

2 Synopsis

Name of finished product: Galvus®/Eucreas®

Name of active ingredient: LAF237/vildagliptin and LMF237 (fixed-dose combination vildagliptin/metformin)

Study number: CLAF237A2403

Title of study: A multinational, multicenter, post-authorization, prospective observational cohort study to assess the profile of vildagliptin and the fixed-dose combination of vildagliptin/metformin relative to comparator oral anti-diabetic drugs in patients with type 2 diabetes in a real-world setting

Investigator(s): Brath H et al.

Study center(s): A total of 2957 centers in 27 countries enrolled at least one patient (number of centers in brackets): Argentina (15), Austria (22), Bahrain (9), Belgium (335), Bulgaria (24), Colombia (25), Czech Republic (39), Ecuador (3), Germany (790), Greece (7), India (472), Jordan (26), Republic of Korea (54), Kuwait (13), Lebanon (53), Luxembourg (2), Mexico (264), Netherlands (129), Oman (15), Palestine (51), Philippines (47), Portugal (359), Russian Federation (87), Slovakia (45), Sweden (31), United Arab Emirates (36) and Venezuela (4).

Publication (reference): None

Study period

First patient enrolled: 04-Sep-2008 (first patient first visit)

Last patient completed: 23-May-2011 (last patient last visit)

Phase of development: IV

Objectives: The **primary objective** was to assess the proportion of patients on vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator oral anti-diabetic drug (OAD) dual therapy in a real-world setting, responding to treatment (defined as decrease in HbA_{1c} > 0.3% from baseline to Month 12 endpoint) without any of the following adverse effects: peripheral edema or proven hypoglycemic event or discontinuation due to gastrointestinal (GI) event or significant weight gain (≥ 5%) after 12 months of treatment

Secondary objectives were:

Effectiveness and tolerability objectives

- To assess, in global sub-populations and corresponding country-specific sub-populations of patients with baseline HbA_{1c} 7.0% or above, the proportion of patients on vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OAD dual therapy in a real-world setting, reaching target HbA_{1c} level of < 7.0% at Month 12 endpoint without ≥ 3% weight gain at 12 months or proven hypoglycemic events. This assessment was done for the entire global population and for country-specific populations with baseline HbA_{1c} 7.0% or above, but also in each subgroup determined by baseline HbA_{1c} (≤8%, >8 - 9%, >9%) and baseline BMI (<25, 25-30, >30 kg/m²).
- To assess the proportion of patients on vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OAD dual therapy in a real-world setting, responding to treatment (defined as decrease in HbA_{1c} > 0.3% from baseline to Month 12 endpoint) without any of the following adverse effects: peripheral edema or proven hypoglycemic event or discontinuation due to GI event or ≥ 3% weight gain.
- To assess the effect of vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) on individual tolerability factors (body weight, peripheral edema, hypoglycemia, GI events) relative to comparator OADs used as add-on dual therapy.

- To assess the proportion of patients on vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OAD dual therapy in a real-world setting, responding to treatment (defined as decrease in HbA_{1c} > 0.3% from baseline to Month 12 endpoint) without ≥ 3% weight gain at 12 months or proven hypoglycemic event.

Safety objectives

- To assess the safety profile of vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OADs used as add-on dual therapy in a real-world setting.
- To assess the proportion of patients on vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OADs used as add-on dual therapy that discontinued index therapy due to serious adverse events (SAEs).
- To assess the proportion of patients on vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OADs used as add-on dual therapy that discontinued index therapy due to adverse events (AEs).
- To assess the proportion of patients on vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OADs used as add-on dual therapy that discontinued index therapy due to any other reason.

Additional secondary objectives

- To describe the baseline demographic and metabolic characteristics of patients on vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OADs used as add-on dual therapy.
- To describe the prescribing practices of physicians prescribing vildagliptin add-on dual therapy or vildagliptin/metformin (fixed-dose) relative to comparator OADs used as add-on dual therapy.

Methodology: This was an multinational, multicenter, post-authorization, prospective observational cohort study conducted in 27 countries (where Galvus® and Eucreas® had market approval) in 5 defined regions :Europe, Latin America, India, East (Asia), and Middle East.

Data were collected on patients (≥ 18 years) with type 2 diabetes mellitus (T2DM) who were inadequately or not controlled by their current OAD monotherapy and who were newly initiating a second OAD (henceforth referred to as “index therapy” or “index medication”). Suitable patients fell into one of two cohorts (vildagliptin or comparator) based on the index therapy or the newly initiated OAD dual therapy.

The study duration was 12 months (a maximum of 2 additional months was allowed for the Final Study Data Collection to provide ample flexibility to reflect real-life practice). The two cohorts consisted of the following patients:

Vildagliptin cohort:

The vildagliptin cohort consisted of the following patients: T2DM patients newly initiating either vildagliptin, or newly initiating fixed-dose vildagliptin/metformin at study start. In accordance with the protocol, a patient had to be on metformin monotherapy prior to initiating fixed-dose vildagliptin/metformin combination. All patients receiving any new OAD at baseline were assigned to a cohort. Patients not receiving any other OAD than the OAD received prior to baseline were not assigned to a cohort.

Non-vildagliptin cohort:

The comparison population (“comparison cohort”) was identified based on T2DM patients newly initiating an OAD other than vildagliptin at study start. All patients receiving any new OAD at baseline were assigned to a cohort. Patients not receiving any other OAD than the medication received prior to baseline were not assigned to a cohort.

Number of patients (planned and analyzed): In this prospective cohort study, approximately 60,000 patients (approximately 30,000 in each cohort) were planned to be included. At the end of the study,

the enrolled population consisted of 45,868 patients with 29,759 in the vildagliptin cohort and 16,078 in the comparator cohort - out of which 40,203 patients completed the study (25,525 in vildagliptin cohort vs. 14,661 in comparator cohort).

Diagnosis and main criteria for inclusion

Cohort inclusion criteria: a) Patients had to give verbal or written informed consent (as defined by local regulations) to have their data collected. Patients did not need to consent to taking drug, as their treatment was decided before entry into the study. b) Male/female patients diagnosed with T2DM, taking OAD monotherapy, who were prescribed a new add-on OAD (i.e. either vildagliptin or vildagliptin/metformin or another OAD (defined as SUs, metformin, TZDs, glinides or α -glucosidase inhibitors) or an OAD fixed-dose combination as dual combination therapy according to local label/prescribing requirements. c) Age $\geq$ 18 years at Baseline Data Collection. d) Patients agreed to follow all local medication labeling or prescribing requirements of the anti-diabetic drug(s) they were taking while participating in the study.

Cohort exclusion criteria: a) Use of any investigational drug at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whatever was longer. b) OAD naïve patients at time of study start. c) Patients who were taking a DPP-4 inhibitor (including vildagliptin) at Baseline Data Collection (Visit 1) or within 1 month prior to Visit 1, or who were planned to initiate DPP-4 inhibitors other than vildagliptin. d) Patients who were taking GLP-1 mimetics/analogues at Baseline Data Collection or within 1 month prior to Visit 1, or who were planned to be started with GLP-1 mimetics/analogues. e) Patients who required three or more OADs at time of study entry. f) Patients who were swapped from one OAD or OAD class to another at time of study entry. g) Patients who were using insulin at the time of study entry. h) History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.

Test product, dose and mode of administration, batch number: Not applicable as study was non-interventional in nature.

Duration of treatment: 12 months

Reference therapy, dose and mode of administration, batch number: Not applicable as the study was non-interventional in nature.

Criteria for evaluation

Effectiveness and tolerability: The primary end point measures the effectiveness by means of a composite end-point. The effectiveness is measured by an HbA_{1c} drop $>0.3\%$ and tolerability is measured by no significant weight gain ($\geq 5\%$), no proven hypoglycemic event, no discontinuation due to GI events, no peripheral edema. Therefore, it is a composite of both effectiveness and tolerability.

A 0.3% HbA_{1c} reduction from baseline has been chosen as the cut-off HbA_{1c}, as it corresponds to the minimum change in which clinically significant benefits would be expected to occur. It was therefore used to define no absolute loss of effectiveness.

The measurement of the secondary endpoint 'Treatment response without occurrence of peripheral edema, proven hypoglycemia, discontinuation due to GI events and weight gain' was performed analogously to the main analysis of the primary objective with the only difference that for weight gain a threshold of $\geq 3\%$ was used instead of $\geq 5\%$.

The measurement of the secondary endpoint 'Treatment response without proven hypoglycemia and weight gain' was performed analogously to the main analysis of the primary objective except that for weight gain a threshold of $\geq 3\%$ was used instead of $\geq 5\%$ and peripheral edema or discontinuation due to GI event was not considered as treatment failures.

The secondary endpoint 'Attainment of HbA_{1c} target level of less than 7.0% at 12 months without weight gain and proven hypoglycemia' was measured for all patients and in region-specific subgroups of patients (based on location of the treating physician) with baseline HbA_{1c} of 7.0% or above. Additionally, these results were presented for subgroups determined by baseline HbA_{1c} ($\geq 7 - \leq 8\%$, $> 8 - 9.0\%$, $> 9.0\%$) and baseline BMI (< 25 , $25 - < 30$, $30 - < 35$, ≥ 35 kg/m²).

Safety: Laboratory testing was performed on patients in line with normal medical practice and/or as defined by local prescribing information and/or at a time period judged appropriate by the physician as no lab testing was required in the context of this study. GI events and peripheral edema events (non-serious, serious and events leading to discontinuation), weight gain (clinically significant weight gain defined as $\geq 5\%$ from baseline to 12 month endpoint and weight gain $\geq 3\%$ from baseline to 12 month endpoint) and hypoglycemic events (i.e. any of the three following events – Symptoms suggestive of hypoglycemia that resolved promptly on the administration of oral carbohydrate/symptoms suggestive of hypoglycemia accompanied by a plasma glucose of < 3.1 mmol/L (< 56 mg/dL)/symptoms suggestive of hypoglycemia and patient unable to initiate self-treatment therefore requiring assistance of a third party or hospitalization) were collected in addition to the standard AEs, SAEs and pregnancies.

“The risk of SAE, death, and AE was assessed as the overall incidence rate (i.e. number of patients with at least one of these events relative to the total person-time of follow-up in the specific cohort).

In addition, an external vildagliptin Hepatic Adjudication Committee reviewed and categorized all the cases that met the following criteria: a) serious adverse hepatic event b) hepatic death c) laboratory abnormalities that are: $\geq 3 \times \text{ULN}$ ALT/AST with $1.5 \times \text{ULN}$ bilirubin and $\geq 5 \times \text{ULN}$ ALT/AST. For this study, the selected events were adjudicated in both treatment cohorts (vildagliptin and comparator).

Bioanalytics: Not applicable.

Statistical methods:

The analysis sets were as follows;

Enrolled population: This population included all patients who were enrolled into the study and gave informed consent. This population was used for the disposition overview, overview of protocol deviations and other criteria leading to exclusion from analysis populations, demographic characteristics, duration of exposure and selected descriptive safety tables.

Intent-to-treat analysis (ITT) population: This population was a subset of the enrolled population and included all patients who were assigned a new OAD at study start. The ITT population was used for the analysis of the secondary safety endpoints and for demographic and baseline characteristics as well as for all safety analyses. Sites and/or patients identified with deviation from good clinical practices and those patients that were not assigned a new OAD at study start were excluded from the ITT analysis population. **Per protocol (PP) analysis population:** This population was a subset of the ITT population who had no protocol deviations. The PP population was used for the analyses of effectiveness endpoints

Supportive analysis population: The supportive analysis population identified evaluable patients in the PP population, who had: a) A tolerability issue (peripheral edema or proven hypoglycemia or discontinuation due to GI event) while on initial dual therapy, or b) Baseline and month 12 data HbA_{1c} and weight data with no change to OAD medication since study start, or c) Had lack of treatment response at Month 12 with no change to OAD medication since study start, or d) Had a clinically significant weight gain at Month 12 with no change to OAD medication since study start.

Analyses of endpoints:

Each patient was categorized as a success, failure or non-evaluable as follows:

- Success = treatment response without any of the tolerability findings
- Failure = lack of treatment response and/or occurrence of any of the tolerability findings
- Non-evaluable = patients who could not be categorized as successes or failures (e.g. due to missing HbA_{1c} or weight data at 12 months).

For the treatment response primary objective, the primary response variable was the proportion of patients responding to treatment without any of the following adverse effects: peripheral edema or proven hypoglycemic event or discontinuation due to GI event or significant weight gain after 12 months of treatment from baseline to month 12 endpoint.

The probability of success was analyzed using a multivariable logistic regression model to calculate odds ratios (ORs) with 95% confidence intervals (95% CIs). The OR expresses the odds in favor of responding to success in vildagliptin or vildagliptin/metformin (fixed-dose) to the odds in favor of responding to success in the comparison OADs.

The components of the primary endpoint: reduction of HbA_{1c}, absence of peripheral edema, absence of proven hypoglycemic events, absence of discontinuation due to GI events and absence of significant weight gain were also analyzed separately adjusted for the same covariate adjustment as for the primary endpoint, stratified by quintiles of the propensity score (PS).

Descriptive analyses of numbers and percentages of successes, failures and non-evaluables was done by region, by baseline HbA_{1c} ($\leq 8\%$, $>8 - 9.0\%$, $>9.0\%$), by baseline BMI (<25 , $25-30$, $30-35$, ≥ 35 kg/m²) and by index medication type (i.e. SUs, metformin, TZDs, glinides, or α -glucosidase inhibitors) in the comparator cohort.

Data on individual tolerability factors (body weight, peripheral edema, hypoglycemia, GI events) were assessed by cohort.

It was planned to enroll a total of approximately 60,000 patients for the study in a 1:1 ratio, i.e. approximately 30,000 subjects in each cohort. The sample size calculations were based on the following assumption: for each patient in the vildagliptin cohort, 1 patient should be accrued in the comparison cohort. The sample size was calculated as driven by the critical secondary objective of SAE profile, which requires a larger sample size, and was also assessed for adequacy for the primary objective of treatment response.

Actual enrollment into the study was not balanced, with approximately 2 patients accrued in the vildagliptin cohort for every 1 patient accrued in the comparison cohort (2:1 ratio). The enrolled population is 45,868 patients.

Summary - Conclusions

Demographic and background characteristics: The overall mean age was 57.8 and was similar in the vildagliptin and comparator cohort (57.9 and 57.6, respectively) in the ITT population. The proportion of patients in the two groups of treatment was balanced across all classes of age. Overall, there were more male than female patients enrolled (54.8% and 45.2%) and this proportion was similar in the two treatment groups. The most prevalent race was Caucasian (47.8%) followed by Asian (32.2%). There were less Asians enrolled in the vildagliptin cohort (27.5%) compared to the comparator group (41.1%). The overall mean weight was 80.2 kg. The mean weight in the vildagliptin cohort was 81.5 kg and 77.7 kg in the comparator cohort. Most of the patients were overweight with an overall mean BMI of 29.0 kg/m² (29.3 kg/m² in the vildagliptin cohort vs. 28.4 kg/m² in the comparator cohort). The baseline demographic characteristics were comparable across all populations for both cohorts in all 3 populations: ITT, enrolled population and supportive analysis population.

The overall mean duration of diabetes was about 5.5 years with the majority (58.4%) having had the disease for < 5 years. Slightly more than half of the patients had an HbA_{1c} of ≤ 8.0 at baseline as expected. The HbA_{1c} values were comparable between the treatment groups. Majority of the patients had normal renal function at baseline when evaluated for renal impairment and 0.5% of the patients were categorized as having severe renal impairment. Overall, the patient population in this study showed characteristics common to patients with T2DM. The baseline background characteristics across regions were generally comparable between both cohorts across both ITT (and supportive analysis populations).

Effectiveness and tolerability results:

- For the primary composite endpoint, i.e. treatment response (defined as decrease in HbA_{1c} $\geq 0.3\%$ from baseline) without occurrence of peripheral edema, proven hypoglycemia, discontinuation due to gastrointestinal events and weight gain $\geq 5\%$ the adjusted odds ratio was 1.48 (CI 95% 1.42-1.55; $p < 0.001$) in favor of vildagliptin.

- Treatment response without occurrence of peripheral edema, proven hypoglycemia, discontinuation due to gastrointestinal events and weight gain $\geq 3\%$ was the secondary effectiveness endpoint 1 and the adjusted odds ratio was 1.64 (CI 95% 1.57-1.72; $p < 0.001$) in favor of vildagliptin.
- Treatment response without proven hypoglycemia and weight gain was the secondary effectiveness endpoint 2 and the adjusted odds ratio was 1.64 (CI 95% 1.57-1.72; $p < 0.001$) in favor of vildagliptin.
- Attainment of HbA1c target level of $< 7.0\%$ at 12 months without weight gain and proven hypoglycemia was the secondary effectiveness endpoint 3 and the adjusted odds ratio was 1.96 (CI 95% 1.85-2.07; $p < 0.001$) in favor of vildagliptin.

The effectiveness and tolerability results are summarized in the following tabular format:

Summary of effectiveness and tolerability results

	Success Rate Vildagliptin Total 28061	Success Rate Comparator Total 15294	OR unadjusted (95% CI)	OR adjusted (95% CI)
Primary End Point				
Decrease HbA1c $> 0.3\%$ from BL to EOS without peripheral edema or proven hypoglycemic event or discontinuation due to gastrointestinal event or weight gain $\geq 5\%$	15536 (55.4)	7852 (51.3)	1.18 [1.13 - 1.22]	1.49 [1.42 - 1.55]
Secondary End Point 1				
Decrease HbA1c $> 0.3\%$ from BL to EOS without peripheral edema or proven hypoglycemic event or discontinuation due to gastrointestinal event or weight gain $\geq 3\%$	15066 (53.7)	7170 (46.9)	1.31 [1.26 - 1.37]	1.64 [1.57 - 1.72]
Secondary End Point 2				
Decrease in HbA1c $> 0.3\%$ from BL to EOS without $\geq 3\%$ weight gain or proven hypoglycemic events	15071 (53.7)	7177 (46.9)	1.31 [1.26 - 1.36]	1.64 [1.57 - 1.72]
Secondary End Point 3				
HbA1c $< 7\%$ at EOS without proven hypoglycemic events or weight gain $\geq 3\%$	8027 (35.1)	2940 (23.2)	1.79 [1.70 - 1.88]	1.96 [1.85 - 2.07]

population and
baseline HbA1c % > 7

BL=baseline; CI=confidence interval; EOS=end of study; OR=odds ratio

Safety results:

- The overall safety is comparable between the two treatment groups. In this observational study, AE/SAE rates are significantly lower than those reported in the phase 3 clinical program as can be expected in this kind of observational study with relevant under-reporting compared to a randomized clinical trial. The overall proportion of cases with ALT ≥ 3 ULN elevation is evenly distributed between the vildagliptin (0.2%) and comparator arm (0.2%), with very low reporting rates of ALT ≥ 10 ULN in both groups. No discernible difference was observed in the reporting of events between the ITT and enrolled populations.
- The overall death incidence rate (events per 100 patient years) with 95% CI was 0.09 (0.059; 0.135) in the vildagliptin cohort and 0.11 (0.062; 0.176) in the comparator cohort. The adjusted hazard ratio (vildagliptin/comparator) with 95% CI for relative death risk was 0.66 (0.34; 1.29) with $p = 0.228$.
- The overall SAE incidence rate (events per 100 patient years) with 95% CI was 0.53 (0.449; 0.626) in the vildagliptin cohort and 0.34 (0.257; 0.453) in the comparator cohort. The adjusted hazard ratio (vildagliptin/comparator) with 95% CI for relative SAE risk was 1.22 (0.87; 1.73) with $p = 0.251$.
- The percentage of patients who discontinued index OAD due to an AE was similar in both the vildagliptin group (0.57%) and the comparator group (0.52%).
- The incidence of discontinuation of index OAD therapy due to SAEs was similar between both cohorts (0.1% each)
- The percentage of patients discontinuing index OAD therapy due to any other reason than AEs/SAEs was comparable between both cohorts

Bioanalytical results: Not applicable

Conclusion:

Summary of the conclusions:

- Under "real-life" conditions vildagliptin had superior overall clinical benefit versus comparator as measured by a composite endpoint assessing effectiveness and tolerability
- In this large "real-life" observational study vildagliptin provided glucose control consistent with data from previous randomized clinical trials
- Overall, adverse events were under-reported if compared to an "explanatory trial" but consistent with those seen in other "real-life studies".
- Overall, adverse events were not different between vildagliptin and comparator and consistent with those seen in LAF237 clinical program (no signals emerged from specific SOC).

Date of report: 30-May-2012 (content final)