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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Sponsor</b><br>Novartis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Generic Drug Name</b><br>Vildagliptin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Therapeutic Area of Trial</b><br>Type 2 diabetes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Approved Indication</b><br>According to the Summary of Product Characteristics (SPC) in Germany:<br>Treatment of type 2 diabetes in combination therapy with <ul style="list-style-type: none"><li>- Metformin, in patients inadequately controlled with maximal tolerated doses of metformin</li><li>- Sulfonylureas, in patients having intolerance of metformin and being inadequately controlled with maximal tolerated doses of sulfonylureas</li><li>- Thiazolidindiones, in patients being inadequately controlled and being eligible for thiazolidindione treatment</li></ul> |
| <b>Study Number</b><br>CLAF237ADE02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Title</b><br>A multicenter, randomized, double-blind, parallel-group study to investigate the glucose lowering effect, safety and tolerability of a 24 week treatment with Vildagliptin 100 mg o.a.d. versus placebo followed by a 12 week treatment period with open-label Vildagliptin 100 mg o.a.d. as add-on therapy in patients with type 2 diabetes inadequately controlled with Metformin monotherapy                                                                                                                                                                          |
| <b>Phase of Development</b><br>Phase IIIb                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Study Start/End Dates</b><br>11-Jun-2007 to 07-Jul-2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Study Design/Methodology</b><br>Multicenter, randomized, double-blind study with open-label follow-up. Patients with T2DM and prior therapy with metformin for at least 3 months prior to screening who were inadequately controlled (HbA1c 6.5-8.0%) were randomized into this study. Eligible patients have been random-                                                                                                                                                                                                                                                            |

ized into 2 treatment arms (ratio 2: 1 for vildagliptin 100 mg o.a.d.: placebo o.a.d.) for a period of 24 weeks. Within the treatment arms patients were randomized to morning or evening administration. After this 24 weeks double-blind phase all patients were treated with open-label vildagliptin 100 mg o.a.d. according to the previous dosing regime.

**Centres**

94 centers in Germany

**Objectives**Primary objective(s)

To confirm the efficacy of vildagliptin 100 mg add-on therapy in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that the HbA<sub>1c</sub> reduction with vildagliptin 100 mg o.a.d. (hierarchically testing of pooled data of a.m. and p.m. dose as well as •within a.m. and p.m. dosing groups) is superior to that with placebo after 24 weeks of treatment.

Secondary objective(s)

To confirm the efficacy of add-on therapy with vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that the FPG reduction with vildagliptin 100 mg o.a.d. (pooled data of a.m. and p.m dose as well as within a.m. and p.m. dosing groups) is superior to that with placebo after 24 weeks of treatment.

**Test Product (s), Dose(s), and Mode(s) of Administration**

Oral tablets of vildagliptin 100 mg once daily

## Reference Product(s), Dose(s), and Mode(s) of Administration

Placebo oral tablets matching vildagliptin 100 mg once daily

## Criteria for Evaluation

### Primary variables

Primary parameter is HbA<sub>1c</sub> after 24 weeks measured by certified methodology.

### Secondary variables

Secondary parameters: Fasting plasma glucose after 24 weeks of treatment.

### Safety and tolerability

Hypoglycemia during 24 weeks of treatment. Biochemistry.

### Pharmacology

None

### Other

None

## Statistical Methods

The **primary analysis** was performed comparing treatments with respect to the primary efficacy variable in an analysis of covariance (ANCOVA) model with the factors treatment and center and baseline HbA<sub>1c</sub> as a covariate. The raw- as well as the adjusted (LS) group means are presented together with a 95% confidence interval and a p-value.

**Multiplicity issues:** The factorial design of this trial with 2 treatments (vildagliptin and placebo), each given in 2 different dosing schedules (a.m.-and p.m.-dosing) yields 4 different treatment arms. The resulting multiplicity was dealt with by applying a closed test procedure. In a first step, vildagliptin was compared to placebo pooled over dosing schedules. The null hypothesis of no difference in HbA<sub>1c</sub> reduction was tested by applying a linear contrast with weights -0.25 for the two placebo arms and with weights +0.25 for the vildagliptin arms.

**Significance Level:** Both null hypothesis tested in step 2 are hierarchically nested within the pooled null hypothesis of step 1 and can't both be true, once the pooled null hypothesis of step 1 has been rejected. Therefore no further adjustment for multiplicity is required, all tests were performed at the two-sided 5% level.

No interim analysis was performed.

## Study Population: Inclusion/Exclusion Criteria and Demographics

### Inclusion criteria

1. Male, non-fertile female or female of childbearing potential using a medically approved birth control method.
2. Patients with T2DM who have received metformin for at least three months prior visit 1 and have been on a stable (maximal tolerated) dose for a minimum of 8 weeks prior to visit 1.
3. Agreement to maintain the same dose of metformin throughout the study.
4. Age in the range of 18-85 years inclusive.
5. HbA<sub>1c</sub> in the range of 6.5 – 8.0 % (inclusive) at visit 1.

### Exclusion criteria

1. A history of:
  - type 1 diabetes, diabetes that is a result of pancreatic injury, or secondary forms of diabetes, e.g. Cushing's syndrome and acromegaly.
  - acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma) within the past 6 months.
2. Evidence of significant diabetic complications, e.g. symptomatic autonomic neuropathy or gastroparesis.
3. Acute infections which may affect blood glucose control within 4 weeks prior to visit 1 and other concurrent medical conditions that may interfere with the interpretation of efficacy and safety data during the study.
4. ALT, AST greater than 2 times the upper limit of the normal range (ULN) at visit 1.
5. Total bilirubin greater than 2 times ULN and direct bilirubin greater than the upper limit of the normal range at visit 1.

### Number of Subjects

|                                         | Vildagliptin | Placebo    |
|-----------------------------------------|--------------|------------|
| Planned N                               | 268          | 134        |
| Randomised n                            | 274          | 131        |
| Intent-to-treat population (ITT) n (%)  | 268 (97.8)   | 127 (96.9) |
| Completed n (%)                         | 239 (87.2)   | 107 (81.7) |
| Withdrawn n (%)                         | 35 (12.8)    | 24 (18.3)  |
| Withdrawn due to adverse events n (%)   | 10 (3.6)     | 2 (1.5)    |
| Withdrawn due to lack of efficacy n (%) | 8 (2.9)      | 12 (9.2)   |
| Withdrawn for other reasons n (%)       | 17 (6.2)     | 10 (7.6)   |

## Demographic and Background Characteristics

|                      | Vildagliptin | Placebo    |
|----------------------|--------------|------------|
| N (ITT)              | 268          | 127        |
| Females: males (%)   | 124 (45.3)   | 64 (48.9)  |
| Mean age, years (SD) | 61.5 (10.1)  | 61.4 (9.8) |
| Mean weight, kg (SD) |              |            |
| Race                 |              |            |
| White n (%)          | 268 (97.8)   | 122 (93.1) |
| Black n (%)          | 0            | 0          |
| Oriental n (%)       | 2 (0.7)      | 2 (1.5)    |
| Other n (%)          | 4 (1.5)      | 7 (5.3)    |
| HbA1c (SD)           | 7.2 (0.4)    | 7.2 (0.5)  |

## Primary Objective Result(s)

Mean Change in HbA1c over 24 weeks pooled over dosing schedules for the ITT population

Variable: change from baseline

|                              | Unadjusted |             | Results from ANCOVA model *) |               |          |
|------------------------------|------------|-------------|------------------------------|---------------|----------|
|                              | N          | Mean (SD)   | LS-Mean                      | 95% CL        | p Diff=0 |
| Vildagliptin                 | 268        | -0.4 (0.67) | -0.4                         |               |          |
| Placebo                      | 127        | 0.2 (0.59)  | 0.2                          |               |          |
| Diff. Vildagliptin - Placebo |            | -0.5        | -0.5                         | [-0.7 , -0.4] | <.0001   |

## Secondary Objective Result(s)

Mean Fasting Plasma Glucose comparison pooled over dosing schedules for the ITT population

Variable: laboratory result (value)

|                 |                              | Unadjusted |               | Results from ANCOVA model *) |                |          |
|-----------------|------------------------------|------------|---------------|------------------------------|----------------|----------|
| vis1n           |                              | N          | Mean (SD)     | LS-Mean                      | 95% CL         | p Diff=0 |
| Day 1 Base-line | Vildagliptin                 | 268        | 122.9 (23.88) | 123.2                        |                |          |
|                 | Placebo                      | 127        | 123.8 (26.11) | 123.2                        |                |          |
|                 | Diff. Vildagliptin - Placebo |            | -0.9          | 0.0                          | [. , .]        | .        |
| Week 12         | Vildagliptin                 | 260        | 111.0 (23.46) | 111.6                        |                |          |
|                 | Placebo                      | 123        | 123.2 (26.58) | 124.5                        |                |          |
|                 | Diff. Vildagliptin - Placebo |            | -12.2         | -12.8                        | [-18.0 , -7.7] | <.0001   |
| Week 24         | Vildagliptin                 | 248        | 113.7 (22.95) | 114.5                        |                |          |
|                 | Placebo                      | 113        | 121.8 (26.38) | 124.0                        |                |          |
|                 | Diff. Vildagliptin - Placebo |            | -8.0          | -9.4                         | [-14.5 , -4.4] | 0.0003   |

## Safety Results

The incidence of SAEs was 5.2% under vildagliptin versus 9.4% under placebo. Mild hypoglycemia occurred in 0.4% of vildagliptin patients versus 0.8% of the placebo group. No severe hypoglycemia and no death occurred during the study.

## Adverse Events by System Organ Class

Number of AEs / patients with AEs with suspected drug relation, by system organ class and preferred term

| System organ class<br>Preferred term        | Vildagliptin |                 |                      | Placebo |                 |                      |
|---------------------------------------------|--------------|-----------------|----------------------|---------|-----------------|----------------------|
|                                             | n            | % of all<br>AEs | % of pats(<br>n=274) | n       | % of all<br>AEs | % of pats(<br>n=131) |
| Randomized patients                         | 274          |                 |                      | 131     |                 |                      |
| <b>All System Organ Classes</b>             |              |                 |                      |         |                 |                      |
| No. of Patients with AEs                    | 16           |                 | (5.8)                | 8       |                 | (6.1)                |
| Total no. of AEs                            | 23           | (100.0)         |                      | 14      | (100.0)         |                      |
| <b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b> |              |                 |                      |         |                 |                      |
| No. of Patients with AEs                    | 1            |                 | (0.4)                | 0       |                 | (0.0)                |
| Total no. of AEs                            | 1            | (4.3)           |                      | 0       | (0.0)           |                      |
| LEUKOCYTOSIS                                | 1            | (4.3)           | (0.4)                | 0       | (0.0)           | (0.0)                |
| <b>CARDIAC DISORDERS</b>                    |              |                 |                      |         |                 |                      |
| No. of Patients with AEs                    | 0            |                 | (0.0)                | 1       |                 | (0.8)                |
| Total no. of AEs                            | 0            | (0.0)           |                      | 1       | (7.1)           |                      |
| TACHYARRHYTHMIA                             | 0            | (0.0)           | (0.0)                | 1       | (7.1)           | (0.8)                |
| <b>GASTROINTESTINAL DISORDERS</b>           |              |                 |                      |         |                 |                      |
| No. of Patients with AEs                    | 6            |                 | (2.2)                | 4       |                 | (3.1)                |
| Total no. of AEs                            | 9            | (39.1)          |                      | 4       | (28.6)          |                      |
| ABDOMINAL DISTENSION                        | 1            | (4.3)           | (0.4)                | 0       | (0.0)           | (0.0)                |
| ABDOMINAL PAIN UPPER                        | 1            | (4.3)           | (0.4)                | 0       | (0.0)           | (0.0)                |
| DIARRHOEA                                   | 1            | (4.3)           | (0.4)                | 1       | (7.1)           | (0.8)                |
| FLATULENCE                                  | 0            | (0.0)           | (0.0)                | 1       | (7.1)           | (0.8)                |
| <b>GASTROINTESTINAL DISORDERS (cont.)</b>   |              |                 |                      |         |                 |                      |
| FREQUENT BOWEL MOVEMENTS                    | 1            | (4.3)           | (0.4)                | 0       | (0.0)           | (0.0)                |
| GINGIVITIS                                  | 0            | (0.0)           | (0.0)                | 1       | (7.1)           | (0.8)                |
| NAUSEA                                      | 3            | (13.0)          | (1.1)                | 1       | (7.1)           | (0.8)                |
| VOMITING                                    | 2            | (8.7)           | (0.7)                | 0       | (0.0)           | (0.0)                |
| <b>HEPATOBIILIARY DISORDERS</b>             |              |                 |                      |         |                 |                      |
| No. of Patients with AEs                    | 0            |                 | (0.0)                | 1       |                 | (0.8)                |

|                                                        |   |        |       |   |        |       |
|--------------------------------------------------------|---|--------|-------|---|--------|-------|
| Total no. of AEs                                       | 0 | (0.0)  |       | 1 | (7.1)  |       |
| HYPERBILIRUBINAEMIA                                    | 0 | (0.0)  | (0.0) | 1 | (7.1)  | (0.8) |
| <b>INVESTIGATIONS</b>                                  |   |        |       |   |        |       |
| No. of Patients with AEs                               | 1 |        | (0.4) | 2 |        | (1.5) |
| Total no. of AEs                                       | 1 | (4.3)  |       | 2 | (14.3) |       |
| BLOOD CREATINE PHOSPHOKINASE INCREASED                 | 0 | (0.0)  | (0.0) | 2 | (14.3) | (1.5) |
| GLYCOSYLATED HAEMOGLOBIN INCREASED                     | 1 | (4.3)  | (0.4) | 0 | (0.0)  | (0.0) |
| <b>METABOLISM AND NUTRITION DISORDERS</b>              |   |        |       |   |        |       |
| FOOD CRAVING                                           | 2 | (8.7)  | (0.7) | 0 | (0.0)  | (0.0) |
| <b>METABOLISM AND NUTRITION DISORDERS (cont.)</b>      |   |        |       |   |        |       |
| INCREASED APPETITE                                     | 1 | (4.3)  | (0.4) | 0 | (0.0)  | (0.0) |
| <b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b> |   |        |       |   |        |       |
| No. of Patients with AEs                               | 1 |        | (0.4) | 0 |        | (0.0) |
| Total no. of AEs                                       | 1 | (4.3)  |       | 0 | (0.0)  |       |
| ARTHRALGIA                                             | 1 | (4.3)  | (0.4) | 0 | (0.0)  | (0.0) |
| <b>NERVOUS SYSTEM DISORDERS</b>                        |   |        |       |   |        |       |
| No. of Patients with AEs                               | 1 |        | (0.4) | 4 |        | (3.1) |
| Total no. of AEs                                       | 1 | (4.3)  |       | 4 | (28.6) |       |
| DIABETIC NEUROPATHY                                    | 0 | (0.0)  | (0.0) | 1 | (7.1)  | (0.8) |
| DIZZINESS                                              | 1 | (4.3)  | (0.4) | 0 | (0.0)  | (0.0) |
| DIZZINESS EXERTIONAL                                   | 0 | (0.0)  | (0.0) | 1 | (7.1)  | (0.8) |
| HEADACHE                                               | 0 | (0.0)  | (0.0) | 1 | (7.1)  | (0.8) |
| TREMOR                                                 | 0 | (0.0)  | (0.0) | 1 | (7.1)  | (0.8) |
| <b>PSYCHIATRIC DISORDERS</b>                           |   |        |       |   |        |       |
| BIPOLAR DISORDER                                       | 1 | (4.3)  | (0.4) | 0 | (0.0)  | (0.0) |
| <b>PSYCHIATRIC DISORDERS (cont.)</b>                   |   |        |       |   |        |       |
| INSOMNIA                                               | 1 | (4.3)  | (0.4) | 0 | (0.0)  | (0.0) |
| <b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>          |   |        |       |   |        |       |
| No. of Patients with AEs                               | 5 |        | (1.8) | 2 |        | (1.5) |
| Total no. of AEs                                       | 5 | (21.7) |       | 2 | (14.3) |       |
| DERMATITIS ALLERGIC                                    | 1 | (4.3)  | (0.4) | 0 | (0.0)  | (0.0) |

|               |   |       |       |   |        |       |
|---------------|---|-------|-------|---|--------|-------|
| ECZEMA        | 1 | (4.3) | (0.4) | 0 | (0.0)  | (0.0) |
| HYPERHIDROSIS | 1 | (4.3) | (0.4) | 2 | (14.3) | (1.5) |
| PRURITUS      | 1 | (4.3) | (0.4) | 0 | (0.0)  | (0.0) |
| URTICARIA     | 1 | (4.3) | (0.4) | 0 | (0.0)  | (0.0) |

  

| <b>10 Most Frequently Reported AEs Overall by Preferred Term n (%)</b> |                     |       |  |                |       |  |
|------------------------------------------------------------------------|---------------------|-------|--|----------------|-------|--|
|                                                                        | <b>Vildagliptin</b> |       |  | <b>Placebo</b> |       |  |
| Nasopharyngitis                                                        | 18                  | (5.5) |  | 5              | (3.9) |  |
| Headache                                                               | 14                  | (4.3) |  | 3              | (2.3) |  |
| Diarrhoea                                                              | 12                  | (3.7) |  | 3              | (2.3) |  |
| Gastroenteritis                                                        | 8                   | (2.4) |  | 2              | (1.6) |  |
| Nausea                                                                 | 8                   | (2.4) |  | 2              | (1.6) |  |
| Urinary tract infection                                                | 5                   | (1.5) |  | 3              | (2.3) |  |
| Glycosylated haemoglobin increased                                     | 2                   | (0.6) |  | 3              | (2.3) |  |
| Osteoarthritis                                                         | 5                   | (1.5) |  | 3              | (2.3) |  |
| Insomnia                                                               | 6                   | (1.8) |  | 3              | (2.3) |  |
| Back pain                                                              | 6                   | (1.8) |  | 5              | (3.9) |  |

  

| <b>Serious Adverse Events and Deaths</b>                                                                                |                     |                        |                   |                        |
|-------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------|-------------------|------------------------|
| <b>Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them</b> |                     |                        |                   |                        |
|                                                                                                                         | <b>Vildagliptin</b> |                        | <b>Placebo</b>    |                        |
|                                                                                                                         | No. (%)<br>of AEs   | No. (%)<br>of patients | No. (%)<br>of AEs | No. (%)<br>of patients |
| <b>Number of Patients</b>                                                                                               |                     | 274                    |                   | 131                    |
| <b>All AEs</b>                                                                                                          | 327 (100.0)         | 143 (52.2)             | 128 (100.0)       | 60 (45.8)              |
| with suspected drug relation                                                                                            | 23 (7.0)            | 16 (5.8)               | 14 (10.9)         | 8 (6.1)                |
| leading to dose adjustment or temp. interruption                                                                        | 5 (1.5)             | 4 (1.5)                | 7 (5.5)           | 5 (3.8)                |
| leading to permanent discontinuation                                                                                    | 20 (6.1)            | 12 (4.4)               | 4 (3.1)           | 4 (3.1)                |
| requiring concomitant medication/non-drug therapy                                                                       | 153 (46.8)          | 93 (33.9)              | 88 (68.8)         | 49 (37.4)              |
| <b>Serious AEs</b>                                                                                                      | 17 (5.2)            | 15 (5.5)               | 12 (9.4)          | 9 (6.9)                |
| Deaths                                                                                                                  |                     | 0 (0.0)                |                   | 0 (0.0)                |
| SAEs with suspected drug relation                                                                                       | 1 (0.3)             | 1 (0.4)                | 1 (0.8)           | 1 (0.8)                |
| SAEs leading to permanent discontinuation                                                                               | 3 (0.9)             | 3 (1.1)                | 0 (0.0)           | 0 (0.0)                |

  

| <b>Other Relevant Findings</b> |  |
|--------------------------------|--|
| None                           |  |



**Date of Clinical Trial Report**

12 February 2009

**Date Inclusion on Novartis Clinical Trial Results Database**

01 July 2009

**Date of Latest Update**

26 June 2009