65	8.66
	Mean change in HbA_{1c} (SE)	-0.80 (0.12)	-0.48 (0.11)	-0.52 (0.17)
Study 2327 (24 weeks)				
vilda 50 mg bid	n	184	275	132
	Baseline mean HbA_{1c}	8.79	8.7	8.71
	Mean change in HbA_{1c} (SE)	-1.27 (0.102)	-1.04 (0.081)	-1.10 (0.119)
rosiglitazone 8 mg qd	n	83	155	76
	Baseline mean HbA_{1c}	8.64	8.79	8.75
	Mean change in HbA_{1c} (SE)	-1.08 (0.175)	-1.43 (0.106)	-1.34 (0.166)

		BMI at baseline (kg/m^2)		
		<30	**≥30**	**≥35**
Study 2327E1 (104 weeks)				
vilda 50 mg bid	n	126	169	86
	Baseline mean HbA_{1c}	8.67	8.55	8.62
	Mean change in HbA_{1c} (SE)	-0.85 (0.12)	-0.73 (0.12)	-0.64 (0.19)
rosiglitazone 8 mg qd	n	53	108	47
	Baseline mean HbA_{1c}	8.54	8.76	8.62
	Mean change in HbA_{1c} (SE)	-1.44 (0.15)	-1.49 (0.13)	-1.41 (0.20)

Baseline is the measurement obtained on the day of randomization, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if the Day 1 (Visit 2) measurement is missing
Endpoint is the final available post-randomization assessment up to the last regular scheduled visit
n is the number of patients with observations at both baseline and endpoint

Table 11 Effect of BMI on changes in HbA_{1c} (%) from baseline to study endpoint in key add-on therapy studies (primary efficacy population)

		BMI at baseline (kg/m^2)		
		<30	**≥30**	**≥35**
Add-on to metformin				
Study 2303 (24 weeks)				
vilda 50 mg bid + met	n	40	103	46
	Baseline mean HbA_{1c}	8.68	8.26	8.42
	Mean change in HbA_{1c} (SE)	-1.07 (0.190)	-0.84 (0.078)	-0.77 (0.134)
Placebo + met	n	44	86	47
	Baseline mean HbA_{1c}	8.4	8.25	8.27
	Mean change in HbA_{1c} (SE)	0.28 (0.229)	0.21 (0.125)	0.14 (0.172)
Study 2308 (104 weeks)				
vilda 50 mg bid + met	n	612	901	418
	Baseline mean HbA_{1c}	7.29	7.32	7.34
	Mean change in HbA_{1c} (SE)	-0.12 (0.038)	-0.02 (0.034)	-0.01 (0.052)
glim (up to 6 mg/day) + met	n	618	852	375
	Baseline mean HbA_{1c}	7.3	7.31	7.32
	Mean change in HbA_{1c} (SE)	-0.22 (0.034)	-0.11 (0.032)	-0.03 (0.049)
Study 2338 (52 weeks)				
vilda 50 mg bid + met	n	186	200	81
	Baseline mean HbA_{1c}	8.49	8.38	8.57
	Mean change in HbA_{1c} (SE)	-0.85 (0.08)	-0.77 (0.08)	-0.85 (0.13)
glic (up to 320 mg/day) + met	n	193	200	67
	Baseline mean HbA_{1c}	8.46	8.44	8.36
	Mean change in HbA_{1c} (SE)	-0.88 (0.10)	-0.86 (0.08)	-0.65 (0.15)
Study 2354 (24 weeks)				
vilda 50 mg bid + met	n	105	158	73
	Baseline mean HbA_{1c}	8.47	8.37	8.49
	Mean change in HbA_{1c} (SE)	-0.95 (0.108)	-0.84 (0.072)	-0.77 (0.126)
pio 30 mg qd + met	n	95	151	70
	Baseline mean HbA_{1c}	8.37	8.42	8.52

		BMI at baseline (kg/m^2)		
		<30	**≥30**	**≥35**
	Mean change in HbA_{1c} (SE)	-0.68 (0.087)	-1.17 (0.075)	-1.14 (0.122)
Add-on to a thiazolidinedione				
Study 2304 (24 weeks)				
vilda 50 mg bid + pio	n	56	80	40
	Baseline mean HbA_{1c}	8.7	8.68	8.6
	Mean change in HbA_{1c} (SE)	-1.00 (0.142)	-1.02 (0.115)	-1.08 (0.152)
Placebo + pio	n	52	86	37
	Baseline mean HbA_{1c}	8.8	8.68	8.61
	Mean change in HbA_{1c} (SE)	-0.48 (0.178)	-0.26 (0.137)	-0.59 (0.145)
Add-on to a sulfonylurea				
Study 2305 (24 weeks)				
vilda 50 mg qd + glim	n	47	85	37
	Baseline mean HbA_{1c}	8.53	8.53	8.52
	Mean change in HbA_{1c} (SE)	-0.56 (0.177)	-0.51 (0.121)	-0.50 (0.225)
Placebo + glim	n	72	72	31
	Baseline mean HbA_{1c}	8.6	8.45	8.39
	Mean change in HbA_{1c} (SE)	0.09 (0.134)	0.14 (0.130)	0.16 (0.177)

vilda = vildaglitpin, met = metformin, glim = glimepiride, glic = gliclazide, pio = pioglitazone

Baseline is the measurement obtained on the day of randomization, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if the Day 1 (Visit 2) measurement is missing
Endpoint is the final available post-randomization assessment up to the last regular scheduled visit
n is the number of patients with observations at both baseline and endpoint

Although in some of the studies (2384, 2309, 2327, 2303 and 2354) there is a trend towards a lower effect with higher BMI, this finding is not consistent across the studies. Clinically relevant efficacy was maintained across all BMI categories. Overall, there appears to be no relevant influence on HbA1c response by BMI.

2.2.4. 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 in combination with insulin (with or without metformin).

Data from four clinical studies have been provided out of which study CLAF237A23135 is considered to be the pivotal study. No dose finding study was performed. The vildagliptin dose selected corresponds to the already approved dosing regimen which is acceptable.

Study CLAF237A23135

The overall study design is acceptable. Both patients with metformin treatment and without such treatment were included and patients were stratified by metformin use, allowing assessment of both combinations. 60 % of patients were to be treated with metformin. The inclusion and exclusion criteria were adequate and would identify a representative population on a stable background therapy. 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 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 key secondary endpoint is relevant for the evaluation of the subgroups of patients treated with or without metformin. Statistical methods were adequate.

The study enrolled 399 patients of which 228 were treated with vildagliptin. The subgroup of patients on background metformin therapy consisted of 267 patients of whom 133 were exposed to vildagliptin, thus the population on triple therapy is limited. Corresponding figures for patients not on metformin were 169 (88). However, since the combination with vildagliptin and metformin has been shown efficient and is already approved, the main objective is to show that the triple combination can provide additional benefit for the patient and thus the study size is acceptable.

Randomisation and blinding procedures were generally adequate, although mis-stratification occurred. This did, however, not result in imbalances with regards to previous insulin therapy.

Patients were to maintain stable metformin and insulin doses throughout the study. Instructions for allowed insulin dose adjustments (within a 10 % increase from baseline) as well as for rescue medication (insulin) were in place. This is of importance considering the study duration of 24 weeks with a placebo control in order not to jeopardise the wellbeing of the participants.

Discontinuation rates were rather low. More patients withdrew from the placebo group with the largest imbalance due to loss of follow-up (7 vs 0 in the placebo and vildagliptin groups respectively).

Treatment groups were well balanced with regards to baseline demographic and background data. An adequate proportion of patients were recruited in Europe. In spite of the mis-stratification, prior insulin treatment was balanced. Mean insulin (39.9 and 41.9 units in the vildagliptin and placebo groups respectively) and metformin doses were adequate (1928 mg/day and 1948 mg/day in the vildagliptin and placebo groups respectively), indicating that the patients included were true treatment failures. Background medical conditions were as expected in a population of patients with type 2 DM of long duration.

The primary endpoint was met for the study. The reduction of HbA1c from baseline was statistically significantly greater in the vildagliptin treated group (-0.72 %, placebo corrected). The reduction was clinically relevant. The sensitivity analyses of the primary endpoint without censoring of data supports the outcome in the primary analyses. An additional sensitivity analysis using BOCF, a theoretically more conservative approach, showed consistent results and, hence supports the primary analysis although, as might be expected, the difference between vildagliptin and placebo is somewhat smaller.

Also the secondary endpoints, i.e. to show superiority for vildagliptin compared to placebo in the two subgroups (with or without concomitant metformin therapy), were met. In the subgroup on concomitant metformin treatment a placebo-adjusted HbA1c change from baseline of -0.63 % was observed and the corresponding result in the group not treated with metformin was -0.84 %.

In the overall population, significantly higher proportions of patients reached the predefined targets. The overall responder rate was 22 %. An additional analysis was performed where all subjects with missing HbA1c at Week 24 and patients who had major change in insulin background therapy were included as non-responders. The results of this analysis are consistent with the results from pre-planned analysis, and therefore support the efficacy of vildagliptin 50 mg bid used in combination with insulin. Also in the subgroups with concomitant metformin or without metformin treatment all responder rates were in favour of vildagliptin treatment although numbers were small. The overall

responder rate was 21 % and 24 % in patients with concomitant metformin and without metformin, respectively.

Although a less prominent effect was observed on FPG there was a trend in favour of vildagliptin treatment in all analyses. Considering the clinically relevant effect on HbA1c, this is acceptable and may reflect a more prominent effect of vildagliptin during daytime compared to night-time.

The subgroup analyses revealed (as expected) a greater reduction in HbA1c in patients with higher HbA1c at baseline. There was no relevant influence on HbA1c response by BMI, gender or race.

Considering the consistent findings both in the primary and secondary endpoints, the data provide sufficient support on the efficacy of vildagliptin to lower HbA1c in combination with insulin both with and without concomitant treatment with metformin.

Supportive data

Study CLAF237A2311 was assessed within the original MAA for vildagliptin. The addition of vildagliptin to insulin therapy resulted in a placebo corrected reduction in HbA1c of -0.27 %. Thus the HbA1c outcome was markedly lower in this study compared to study CLAF237A23135. At the time of the initial application, the CHMP had concerns, whether this difference would be clinically meaningful. It should be noted that study CLAF237A2311 included patients with longer diabetes duration and a longer history of insulin treatment as well as higher insulin doses than study CLAF237A23135. It could be speculated that the lower response is due to lower endogenous insulin secretion in patients with longer duration and thus a diminished effect of vildagliptin. It is, however, noteworthy that although the effect on HbA1c was modest, the incidence of hypoglycaemias was lower in the vildagliptin treated group. The data from study CLAF237A2311 is therefore considered to lend some additional support to the efficacy of vildagliptin in combination with insulin.

Studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149 with the aim of including a posology for patients with moderate to severe renal impairment. A majority of patients in both studies were on a background treatment with insulin in monotherapy or in combination with OADs. A reduced vildagliptin dose was used due to the increased exposure of vildagliptin in patients with renal impairment. Also in this population, a clinically relevant reduction of HbA1c was observed when vildagliptin was added to insulin.

Long-term data on the efficacy of vildagliptin 50 mg bid add-on therapy in patients with T2DM inadequately controlled by insulin with or without concomitant metformin treatment beyond the 24 week treatment period in study CLAF237A23135 are not available. However, the long term efficacy of vildagliptin has been established in earlier clinical studies, which is considered sufficient.

In conclusion – the efficacy of vildagliptin in providing a clinically relevant lowering of HbA1c when added to insulin therapy with or without concomitant metformin treatment has been adequately shown.

2.3. Clinical Safety aspects

A list of all studies relevant for this application is given in **Table 1** and **Table 2**. Descriptions of study design are given in the efficacy section of this report.

2.3.1. Methods – analysis of data submitted

Primary safety population

The primary safety population is comprised of patients from the two studies providing key safety information for the indication, Study CLAF237A23135 and Study CLAF237A2311. Study CLAF237A23135 enrolled 449 patients (228 vildagliptin and 221 placebo), and study CLAF237A2311 enrolled 296 patients (144 vildagliptin and 152 placebo).

At baseline, both study populations were similar with respect to age, percentage of patients ≥65 years and male/female ratio. More patients from the Caucasian and Black races were enrolled in Study CLAF237A2311, while more than one-third of patients in CLAF237A23135 were of Indian or Chinese ethnicity. Consequently BMI was higher in Study CLAF237A2311 and a higher percentage of patients had BMI of ≥30 kg/m^2 compared with patients in Study CLAF237A23135.

Baseline disease characteristics of patients in the Primary safety population showed characteristics common to insulin treated patients with a long history of T2DM. Patients in Study CLAF237A2311 had a longer history of T2DM and use of insulin. They were treated with higher daily number of insulin injections (mean 2.8 vs 1.8 injections/day) and a higher daily dose of insulin (mean 82U vs 41 U/day) indicating the use of a more intensive insulin regimen than in Study CLAF237A23135. This difference in insulin treatment should be considered when evaluating the hypoglycaemic events in the two studies.

In spite of the differences between the study populations in studies CLAF237A23135 and CLAF237A2311, the pooling of the safety data is endorsed.

Safety population in the supportive studies

Two safety studies, CLAF237A23137 and CLAF237A23138, with 525 and 148 patients respectively, were previously submitted to support the removal of the label restriction of vildagliptin in patients with moderate and severe renal impairment. The data from the safety populations in these two studies are included since the majority of patients (68% to 82% across studies and degree of renal impairment) were treated with insulin and thus represent an additional source of safety data for the use of vildagliptin in combination with insulin.

The demographic and disease characteristics in Study CLAF237A23137 and Study CLAF237A23138 were well-balanced between treatment groups at baseline. Most patients were Caucasian.

Evaluations

Adverse events (AEs) reported by patients in the Primary safety population and the safety population in the supportive studies were coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). The most recent version of MedDRA available at the time of study completion was used to code AEs for that particular study. Since each study had a different completion date, four different versions of MedDRA were used to code AEs: Version 8.0 (Study CLAF237A2311), 13.0 (Study CLAF237A23138), 13.1 (Study CLAF237A23137) and 14.0 (Study CLAF237A23135).

The number and percentage of patients with treatment-emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity), were summarized by primary SOC, preferred term, maximum severity and relationship to study drug. The number and percentage of patients who died, had serious adverse events (SAEs) or AEs leading to discontinuation were tabulated separately.

Table 12 Population groupings for safety assessment

Database	Studies	Number of patients (safety population)	Safety topics Subgroup analyses
Primary safety population (2 double-blind, placebo-controlled studies of 24 weeks duration)	CLAF237A23135 CLAF237A2311	448 296	Topics: deaths, SAEs, other significant AEs, all AEs, clinical laboratory results
	Pooled set (both studies)	744	Determining ADRs Study CLAF237A23135 only: subgroup analyses for AEs by age group and treatment with/without concomitant metformin
Other populations from supportive safety trials (2 double-blind controlled studies of 24 weeks duration in renal impairment)	CLAF237A23137 CLAF237A23138	513 148	Topics: deaths, SAEs, other significant AEs, all AEs, clinical laboratory results, eGFR (MDRD)

By pooling of data, a relatively large safety population was obtained. Safety data beyond 24 weeks is not available for the current combination. This is acceptable considering that the safety profile of vildagliptin is rather well known.

2.3.2. Results

Patient exposure

In the Primary safety population the mean duration of exposure to study medication ranged from 21 to 23 weeks across all treatments and was close to the intended duration of 24 weeks. The majority of patients (>60% in all treatment groups) were exposed to study medication for ≥24 weeks.

Table 13 Duration of exposure to study drug in the Primary safety population - Studies CLAF237A23135 and CLAF237A2311 (randomized population)

	Study CLAF237A23135		**Study CLAF237A2311**	
Duration of Exposure (Weeks)	**Vilda 50 mg bid + insulin N=228 n (%)**	**Placebo + insulin N=221 n (%)**	**Vilda 50 mg bid + insulin N=144 n (%)**	**Placebo + insulin N=152 n (%)**
Exposure				
n	228	221	144	152
Mean	23.1	22.8	20.99	21.42
SD	5.01	5.06	6.92	6.69
Min	0	0.3	0.57	0.71
Median	24.0	24.0	24.00	24.00
Max	32.4	30.0	28.57	25.86
Exposure categories				
0 - <4	5 (2.2)	7 (3.2)	10 (6.9)	9 (5.9)
4 - <8	4 (1.8)	1 (0.5)	4 (2.8)	6 (3.9)
8 - <12	6 (2.6)	6 (2.7)	7 (4.9)	5 (3.3)
12 - <16	2 (0.9)	5 (2.3)	4 (2.8)	2 (1.3)
16 - <20	0	3 (1.4)	3 (2.1)	3 (2.0)
20 - <24	35 (15.4)	54 (24.4)	29 (20.1)	18 (11.8)
≥24	176 (77.2)	145 (65.6)	87 (60.4)	109 (71.7)

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
Vilda = vildagliptin

In Study CLAF237A23137, the mean duration of exposure to study medication in patients with moderate or severe renal impairment in the randomized population was comparable between treatment groups, and was approximately 23 weeks (median 24 weeks). The majority of patients (>70% in both treatment groups) were exposed to study medication for 24 weeks or more.

In Study CLAF237A23138, the mean duration of exposure to study medication in patients with severe renal impairment in the randomized population was 1.5 weeks longer in the sitagliptin group (22.9 weeks) compared with the vildagliptin group (21.4 weeks), though median values were similar (approximately 24 weeks). The majority of patients (70% and 75% in the vildagliptin and sitagliptin groups, respectively) were exposed to study medication for 24 weeks or more.

In line with the low drop-out rate, the mean exposure in all studies was close to 24 weeks. Time of exposure was similar between active treatment and placebo/active comparator in all trials.

Adverse events

Primary safety population

In Study CLAF237A23135, AEs were reported by a higher percentage of patients in the vildagliptin group compared with the placebo group (57.7% vs. 47.5%, respectively). A higher percentage of patients in the vildagliptin group compared with the placebo group reported an AE in the primary SOC infections and infestations (22.5% vs. 14.5%, respectively) and gastrointestinal disorders (13.7% vs. 7.2%, respectively) (Table 14). These imbalances were largely driven by a higher percentage of patients reporting upper respiratory tract infection (RTI) (7.0% vs. 3.2%, respectively) or diarrhoea (4.4% vs. 1.8%, respectively) in the vildagliptin group compared with the placebo group.

In Study CLAF237A2311, similar proportion of patients reported AEs in the vildagliptin and placebo groups (81.3% vs. 82.9%, respectively). Vildagliptin patients had higher incidences of gastrointestinal disorders (25.7% for vildagliptin vs. 11.8% for placebo), while placebo patients had higher incidences of infections and infestations (30.6% for vildagliptin vs. 44.7% for placebo), and skin and subcutaneous tissue disorders (22.2% for vildagliptin vs. 31.6% for placebo); (Table 14).

Taken together, vildagliptin treated patients had higher incidences of gastrointestinal disorders while placebo treated patients had higher incidences of skin and subcutaneous tissue disorders.

Table 14 Adverse events by primary system organ class regardless of relationship to treatment in the Primary safety population –Studies CLAF237A23135 and CLAF237A2311 (Safety population)

	Study CLAF237A23135[1]		Study CLAF237A2311[2]	
Primary system organ class	Vilda 50 mg b.i.d. + insulin N=227 n (%)	Placebo + insulin N=221 n (%)	Vilda 50 mg b.i.d. + insulin N=144 n (%)	Placebo + insulin N=152 n (%)
Any primary SOC	**131 (57.7)**	**105 (47.5)**	**117 (81.3)**	**126 (82.9)**
Blood and lymphatic system disorders	4 (1.8)	1 (0.5)	1 (0.7)	0
Cardiac disorders	10 (4.4)	8 (3.6)	4 (2.8)	1 (0.7)
Congenital, familial and genetic disorders	1 (0.4)	0	NR	NR
Ear and labyrinth disorders	3 (1.3)	0	2 (1.4)	0
Eye disorders	13 (5.7)	9 (4.1)	14 (9.7)	11 (7.2)
Gastrointestinal disorders	31 (13.7)	16 (7.2)	37 (25.7)	18 (11.8)
General disorders and administration site conditions	30 (13.2)	28 (12.7)	41 (28.5)	38 (25.0)
Hepatobiliary disorders	2 (0.9)	1 (0.5)	0	1 (0.7)
Immune system disorders	0	1 (0.5)	2 (1.4)	1 (0.7)
Infections and infestations	51 (22.5)	32 (14.5)	44 (30.6)	68 (44.7)
Injury, poisoning and procedural complications	8 (3.5)	8 (3.6)	11 (7.6)	9 (5.9)
Investigations	10 (4.4)	8 (3.6)	19 (13.2)	16 (10.5)
Metabolism and nutrition disorders	28 (12.3)	22 (10.0)	38 (26.4)	50 (32.9)
Musculoskeletal and connective tissue disorders	25 (11.0)	23 (10.4)	25 (17.4)	30 (19.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.3)	0	3 (2.1)	0
Nervous system disorders	42 (18.5)	34 (15.4)	52 (36.1)	58 (38.2)
Psychiatric disorders	12 (5.3)	4 (1.8)	18 (12.5)	21 (13.8)
Renal and urinary disorders	1 (0.4)	1 (0.5)	2 (1.4)	6 (3.9)
Reproductive system and breast disorders	NR	NR	0	6 (3.9)
Respiratory, thoracic and mediastinal disorders	10 (4.4)	9 (4.1)	11 (7.6)	11 (7.2)
Skin and subcutaneous tissue disorders	31 (13.7)	32 (14.5)	32 (22.2)	48 (31.6)
Vascular disorders	4 (1.8)	3 (1.4)	6 (4.2)	5 (3.3)

1Coded using MedDRA version 14.0

2Coded using MedDRA version 8.0

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

Vilda = vildagliptin

In study CLAF237A23135, the reporting of adverse events was higher in the vildagliptin treated group than in the placebo groups whereas reporting rates were similar in both groups in study CLAF237A2311. The overall reporting pattern did not differ between studies, with a distinctly higher reporting of gastrointestinal disorders in the vildagliptin treated groups compared to placebo. Generally the reporting rate was lower in study CLAF237A23135 which may reflect that this study included patients with less advanced T2DM than study CLAF237A2311.

Supportive studies

In Study CLAF237A23137, the overall incidence of AEs in patients with moderate renal impairment and in patients with severe renal impairment was similar between the vildagliptin and placebo groups (Moderate: 67.5% vs 72.9%; Severe: 72.6% vs 74.2%, respectively). An imbalance was seen in the incidence of infections and infestations in the patients with severe renal impairment which was higher in the vildagliptin group compared with the placebo group (30.6% vs. 19.6%, respectively), however this was explained by existing imbalance in the medical history. Overall, the most commonly reported SOCs were similar across treatment groups and were not driven by any specific AEs.

In Study CLAF237A23138, the overall incidence of AEs was similar in the vildagliptin group compared to the sitagliptin group (81.9% vs. 86.2%, respectively). For the following SOCs slightly higher incidences were reported with sitagliptin than with vildagliptin: gastrointestinal disorders (24.1% vs. 33.8% in the vildagliptin and the sitagliptin groups, respectively), general disorders and administrative site conditions (37.3% vs. 47.7%), and nervous system disorders (25.3% vs. 36.9%). Slightly higher incidences were reported with vildagliptin than with sitagliptin for the SOCs of metabolism and nutrition disorders (38.6% vs. 29.2%).

Safety data from studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149. In this procedure it was concluded that no new or unexpected safety concerns were identified and that the safety profile in patients with impaired renal function was similar to that of the overall population.

Deaths

A total of 3 patients died during the treatment period in the following studies: Study CLAF237A23135 (1 patient), Study CLAF237A2311 (2 patients). One death in Study CLAF237A23135 was suspected by the investigator to be study drug related, however this patient was in the placebo group.

There was no imbalance in the deaths in the two studies in patients with T2DM and moderate or severe renal impairment. Nine patients died in Study CLAF237A23137 (4 in the vildagliptin and 5 in the placebo group) and 4 patients died in Study CLAF237A23138 (2 patients in each treatment group). None of these deaths were suspected to be related to the study drug.

There was no imbalance between groups with regards to death across the four studies. More deaths were observed in the studies including patients with renal impairment which could be explained by the more advanced disease in these patients.

Serious adverse events

Primary safety population

In Study CLAF237A23135, SAEs were reported by 9 patients in both treatment groups (4.0% and 4.1% for vildagliptin and placebo groups, respectively). Most SAEs were isolated events and reported by not more than one patient each. There were two hypoglycemia SAEs reported for each treatment group.

In Study CLAF237A2311, SAEs were reported by similar percentages of patients in the vildagliptin group and placebo group (8.3% vs. 9.2%, respectively). Most SAEs were isolated events and reported by not more than one patient each, with the exception of hypoglycemia, which was reported by 4 patients in the placebo group but none in the vildagliptin group.

Overall, the incidence of SAEs was low in both studies. More hypoglycaemia SAEs were reported by patients in the placebo groups compared to the vildagliptin patients. Most SAEs were isolated events reported by not more than one patient each. Cardiovascular events (i.e. MI or stroke) were reported more frequently in the placebo groups than in the vildagliptin treated groups (1 vs 7 events for vildagliptin and placebo respectively). Infections were reported more frequently in the vildagliptin treated groups (7 vs 3 events). Four malignancies (prostate cancer, squamous cell carcinoma of the skin, gastric cancer and breast cancer) were reported in the vildagliptin treated groups versus none in the placebo treated groups. Narratives of these events have been provided. One case of breast cancer was recorded in study CLAF237A23135. The patient underwent mammography which revealed a suspicious spot. On Day 39, she underwent a biopsy and the histology revealed mammary carcinoma. In study CLAF237A2311, three malignancies were reported. One case of gastric cancer was diagnosed on day 79 of study treatment, one case of prostate cancer was diagnosed on day 5 of study treatment and one case of squamous cell carcinoma of the skin was diagnosed on day 39 of study treatment. Any relationship with the vildagliptin treatment is unlikely due to the very short duration of exposure to vildagliptin.

Supportive studies

In Study CLAF237A23137, there were no trends in SAEs reported in patients with moderate or severe renal impairment. The majority of SAEs was isolated events across many different SOCs and was reported by ≤2 patients each.

In Study CLAF237A23138, there were no consistent trends in SAEs reported in patients with severe renal impairment. The most notable differences were seen in the cardiac disorder SOC (4.8% with vildagliptin vs. 10.8% with sitagliptin), not driven by a specific AE, and in the respiratory, thoracic and mediastinal disorders SOC (2.4% with vildagliptin vs. 6.2% with sitagliptin).

Safety data from studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149. In this procedure no trends with regards to SAEs were observed for any of the treatment groups. Considering the underlying disease no unexpected SAEs were observed.

Adverse events of pre-defined 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, 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. The primary safety population and the Supportive studies discussed in the present application have been reviewed for these identified and potential risks.

Primary safety population

In Study CLAF237A23135, events of pre-defined risk were generally balanced between the vildagliptin group and in the placebo group with the exception of events in the Infections and Infestations SOC (22.5% vs. 14.5%, respectively). The majority of these events were mild in severity.

In Study CLAF237A2311, the incidence of events of pre-defined risk in any category was lower in the vildagliptin group compared with the placebo group and did not indicate an increased risk with vildagliptin for any of these risk categories.

Table 15 Incidence of adverse events by pre-defined risk, maximum severity and treatment in the Primary safety population –Studies CLAF237A23135 and CLAF237A2311 (safety population)

	Study CLAF237A23135		Study CLAF237A2311	
Pre-defined Risk Category Preferred term Maximum severity	**Vilda 50 mg bid + insulin N=227 n (%)**	**Placebo + insulin N=221 n (%)**	**Vilda 50 mg bid + insulin N=144 n (%)**	**Placebo + insulin N=152 n (%)**
Pre-defined Risk Category				
Total	56 (24.7)	38 (17.2)	47 (32.6)	74 (48.7)
Mild	47 (20.7)	36 (16.3)	25 (17.4)	43 (28.3)
Moderate	8 (3.5)	2 (0.9)	18 (12.5)	25 (16.4)
Severe	1 (0.4)	0	4 (2.8)	6 (3.9)
Acute pancreatitis AEs				
Total	0	0	0	0
Hepatic disorder AEs				
Total	4 (1.8)	1 (0.5)	0	2 (1.3)
Mild	3 (1.3)	1 (0.5)	0	2 (1.3)
Severe	1 (0.4)	0	0	0
Infections AEs				
Total	51 (22.5)	32 (14.5)	44 (30.6)	68 (44.7)
Mild	43 (18.9)	30 (13.6)	23 (16.0)	40 (26.3)
Moderate	8 (3.5)	2 (0.9)	17 (11.8)	22 (14.5)
Severe	0	0	4 (2.8)	6 (3.9)
Muscle event-related terms				
Total	2 (0.9)	2 (0.9)	1 (0.7)	2 (1.3)
Mild	2 (0.9)	2 (0.9)	1 (0.7)	1 (0.7)
Moderate	0	0	0	1 (0.7)
Neuropsychiatric-related AEs				
Total	1 (0.4)	3 (1.4)	4 (2.8)	5 (3.3)
Mild	1 (0.4)	3 (1.4)	2 (1.4)	3 (2.0)
Moderate	0	0	1 (0.7)	2 (1.3)
Severe	0	0	1 (0.7)	0
Skin and/or vascular-related AEs				
Total	2 (0.9)	0	3 (2.1)	4 (2.6)
Mild	2 (0.9)	0	1 (0.7)	3 (2.0)
Moderate	0	0	2 (1.4)	1 (0.7)

Risk categories are presented alphabetically; preferred terms are sorted within event category 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 severity ratings for an AE while on a treatment, is only counted under the maximum rating

Vilda = vildagliptin

With regards to the identified and potential risks: hepatic, muscle, skin and/or vascular, neuropsychiatric-related events, acute pancreatitis and infections, no imbalances were observed when both studies CLAF237A23135 and CLAF237A2311 were considered. A higher reporting of infections

were observed in study CLAF237A23135, however, in study CLAF237A2311 the reporting was higher in the placebo group. The potential/identified risk breast cancer (one case reported for vildagliptin in study CLAF237A23135) and hypoglycaemia were not included in this analysis. Hypoglycaemia is further discussed below.

Supportive studies

In studies CLAF237A23137 and CLAF237A23138 no clinically meaningful differences in AEs of pre-defined risk were found between vildagliptin and comparators in patients with moderate or severe renal impairment, except infections AEs, more frequently reported in vildagliptin-treated patients with severe renal impairment, compared to placebo-treated patients, which was explained by imbalance in medical history in those groups.

Safety data from studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149. In this procedure it was concluded that the data provided in patients with moderate renal impairment, although limited, did not evoke any concerns that patients with moderate renal impairment are more prone to develop AEs of special interest. In most cases the rates were numerically in favour of vildagliptin and no statistically significant differences were observed compared to placebo. Oedema-related AEs and infections were more common in patients with severe renal impairment which is what could be expected in this more severely ill population. However, apart from infections being more common in the vildagliptin group no statistically significant differences were observed.

In study CLAF237A23138, no statistically significant differences were observed between treatments. Oedema-related AEs and infections were more commonly reported in this study compared to CLAF237A23137. More skin/vascular related events were reported in the vildagliptin treated group (12 % vs 6.2 %) than in the group treated with sitagliptin.

Adverse drug reactions

Safety data were pooled across studies CLAF237A23135 and CLAF237A2311, re-coded to a common MedDRA dictionary version and analyzed according to a pre-defined algorithm used to define ADRs for previously approved indications. Pooling of data was performed to be able to cover a broad patient population treated with different insulin regimens, including also patients taking metformin as concomitant medication.

An adverse event was considered as an ADR if the following two criteria are met:

- ≥1% greater in the vildagliptin 50mg bid plus insulin group than in placebo plus insulin group;
- Among adverse events which the investigator suspected to be related to study drug, a difference of > 0.2% where there is > 1 event difference in the vildagliptin 50mg bid plus insulin group than in placebo plus insulin group.

Table 16 Number (%) of patients reporting AEs in vildagliptin 50mg bid group with incidence rate >= 1% compared to placebo group by preferred term Pooled LAF2311 and LAF23135 safety set

Preferred term	Vilda 50mg bid + insulin N= 371 N (%)	Placebo + insulin N= 373 N (%)
Headache	22 (5.93)	11 (2.95)
Blood glucose decreased	19 (5.12)	13 (3.49)
Diarrhoea	18 (4.85)	7 (1.88)
Nausea	14 (3.77)	8 (2.14)
Chills	8 (2.16)	1 (0.27)
Constipation	8 (2.16)	3 (0.8)
Dyspepsia	7 (1.89)	2 (0.54)
Gastrooesophageal reflux disease	6 (1.62)	0 (0)
Flatulence	5 (1.35)	0 (0)
Paraesthesia	5 (1.35)	1 (0.27)
Cataract	4 (1.08)	0 (0)

Table 17 Number (%) of patients reporting suspected drug-related AEs in vildagliptin 50 mg bid group with incidence rate greater than 0.2% and incidence greater than 1 event compared to placebo group by preferred term in the Primary safety population – Pooled studies CLAF237A23135 and CLAF237A2311 (safety population)

Preferred term	**Vilda 50 mg bid + insulin N=371 n (%)**	**Placebo + insulin N=373 n (%)**
Blood glucose decreased	12 (3.23)	7 (1.88)
Vision blurred	9 (2.43)	5 (1.34)
Chills	7 (1.89)	1 (0.27)
Headache	5 (1.35)	1 (0.27)
Gastrooesophageal reflux disease	4 (1.08)	0
Muscular weakness	4 (1.08)	1 (0.27)
Nausea	4 (1.08)	1 (0.27)
Appetite disorder	3 (0.81)	1 (0.27)
Diarrhoea	3 (0.81)	0
Disorientation	2 (0.54)	0
Flatulence	2 (0.54)	0
Hepatic enzyme increased	2 (0.54)	0
Muscle spasms	2 (0.54)	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
Vilda = vildagliptin

The following ADRs and frequencies were identified:

Nervous system disorders		
	Common	Headache, chills
Gastrointestinal disorders		
	Common	Nausea, gastroesophageal reflux disease
	Uncommon	Diarrhea, flatulence
Metabolism and nutritional disorders		
	Common	Decreased blood glucose

The proposed frequency categories to these ADRs are based on the requirements outlined in the EMA SmPC guidance and the actual incidence of suspected drug-related AEs presented in Table 18 that meet the ADR definition described above.

The overall incidence of withdrawals due to the above adverse reactions was 0.3% in the vildagliptin treatment group and there were no withdrawals in the placebo group.

The incidence of hypoglycemia was similar in both treatment groups (14.0% in the vildagliptin group vs 16.4 % in the placebo group). Two patients reported severe hypoglycaemic events in the vildagliptin group, and 6 patients - in the placebo group.

Change in body weight was also analyzed to provide the complete list of side effects expected with anti-diabetic treatments. At the end of the study, effect on mean body weight was neutral (+ 0.6 kg change from baseline in the vildagliptin group and no weight change 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.

Hypoglycaemic events

Primary safety population

The number (%) of patients with hypoglycaemic events in the Primary safety population is summarized in Table 18.

In Study A23135, the percentage of patients who experienced hypoglycaemic events was low and comparable in both treatment groups (8.4% and 7.2% in the vildagliptin and placebo groups, respectively). Two patients in each treatment group experienced severe hypoglycaemic events classified as either grade 2 or suspected grade 2 hypoglycemia. One patient in the vildagliptin group discontinued due to a severe hypoglycaemic event.

The total number of hypoglycaemic events occurring in the vildagliptin group was higher than in the placebo group. Among patients reporting a hypoglycaemic event, most patients reported only one hypoglycaemic event during the study and most of hypoglycaemic events were assessed as mild. The relationship to study drug was more frequently suspected in the vildagliptin group compared with the placebo group (68.6% vs. 41.7% of events, respectively) while glucose levels ≤2.2 mmol/L were reported by a higher percentage of patients in the placebo group than in the vildagliptin group (13.9% vs. 7.8% of events, respectively).

The proportion of patients experiencing hypoglycaemic events by age group was similar in the vildagliptin and placebo groups (8.1% vs. 7.1% of patients <65 years, and 9.0% vs. 7.5% of patients ≥ 65 years, respectively).

In Study A2311, the percentage of patients experiencing at least one hypoglycaemic event was lower in the vildagliptin group (22.9%) compared with the placebo group (29.6%). Fewer patients in the

vildagliptin group experienced one hypoglycaemic event compared with the placebo group. The number of patients experiencing two, or more than two hypoglycaemic events was similar in both treatment groups (Table 18).

The total number of hypoglycaemic events occurring in the placebo group (185 events) was higher than in the vildagliptin group (113 events). All of the hypoglycaemic events recorded in the vildagliptin group were categorized as Grade 1, while 6 events (4 patients) in the placebo group were categorized as either Grade 2 or suspected Grade 2. More events in the placebo group were considered moderate or severe in nature (15.9% in vildagliptin vs. 24.9% in placebo). No patient discontinued due to hypoglycaemic events. The number of asymptomatic low blood glucose occurrences was similar in both treatment groups.

Both the percentage of patients experiencing hypoglycemia and the number of hypoglycaemic events were lower in Study CLAF237A23135 than in Study CLAF237A2311which could be explained with the use of more intensive insulin treatment regimen in study CLAF237A2311.

Table 18 Hypoglycaemic events by event profile and treatment in the Primary safety population - Studies A23135 and A2311 (Safety population)

	Study A23135		Study A2311	
	Vilda 50 mg b.i.d. + insulin N=227 n (%)	Placebo + insulin N=221 n (%)	Vilda 50 mg b.i.d. + insulin N=144 n (%)	Placebo + insulin N=152 n (%)
Number of patients with at least one hypoglycemic event	19 (8.4)	16 (7.2)	33 (22.9)	45 (29.6)
Number (%) of patients with:				
One hypoglycemic event	14 (6.2)	10 (4.5)	13 (9.0)	22 (14.5)
Two hypoglycemic event	1 (0.4)	1 (0.5)	6 (4.2)	7 (4.6)
>2 hypoglycemic events	4 (1.8)	5 (2.3)	14 (9.7)	16 (10.5)
Number of patients who discontinued due to hypoglycemic events	1 (0.4)	0	0	0
Number of hypoglycemic events	51	36	113	185
Grade				
Grade 1 [n (% of events)]	49 (96.1)	34 (94.4)	113 (100.0)	179 (96.8)
Grade 2 (or suspected Grade 2) [n (% of events)]	2 (3.9)	2 (5.6)	0	6 (3.2)
Severity				
Mild [n (% of events)]	46 (90.2)	34 (94.4)	95 (84.1)	133 (71.9)
Moderate [n (% of events)]	3 (5.9)	0	18 (15.9)	46 (24.9)
Severe [n (% of events)]	2 (3.9)	2 (5.6)	0	6 (3.2)

1 mmol/L glucose = 18.0 mg/dL glucose

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

The number of hypoglycaemic events were balanced (study CLAF237A23135) or lower in the vildagliptin treated groups (CLAF237A2311). There is no indication of an increase in severity of

hypoglycaemic events when vildagliptin is used in combination with insulin. In study CLAF237A23135, insulin doses could be reduced for safety reasons at the investigator's discretion. This could include insulin dose decreases for safety reasons at anytime without specific dose limits. The need for insulin dose decreases was not markedly different between groups albeit slightly higher in the vildagliptin group (21.9 % on vildagliptin vs 19.9 % on placebo had any decrease from baseline). Considering that the difference in risk for hypoglycaemia was small (8.4% vs 7.2%, vildagliptin and placebo, respectively), no amendments of the SmPC with warnings regarding risk of hypoglycaemia when vildagliptin is used in combination with insulin are needed.

The lower incidence of hypoglycaemias while still achieving a modest lowering of HbA1c in study CLAF237A2311, give some indication that also patients with advanced T2DM may have some benefit from the addition of vildagliptin to insulin considering that frequent hypoglycaemias hinders further increases of the insulin dose.

Hypoglycaemic events in supportive studies

In Study A23137, the percentage of patients with moderate renal impairment who experienced hypoglycaemic events was slightly higher in the vildagliptin treatment group compared with the placebo group (17.2% vs. 11.6%, respectively). Grade 2 or suspected grade 2 hypoglycaemic events were experienced by 2 patients in each treatment group. No patients discontinued treatment due to hypoglycaemic events.

In Study A23137, the percentage of patients with severe renal impairment who experienced hypoglycaemic events was similar in the vildagliptin treatment group compared with the placebo group (15.3% vs. 12.4%, respectively). Grade 2 or suspected grade 2 hypoglycaemic events were experienced by 2 patients in each treatment group. Two patients in the vildagliptin group discontinued due to hypoglycaemic events. Both patients discontinuing due to hypoglycaemia were on insulin background therapy.

In Study A23138, the percentage of patients with severe renal impairment who experienced hypoglycaemic events was similar in both treatment groups (15.7% vs. 15.4% in the vildagliptin and sitagliptin groups, respectively). No patients discontinued treatment because of hypoglycaemic events in either treatment group. Grade 2 hypoglycaemic events were reported in one patient in each treatment group, and an additional patient in the sitagliptin group had a suspected grade 2 hypoglycaemia.

Overall, the percentage of patients with renal impairment who experienced hypoglycaemic events was slightly higher in the vildagliptin group compared to placebo. The number of patients experiencing Grade 2 or suspected grade 2 (severe) hypoglycaemia was very low and similar across the vildagliptin and comparator groups.

Safety data from studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149. Although reporting of hypoglycaemia was slightly higher in the vildagliptin treated groups, the incidence of grade 2 hypoglycaemia was low.

AEs suggestive to hypoglycaemia

In Study CLAF237A23135, AEs suggestive of hypoglycaemia (dizziness, headache, tremor, palpitations, hyperhidrosis, hunger, asthenia, chills, fatigue, malaise) occurring with frequency ≥ 2% were overall balanced between vildagliptin 50 mg bid and placebo. Insulin doses could be reduced for safety reasons at the investigator's discretion. Differences in the frequencies of any dose decrease, and for dose decreases of ≥ 5%, ≥10% and ≥20%, between vildagliptin and placebo were small. An additional analysis was performed to assess the frequencies of AEs suggestive of hypoglycaemia in subjects who had at least one reduction of their insulin dose from baseline by ≥ 5%. This cut-off for dose reduction

was chosen to include also minor changes in insulin dose which may be triggered by signs and symptoms of hypoglycaemia without confirmatory blood glucose measurement. Similar to the reported incidence of hypoglycaemia AEs in vildagliptin and placebo patients, most of the AEs suggestive of hypoglycaemia were also balanced between the vildagliptin and the placebo groups. An imbalance was only seen in the PT blood glucose decreased (asymptomatic low blood glucose), documented in more patients in the placebo group (14.6% vs. 4.3 with vildagliptin), and tremor reported by more patients in the vildagliptin group (21.7% vs. 9.8%). Overall, a similar overall distribution of the AEs of hypoglycaemia and hypoglycaemia symptoms was observed for vildagliptin and placebo. Therefore, the observed reductions in insulin are likely not due to an increased risk of hypoglycaemia with vildagliptin in these patients.

Although there were some imbalances (i.e. more tremor and chills reported for vildagliptin and more blood glucose decreased reported for placebo) the overall pattern and reporting rates are similar between groups.

Body weight

In Study CLAF237A23135 body weight at Week 24 remained unchanged in the vildagliptin group (78.0 kg at baseline, 78.2 kg at Week 24) and slightly decreased in the placebo group (79.0 kg at baseline, 78.3 kg at Week 24), mean difference to placebo 0.9 kg. In Study CLAF237A2311 body weight slightly increased in both groups and the mean difference to placebo was 0.86 kg.

Only modest increases in body weight were observed in both studies.

Hypoglycaemia and changes in body weight in the groups with and without metformin

The incidence of hypoglycaemic events in the subgroup taking concomitant metformin was comparable in both treatment groups (7.2% with vildagliptin and 8.0% with placebo). One patient in each treatment group had Grade 2 hypoglycaemia, and one patient in the placebo group had suspected Grade 2 hypoglycaemia. A slightly higher percentage of patients in the vildagliptin group compared with the placebo group experienced hypoglycaemic events in the subgroup of patients without concomitant metformin (10.1% vs. 6.0%, respectively). One patient in the vildagliptin group experienced Grade 2 hypoglycaemia and no patients in the placebo group had Grade 2 hypoglycaemia. These small differences in the incidence of hypoglycaemia between vildagliptin-treated and placebo within in the subgroups with or without concomitant metformin therapy are not considered clinically meaningful. The slightly higher incidence of hypoglycaemia in the insulin only subgroup might be due to the slightly better improvement in HbA1c than in the insulin-metformin subgroup (-0.84% and -0.63%, respectively).

Very similar hypoglycaemia rates (vildagliptin 7.2% and placebo 8.0%) were observed in patients on background metformin therapy whereas a higher percentage was observed with vildagliptin (10.1 %) compared to placebo (6.0%) in patients without metformin. The MAH's interpretation, that this could be explained by the larger effect on HbA1c by vildagliptin in the group only treated with insulin, is endorsed.

An additional analysis was performed for changes in body weight (

Table 20). There was no change in weight in vildagliptin-treated patients, overall and in the subgroups with or without concomitant metformin. Vildagliptin was weight-neutral in both groups.

Table 19 Summary results for baseline and change from baseline to study endpoint in body weight (kg) by treatment (Full analysis set)

Treatment	N	Baseline mean (SE)	Endpoint mean (SE)	Change from baseline mean (SE)
Full analysis set				
Vilda 50mg bid	222	78.05 (1.098)	78.18 (1.103)	0.13 (0.158)
Placebo	215	78.81 (1.136)	78.38 (1.127)	-0.44 (0.164)
Full analysis set (insulin + met)				
Vilda 50mg bid	134	79.73 (1.472)	79.87 (1.475)	0.13 (0.190)
Placebo	134	81.32 (1.504)	80.62 (1.501)	-0.70 (0.218)
Full analysis set (insulin only)				
Vilda 50mg bid	88	75.50 (1.598)	75.61 (1.613)	0.11 (0.275)
Placebo	81	74.67 (1.614)	74.67 (1.596)	0.00 (0.240)

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. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24.
n is the number of patients with observations at both baseline and endpoint.

Discontinuations due to AEs

Primary safety population

In Study CLAF237A23135, the percentage of patients with an AE that resulted in discontinuation was low in both treatment groups (4.0% with vildagliptin and 2.3% with placebo). Most AEs were isolated events and reported in not more than one patient each. Discontinuations suspected to be related to study drug were one case each of: elevation of liver enzymes, hypoglycemia, diarrhea and dyspepsia in the vildagliptin group, and death in the placebo group.

In Study CLAF237A2311, the percentage of patients reporting an AE leading to discontinuation was low but greater in the vildagliptin group compared with the placebo group (6.9% vs. 1.3%, respectively). Discontinuations suspected to be related to study drug were hypersensitivity (1 case of moderate exanthema of the forearm; no other associated symptoms) and muscle spasm (1 case) in the vildagliptin group, and gastritis (1 case) in the placebo group. All other discontinuations were not suspected to be related to study drug.

Overall, the incidence of AEs leading to discontinuation was low, and most were isolated events reported by not more than one patient each.

Supportive studies

In Study CLAF237A23137, there were no meaningful imbalances in the incidence of AEs leading to discontinuation in either treatment group in patients with moderate or severe renal impairment. Most of the individual AEs leading to discontinuation were reported by no more than one patient each, with the exception of hypoglycemia and peripheral edema which were each reported by two patients in the vildagliptin group. Both patients discontinuing due to hypoglycemia were on insulin background therapy.

In Study CLAF237A23138, there were no meaningful imbalances in the incidence of AEs leading to discontinuation in either treatment group in patients with severe renal impairment. The most notable difference between treatments was for the respiratory, thoracic and mediastinal disorders SOC (0% with vildagliptin vs. 6.2% with sitagliptin), which was not driven by a specific AE. Most of the individual

AEs leading to discontinuation were experienced by no more than one patient, with only discontinuation due to chronic renal failure being reported by two patients in the vildagliptin group.

Overall, the incidence of AEs leading to discontinuation was low, and most were isolated events reported by not more than one patient each. Most frequent AEs leading to discontinuation were reported by patients in the sitagliptin and the placebo groups in the cardiac disorders or respiratory, thoracic and mediastinal disorders SOCs.

Studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149. In patients with severe renal impairment, discontinuations due to AEs were slightly more common in the vildagliptin group compared to the placebo group and the rate was somewhat higher than in patients with moderate renal impairment. It is, however, agreed that there were no meaningful imbalances observed.

2.3.3. Discussion

In support of the current application for the new indication: "*Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control*", safety data from four clinical studies have been provided. Two of these studies, CLAF237A23135 and CLAF237A2311 were performed in a typical T2DM population, whereas studies CLAF237A23137 and CLAF237A23138 were performed in patients with impaired renal function. Study CLAF237A2311 was included in the original MAA for vildagliptin and studies CLAF237A23137 and CLAF237A23138 have been assessed within a previous type II variation with the aim of amending a posology for the use of vildagliptin in patients with renal impairment.

The safety data from studies CLAF237A23135 and CLAF237A2311 were pooled in order to get a larger safety database with patients treated with the combination of vildagliptin and insulin. In study CLAF237A23135, 60 % of patients included were treated with the triple combination vildagliptin, insulin and metformin. Patients included in study CLAF237A2311 had a longer duration of diabetes and had been treated with insulin for a longer time than patients included in study CLAF237A23135. In spite of the differences between the study populations in studies CLAF237A23135 and CLAF237A2311, the pooling of the safety data is endorsed.

By pooling of data a relatively large safety population of 744 patients, out of which 372 were treated with vildagliptin, was obtained. In line with the low drop-out rates, the mean exposure in all studies was close to 24 weeks. Time of exposure was similar between active treatment and placebo/active comparator in all trials. Safety data beyond 24 weeks is not available for the currently investigated combination. This is acceptable considering that the safety profile of vildagliptin is rather well known.

In study CLAF237A23135, the reporting of adverse events was higher in the vildagliptin treated group than in the placebo groups (57.7 % vs 47.5 %) whereas reporting rates were similar in both groups in study CLAF237A2311 (81.3 % vs 82.9 %). The reporting rate was lower in study CLAF237A23135 which may reflect that this study included patients with less advanced T2DM than study CLAF237A2311. The overall reporting pattern did not differ between studies, with a distinctly higher reporting of gastrointestinal disorders in the vildagliptin treated groups compared to placebo.

There was no imbalance between groups with regards to death across the four studies. Only three deaths were reported in studies CLAF237A23135 and CLAF237A2311, of which two occurred in the placebo treated groups. More deaths were observed in the studies including patients with renal impairment which could be explained by the more advanced disease in these patients.

Overall, the incidence of SAEs was low in both studies (4.0 %/4.1 % and 8.3 %/9.2 % for vildagliptin/placebo). More hypoglycaemia SAEs were reported by patients in the placebo groups

compared to the vildagliptin patients. Most SAEs were isolated events reported by not more than one patient each. Cardiovascular events (i.e. MI or stroke) were reported more frequently in the placebo groups than in the vildagliptin treated groups (1 vs 7 events for vildagliptin and placebo respectively). Infections were reported more frequently in the vildagliptin treated groups (7 vs 3 events). Four malignancies (prostate cancer, squamous cell carcinoma of the skin, gastric cancer and breast cancer) were reported in the vildagliptin treated groups versus none in the placebo treated groups. Narratives of these events have been provided. All cases were diagnosed after 5 to 79 days of vildagliptin treatment. Any relationship with the vildagliptin treatment is unlikely due to the very short duration of exposure to vildagliptin. Breast cancer is included as a potential risk in the RMP.

With regards to the identified and potential risks: hepatic, muscle, skin and/or vascular, neuropsychiatric-related events, acute pancreatitis and infections, no imbalances were observed when both studies CLAF237A23135 and CLAF237A2311 were considered. A higher reporting of infections were observed in study CLAF237A23135, however, in study CLAF237A2311 the reporting was higher in the placebo group. The potential/identified risk breast cancer (one case reported for vildagliptin in study CLAF237A23135) and hypoglycaemia were not included in this analysis.

The number of hypoglycaemic events were balanced (study CLAF237A23135) or lower in the vildagliptin treated groups (CLAF237A2311). There is no indication of an increase in severity of hypoglycaemic events when vildagliptin is used in combination with insulin. In study CLAF237A23135, insulin doses could be reduced for safety reasons at the investigator's discretion. This could include insulin dose decreases for safety reasons at anytime without specific dose limits. The need for insulin dose decreases was not markedly different between groups albeit slightly higher in the vildagliptin group (21.9 % on vildagliptin vs 19.9 % on placebo had any decrease from baseline). Considering that the difference in risk for hypoglycaemia was small (8.4% vs 7.2%, vildagliptin and placebo, respectively), no amendments of the SmPC with warnings regarding risk of hypoglycaemia when vildagliptin is used in combination with insulin are needed.

The lower incidence of hypoglycaemias while still achieving a modest lowering of HbA1c in study CLAF237A2311, give some indication that also patients with advanced T2DM may have some benefit from the addition of vildagliptin to insulin considering that hypoglycaemias limit the possibility of increasing the insulin dose.

Only modest increases in body weight were observed in both studies. Considering the improvement in HbA1c (which usually results in some weight gain) with vildagliptin, the MAH's conclusion that the effect on body weight was neutral is endorsed.

Overall, the incidence of AEs leading to discontinuation was low, and most were isolated events reported by not more than one patient each.

Safety data from studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149. In this procedure it was concluded that no new or unexpected safety concerns were identified and that the safety profile in patients with impaired renal function was similar to that of the overall population.

The MAH also performed an analysis across studies CLAF237A23135 and CLAF237A2311 in order to identify adverse drug reactions, applying the same algorithm as for previously approved indications. The adverse reactions selected for inclusion in the SmPC section 4.8 as well as the proposed frequencies are endorsed.

In conclusion, safety data have been provided in a relatively large population treated with the combination of vildagliptin and insulin. Limited data are also available in a population treated with the triple combination of vildagliptin, insulin and metformin. The data provided give no indication of a

significantly different safety profile with these combinations compared to combinations already approved and no new safety issues have been identified.

2.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed (new text underlined and deleted text marked as strikethrough):

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.

Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin 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, with ~~or~~ a thiazolidinedione or with insulin (with or without metformin), 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.

[…]

4.8 Undesirable effects

[…]

Clinical trials of up to 2 years' duration did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Combination with insulin

Table 5 Adverse reactions reported in patients who received Galvus 100 mg daily in combination with insulin (with or without metformin) in double-blind studies (N=371)

Metabolism and nutrition disorders	
Common	Decreased blood glucose
Nervous system disorders	
Common	Headache, chills
Gastrointestinal disorders	
Common	Nausea, gastro-oesophageal reflux disease
Uncommon	Diarrhoea, flatulence

Description of selected adverse reactions
In controlled clinical trials using vildagliptin 50 mg twice daily in combination with insulin, with or without concomitant metformin, the overall incidence of withdrawals due to adverse reactions was 0.3% in the vildagliptin treatment group and there were no withdrawals in the placebo group.

The incidence of hypoglycaemia was similar in both treatment groups (14.0% in the vildagliptin group vs 16.4% in the placebo group). Two patients reported severe hypoglycaemic events in the vildagliptin group, and 6 patients in the placebo group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg change from baseline in the vildagliptin group and no weight change in the placebo group).

[…]

5.1 Pharmacodynamic properties

[…]

A 24-week randomised, double-blind, placebo-controlled trial was conducted in 449 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with a stable dose of basal or premixed insulin (mean daily dose 41 units), with concomitant use of metformin (N=276) or without concomitant metformin (N=173). Vildagliptin in combination with insulin significantly decreased HbA_{1c} compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA_{1c} 8.8% was -0.72%. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA_{1c} was -0.63% and -0.84%, respectively. The incidence of hypoglycaemia in the overall population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. Patients receiving vildagliptin experienced no weight gain (+0.2 kg) while those receiving placebo experienced weight reduction (-0.7 kg).

In another 24-week study in patients with more advanced type 2 diabetes not adequately controlled on insulin (short and longer acting, average insulin dose 80 IU/day), the mean reduction in HbA_{1c} when vildagliptin (50 mg twice daily) was added to insulin was statistically significantly greater than with placebo plus insulin (0.5% vs. 0.2%). The incidence of hypoglycaemia was lower in the vildagliptin group than in the placebo group (22.9% vs. 29.6%).

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. Despite the benefits patients have from combination treatment of insulin and OAD, the use of certain OADs is associated with increased risk of hypoglycemia and/or weight gain.

The current type II variation is an application for a new indication: "*Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin 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).

The Package Leaflet was updated accordingly.

Benefits

Beneficial effects

One of the main targets in the treatment of type 2 diabetes mellitus is to control the hyperglycaemia while maintaining or lower body weight and without inducing too much hypoglycaemia. With the current variation the MAH has provided data from one pivotal study (CLAF237A23135) and three supportive studies (CLAF237A2311, CLAF237A23137 and CLAF237A23138) to support the concomitant use of vildagliptin and insulin with or without concomitant metformin.

In the pivotal study, which enrolled 399 patients and included patients both on dual therapy with vildagliptin and insulin (40 %) and triple therapy (vildagliptin/insulin/metformin, 60 % of patients), a clinically relevant and statistically significant placebo-adjusted lowering of HbA1c (-0.72 %) was observed. Patients who needed rescue with additional insulin doses (> 10 % increase from baseline) were censored. The sensitivity analyses of the primary endpoint without censoring of data supports the outcome in the primary analyses. Also the secondary endpoints, i.e. to show superiority for vildagliptin compared to placebo in the two subgroups, were met. In the subgroup on concomitant metformin treatment a placebo-adjusted HbA1c change from baseline of -0.63 % was observed and the corresponding result in the group not treated with metformin was -0.84 %. These data are further supported by the responder analysis where significantly higher proportions of patients reached the predefined targets. The responder rate was 21-24 % both in the overall population and in the two subsets (with or without concomitant metformin). Additional sensitive analyses were provided, which all supported the primary analysis.

In study CLAF237A2311, which was assessed within the original MAA for vildagliptin, the addition of vildagliptin to insulin therapy resulted in a placebo corrected reduction in HbA1c of -0.27 %. Thus the HbA1c outcome was markedly lower in this study compared to study CLAF237A23135. At the time of the initial application, the CHMP had concerns, whether this difference would be clinically meaningful. It should be noted that study CLAF237A2311 included patients with longer diabetes duration and a longer history of insulin treatment as well as higher insulin doses than study CLAF237A23135. It could be speculated that the lower response is due to lower endogenous insulin secretion in patients with longer duration and thus a diminished effect of vildagliptin. It is, however, noteworthy that although the effect on HbA1c was modest, the incidence of hypoglycaemias was lower in the vildagliptin treated group than in the placebo group. Thus the data from study CLAF237A2311 indicate that also patients with long-standing T2DM could benefit from the addition of vildagliptin to insulin considering that hypoglycaemias limit the possibility of increasing the insulin dose.

Studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149 with the aim of including a posology for patients with moderate to severe renal impairment. A majority of patients in both studies were on a background treatment with insulin in monotherapy or in combination with OADs. A reduced vildagliptin dose was used due to the increased exposure of vildagliptin in patients with renal impairment. Also in this population, a post-hoc

analysis showed a clinically relevant reduction of HbA1c (about -0.50 %) when vildagliptin was added to insulin.

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 insulin with or without concomitant metformin treatment 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

The safety data from studies CLAF237A23135 and CLAF237A2311 were pooled in order to get a larger safety database with patients treated with the combination of vildagliptin and insulin. In spite of the differences between the study populations in studies CLAF237A23135 and CLAF237A2311, the pooling of the safety data is endorsed. By pooling of data a relatively large safety population of 744 patients, out of which 372 were treated with vildagliptin, was obtained. Safety data beyond 24 weeks is not available for the currently investigated combination. This is acceptable considering that the safety profile of vildagliptin is rather well known.

In study CLAF237A23135, the reporting of adverse events was higher in the vildagliptin treated group than in the placebo groups (57.7 % vs 47.5 %) whereas reporting rates were similar in both groups in study CLAF237A2311 (81.3 % vs 82.9 %). The reporting rate was lower in study CLAF237A23135 which may reflect that this study included patients with less advanced T2DM than study CLAF237A2311. The overall reporting pattern did not differ between studies, with a distinctly higher reporting of gastrointestinal disorders in the vildagliptin treated groups compared to placebo. This is in line with the safety profile as previously described for vildagliptin.

Overall, the incidence of SAEs was low in both studies (4.0 %/4.1 % and 8.3 %/9.2 % for vildagliptin/placebo) and there were no imbalances with regards to deaths. More hypoglycaemia SAEs were reported by patients in the placebo groups compared to the vildagliptin patients. Most SAEs were isolated events reported by not more than one patient each.

With regards to the identified and potential risks: hepatic, muscle, skin and/or vascular, neuropsychiatric-related events, acute pancreatitis and infections, no imbalances were observed when both studies CLAF237A23135 and CLAF237A2311 were considered.

The number of hypoglycaemic events were balanced (study CLAF237A23135) or lower in the vildagliptin treated groups (CLAF237A2311). There is no indication of an increase in severity of hypoglycaemic events when vildagliptin is used in combination with insulin. In study CLAF237A23135, the need for insulin dose reductions did not markedly differ between treatment groups, It is therefore concluded that no recommendations on insulin dose adjustments when vildagliptin is added are warranted. The effect on body weight was neutral.

Safety data from studies CLAF237A23137 and CLAF237A23138 were assessed in the Type II variation procedure EMEA/H/C/771/1048/1051/WS/149. In this procedure it was concluded that no new or unexpected safety concerns were identified and that the safety profile in these more vulnerable patients with impaired renal function was similar to that of the overall population.

Uncertainty in the knowledge about the unfavourable effects

Four malignancies (prostate cancer, squamous cell carcinoma of the skin, gastric cancer and breast cancer) were reported in the vildagliptin treated groups versus none in the placebo treated groups in studies CLAF237A23135 and CLAF237A2311. However, any relationship with the vildagliptin treatment is unlikely due to the very short duration of exposure to vildagliptin (5-79 days) at diagnosis. Breast cancer is included as a potential risk in the RMP.

Balance

Importance of favourable and unfavourable effects

Considering the consistent findings in the pivotal study, both for the primary and secondary endpoints, the data provide sufficient support on the efficacy of vildagliptin to lower HbA1c in combination with insulin both with and without concomitant treatment with metformin.

The safety data provided does not indicate that the safety profile with this new combination differs from that observed in previous studies with vildagliptin. Hypoglycaemias were reported at similar frequencies in the vildagliptin treated and placebo groups and there was no indication of an increased severity of events in spite of improved glucose control. Patients with significant CV disease were excluded from the pivotal study; however, safety data from the supportive studies performed in patients with impaired renal function have not evoked any new safety concerns.

Benefit-risk balance

Discussion on the benefit-risk assessment

The efficacy of vildagliptin in providing a clinically relevant lowering of HbA1c when added to insulin therapy with or without concomitant metformin treatment has been adequately shown. Some additional analyses of the data were requested to ensure the robustness of the outcome.

Safety data have been provided in a relatively large population treated with the combination of vildagliptin and insulin. Somewhat limited data are also available in a population treated with the triple combination of vildagliptin, insulin and metformin. The data provided give no indication of a significantly different safety profile with these combinations compared to combinations already approved and no new safety issues have been identified.

Conclusion

The benefit risk balance for vildagliptin in combination with insulin with or without concomitant metformin is considered positive.

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 change:

Variation(s) 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 use of vildagliptin and vildagliptin/metformin in combination with insulin affecting sections 4.1, 4.2, 4.8 and 5.1 of the SmPC. The Package Leaflet is updated accordingly.

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 version 10.0 for vildagliptin and version 8.0 for vildagliptin/metformin 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