NOVARTIS

Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 Diabetes

Approved Indication

Galvus is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

- **as monotherapy**
- **in dual combination**
  - with metformin, when diet, exercise and metformin alone do not result in adequate glycemic control.
  - with a sulphonylurea (SU), when diet, exercise and a SU alone do not result in adequate glycemic control.
  - with a thiazolidinedione (TZD) when diet, exercise and a TZD do not result in adequate glycemic control.
- **in triple combination (in Europe)**
  - with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycemic control.

Galvus is also indicated in combination with insulin (with or without metformin) when diet, exercise and a stable dose of insulin do not result in adequate glycemic control (in Europe). Galvus is also indicated as initial combination therapy with metformin in patients with T2DM whose diabetes is not adequately controlled by diet and exercise alone.

Galvus is currently approved in more than 100 countries across Europe, Asia Pacific, Africa, Middle East and Latin America including Australia, Argentina, Brazil, Chile, China, Columbia, Costa Rica, Denmark, Dominican Republic, Ecuador, El Salvador, Egypt, EU, France, Honduras, Hong Kong, Germany, Greece, Guatemala, Iceland, India, Indonesia, Ireland, Israel, Italy, Japan, Kuwait, Liechtenstein, Malaysia, Malta, Mexico, Netherlands, Nicaragua, Norway, Peru, Philippines, Poland, Qatar, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, UAE, United Kingdom, Venezuela.

Protocol Number

CLAF237A23152

Title

A multi-center, randomized, double-blind placebo controlled study to evaluate the efficacy and safety of 24 weeks treatment with vildagliptin 50 mg bid as add-on therapy to metformin plus glimepiride in patients with type 2 diabetes

Phase of Development

Phase III

Study Start/End Dates

12-Oct-2010 to 21-Nov-2011

Study Design/Methodology

This was a multi-center, double-blind, randomized, placebo-controlled study of vildagliptin as add-on therapy to metformin plus glimepiride in T2DM patients with inadequate glycemic control (HbA1c ≥7.5 and ≤11%) with dual combination of metformin (≥ 1500 mg) and glimepiride (≥ 4 mg). The study consisted of screening period, up to 12-week titration and/or stabilization period and 24-week double blind treatment period. In addition to their continued metformin + glimepiride treatment, patients were randomized to vildagliptin 50 mg bid or vildagliptin 50 mg placebo bid in a ratio of 1:1.

Centres

40 centers in 11 countries: Australia (3), Germany (3), Hungary (2), India (10), Italy (2), Korea (5), Mexico (4), Philippines (2), Romania (4), Taiwan (4) and United Kingdom (1).

Publication

Not applicable.

Outcome measures

Primary outcome measures(s)

- Change in baseline Hemoglobin A1c (HbA1c) after 24-week treatment.

Secondary outcome measures(s)

- Change in baseline fasting plasma glucose (FPG) (mmol/L) after 24-week treatment.
- Safety and tolerability of vildagliptin after 24-week treatment.
- Responder rate of vildagliptin after 24-week treatment.

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

The test drugs (vildagliptin 50 mg tablets and matching placebo tablets) were to be taken by mouth twice daily, one table before breakfast and evening meal.

The sponsor also provided the following unblinded study medications:

- Glimepiride 2 and 4 mg tablets

The patients provided the following unblinded study medication:

- Metformin ≥1500 mg, current dose was to be maintained. The country-specific, commercial forms of metformin were used.

Statistical Methods

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

H0: δVilda 50 mg bid=δPlacebo versus Ha: δVilda 50 mg bid < δPlacebo,

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

An analysis of covariance (ANCOVA) model including terms for treatment, baseline HbA1c

(centered by subtracting the overall mean baseline HbA1c of all treatment groups and pooled center) was used to compare the treatment effect. The possibility of a treatment by pooled center interaction or a treatment by baseline HbA1c interaction was examined, although the interaction terms were not included in the primary analysis model. The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (vildagliptin – placebo), and the two-sided adjusted 95% confidence interval along with the p-value for the difference was obtained from the primary analysis model. The analysis of the primary efficacy variable using the FAS was the primary basis of conclusion. The analysis based on the Per Protocol Set was performed to assess the robustness of the conclusion. The same testing procedure as for the FAS analysis was used.
For the secondary efficacy variable, the percentage of patients meeting each predefined responder criteria based on HbA1c targets at study endpoint as well as the percentage of patients meeting at least one of the criteria was computed and compared using a Chi-square test in the FAS. The change from baseline in FPG at study endpoint was analyzed using ANCOVA model in the same way as the primary efficacy variable.
The number and percentage of patients with treatment emergent adverse events was summarized by primary system organ class, preferred term, maximum severity and relationship to study drug. The number and percentage of patients who died, had serious adverse events (SAEs), adverse events leading to discontinuation and adverse events requiring temporarily study drug interruption were tabulated separately. The incidence rates of AEs confirmed by various adjudication committees, AEs of predefined risk and hypoglycemic events were also summarized.
Hematology and biochemistry data were summarized for absolute values, changes from baseline, and treatment emergent notable abnormalities. Vital signs, body weight ECG findings and urinalysis by category were evaluated descriptively.
Patient disposition, Demographic and baseline background characteristics data were summarized by treatment.

Study Population: Inclusion/Exclusion Criteria

Inclusion Criteria

1. Treatment with oral anti-diabetic therapy, on stable dose for at least 12 weeks prior to the screening visit. Acceptable background anti-diabetic therapy included: metformin (≥ 1500 mg) as monotherapy or in combination with SU, TZDs, or glinides at visit 1 with:
   - Monotherapy $HbA_{1c} \geq 8.5$ and $\leq 11.0\%$
   - Dual therapy $HbA_{1c} \geq 7.5\%$ and $\leq 11.0\%$
2. Age: ≥18 to ≤ 80 years at Visit 1.
3. HbA_{1c} of ≥ 7.5 and ≤ 11.0% at Visit 105.
4. Body Mass Index (BMI) ≥22 to ≤45 kg/m^2 at Visit 1.
5. Patients not already treated with glimepiride had to agree to switch to that drug.
6. Males or females.
7. Females of childbearing potential had to use a medically approved birth control method by the local regulatory authority and ethics committee.
8. Agreement to continue their current diet/exercise regimen throughout the duration of the study, unless otherwise instructed by the trial's physician.
9. Ability to comply with all study requirements
10. Patients had to give written informed consent before any assessment was performed.

Exclusion criteria

1. FPG ≥ 270 mg/dL (≥ 15.0 mmol/L) at Visit 1 and at Visit 105 (Week -1).

2. Pregnant or nursing (lactating) women.
3. Use of any of the following medications as assessed at Visit 1*:*
   - Treatment with any oral anti-diabetic therapy other than metformin, SU, TZD and glinide within 12 weeks of Visit 1.
4. Any of the following significant laboratory abnormalities:
   - Clinically significant TSH outside of normal range at visit 1
   - Clinically significant renal dysfunction as indicated by serum creatinine levels at Visit 1 and Visit 105: serum creatinine ≥ 1.5 mg/dL (132 µmol/L) for males and ≥ 1.4 mg/dL (123 µmol/L) for females
   - Elevated fasting triglycerides >500 mg/dL (> 5.62 mmol/L) at visit 1, confirmed by a repeat measure within 3 working days
   - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2x upper limit of normal (ULN) at Visit 1 or Visit 105 (Week -1), confirmed by repeat measure within 3 working days
   - Total bilirubin > 2x ULN and/or direct bilirubin >ULN at Visit 1 or Visit 105 (Week-1), confirmed by repeat measure within 3 working days
   - Positive Hepatitis B surface antigen (HbsAg) at Visit 1
   - Positive Hepatitis C antibody test (anti-HCV) at Visit 1
   - Clinically significant laboratory abnormalities which in the opinion of the investigator, cause the patient to be considered inappropriate for inclusion in the study
5. A history or evidence of any of the following:
   - Acute metabolic conditions such as ketoacidosis, lactic acidosis or hyperosmolar state (including coma) within the past 6 months.
   - Current diagnosis of congestive heart failure (NYHA III or IV).
   - Myocardial infarction (MI) within the past 6 months
   - Coronary artery bypass surgery or percutaneous coronary intervention within the past 6 months
   - Stroke or transient ischemic attack (TIA) within the past 6 months
   - Unstable angina within the past 3 months
   - Sustained and clinically relevant ventricular arrhythmia
   - Type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes (e.g. Cushing's syndrome or acromegaly-associated diabetes).
   - Hepatic disorder defined as:
     - acute or chronic liver disease, evidence of hepatitis, cirrhosis or portal hypertension
     - history of imaging abnormalities that suggest liver disease (except hepatic steatosis), such as portal hypertension, capsule scalloping, cirrhosis
   - history of hypersensitivity, intolerance or a contraindication to the use of sulfonylurea agents and metformin
6. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
7. Any of the following ECG abnormalities:
   - Second or third degree AV block without a pace maker
   - Long QT syndrome or QTc > 500ms

8. Concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study.

Participant Flow (Randomized Set)

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

* Vilda = vildagliptin, Met = metformin, Glim= glimepiride

Baseline Characteristics (Randomized set)

Demographic Variable	Vilda 50mg bid + Met + Glim N=158	Placebo + Met + Glim N=160	Total N=318
Age (Yrs)			
n	158	160	318
Mean (SD)	55.3 (10.15)	55.0 (11.08)	55.1 (10.61)
Min - Max	24.0 - 80.0	26.0 - 79.0	24.0 - 80.0
Median	56.0	54.0	55.5
Age group			
< 65 yrs	129 (81.6%)	122 (76.3%)	251 (78.9%)
≥65 yrs	29 (18.4%)	38 (23.8%)	67 (21.1%)
< 75 yrs	153 (96.8%)	153 (95.6%)	306 (96.2%)
≥75 yrs	5 (3.2%)	7 (4.4%)	12 (3.8%)
Sex			
Female	78 (49.4%)	88 (55.0%)	166 (52.2%)
Male	80 (50.6%)	72 (45.0%)	152 (47.8%)
Race			
Caucasian	34 (21.5%)	38 (23.8%)	72 (22.6%)
Asian	116 (73.4%)	116 (72.5%)	232 (73.0%)
Native american	3 (1.9%)	2 (1.3%)	5 (1.6%)
Other	5 (3.2%)	4 (2.5%)	9 (2.8%)
Ethnicity			
Hispanic/Latino	11 (7.0%)	9 (5.6%)	20 (6.3%)
Indian (Indian subcontinent)	81 (51.3%)	77 (48.1%)	158 (49.7%)
Chinese	12 (7.6%)	21 (13.1%)	33 (10.4%)
Mixed Ethnicity	1 (0.6%)	0 (0.0%)	1 (0.3%)
Unknown	5 (3.2%)	4 (2.5%)	9 (2.8%)
Other	48 (30.4%)	49 (30.6%)	97 (30.5%)
Height (cm)			

n	158	160	318
Mean (SD)	161.3 (10.34)	160.5 (9.68)	160.9 (10.01)
Min - Max	141.0 - 184.0	140.0 - 194.0	140.0 - 194.0
Median	160.0	159.5	160.0
Body weight (kg)			
n	158	160	318
Mean (SD)	73.2 (15.94)	72.4 (15.01)	72.8 (15.46)
Min - Max	47.8 - 133.0	46.0 - 136.0	46.0 - 136.0
Median	70.6	70.2	70.4
BMI (kg/m^2)			
n	158	160	318
Mean (SD)	27.9 (4.55)	28.0 (4.53)	28.0 (4.53)
Min-Max	22.0 - 44.9	22.0 - 42.0	22.0 - 44.9
Median	26.9	27.1	27.1
BMI group			
<30 (kg/m^2)	117 (74.1%)	114 (71.3%)	231 (72.6%)
≥30(kg/m^2)	41 (25.9%)	46 (28.8%)	87 (27.4%)
≥35(kg/m^2)	12 (7.6%)	15 (9.4%)	27 (8.5%)

Outcome measures

Primary Outcome Result(s)

ANCOVA results for change in HbA_{1c} (%) from baseline to endpoint by treatment (Full Analysis Set and Per Protocol Set)

				Difference in adjusted mean change (Vilda-Placebo)		
Treatment	**n**	**Baseline mean (SE)**	**Adjusted mean change (SE)**	**mean (SE)**	**(95% CI)**	**P-Value**
Full analysis Set						
Vilda[1] 50mg bid + Met[1] + Glim[1]	152	8.75 (0.07)	-1.01 (0.09)	-0.76 (0.12)	(-0.98 , -0.53)	<0.001*
Placebo + Met + Glim	160	8.80 (0.07)	-0.25 (0.09)			
Per protocol Set						
Vilda 50mg bid + Met + Glim	144	8.78 (0.07)	-1.05 (0.09)	-0.80 (0.12)	(-1.03 , -0.57)	<0.001*
Placebo + Met + Glim	155	8.79 (0.07)	-0.25 (0.09)			

Baseline is measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement is missing. Endpoint is defined as the final available post-baseline assessment obtained at any visit (scheduled or unscheduled), prior to or at the start of rescue medication use, up to final scheduled study visit.

n is the number of patients with observations at both baseline and endpoint.

Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p values were from an ANCOVA model containing terms for treatment, baseline and pooled centers.

* indicates statistical significance at one-sided 2.5% level. Primary analysis is based on Full analysis set.

1. Vilda = vildagliptin, Met = metformin, Glim= glimepiride

Secondary Outcome Result(s)

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

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

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

ANCOVA results for change in Fasting Plasma Glucose (mmol/L) from baseline to endpoint by treatment (Full analysis set)

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

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

Safety Results

Adverse Events by System Organ Class (Safety set)

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

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

Most Frequently Reported AEs (greater or equal to 2% in any group) by Preferred Term N (%)

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

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

Serious Adverse Events, Deaths and discontinuation due to AEs

Event category	Vilda 50mg bid + Met + Glim N=157 n (%)	Placebo + Met + Glim N=160 n (%)
Deaths	0 (0.0)	1 (0.6)
SAEs	3 (1.9)	2 (1.3)
Discontinuation due to AEs	1 (0.6)	2 (1.3)

Other Relevant Findings

No other important or notable findings were reported in this study.

Date of Clinical Trial Report
22-Feb-2012

Date Inclusion on Novartis Clinical Trial Results Database
07 NOV 2012

Date of Latest Update
07 NOV 2012