Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 Diabetes Mellitus

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**
    - 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.

Approved indications may vary by country.

Protocol Number

CLAF237A23118

Title

A multi-center, randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of 52 weeks treatment with vildagliptin on left ventricular function in patients with type 2 diabetes and congestive heart failure

Study Phase

Phase III

Study Start/End Dates

04-May-2009 to 13-Aug-2012

Study Design/Methodology

This was a multi-center, randomized, double-blind clinical trial to evaluate the safety of vildagliptin versus placebo when given as monotherapy or as add on therapy to other anti-diabetic drugs for 52 weeks in patients with T2DM and CHF (NYHA class I - III). Patients who met the inclusion/exclusion criteria at the screening visit entered a 2-week run-in period (Period I). Patients continued their current anti-diabetic diet, exercise and therapy if on treatment at screening. The run-in period could be extended up to 4 weeks if necessary, but had to be at minimum 2 weeks. After completing the run-in period (Period I), eligible patients entered Period II at Visit 2 (Day 1) and were randomized in a 1:1 ratio to receive either vildagliptin or placebo. Patients continued their current anti-diabetic diet, exercise and therapy if on treatment at screening. The randomization was stratified by baseline CHF status (NYHA class I, II or III).The dose regimen was according to the approved dosage: vildagliptin 50 mg bid for patients not taking background sulfonylurea therapy, and vildagliptin 50 mg qd for patients taking background sulfonylurea therapy at study entry.

Centers

67 centres in 15 countries: Czech Republic (5), Denmark (4), Estonia (3), Germany (7), Greece (1), Guatemala (2), India (10), Italy (6), Latvia (1), Lithuania (3), Poland (3), Romania (2), Russia (13), Singapore (2), Solvakia (5)

Publication

Not yet available.

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

The test drugs (Vildagliptin 50 mg tablets or matching placebo) were provided as tablets which were to be taken once daily before breakfast (for patients taking background sulfonylurea therapy) or twice daily, before breakfast and before the evening meal (for patients not taking background sulfonylurea therapy).

Statistical Methods

The primary outcome variable was change from baseline in LVEF (%) at Week 52, regardless of rescue medication use. The test for the non-inferiority of vildagliptin to placebo in the primary outcome variable was based on the following null hypothesis and one-sided alternative hypothesis:

H_0: δ vilda 50mg qd/bid $\leq$ δ placebo -3.5 vs. H_a: δ vilda 50mg qd/ bid $>$ δ placebo -3.5

where δvilda 50mg qd/ bid and δplacebo are the mean changes in LVEF from baseline to Week 52 for vildagliptin (50 mg qd and 50 mg bid combined) and placebo, respectively.

The hypothesis testing procedure was carried out through a confidence interval approach. The null hypothesis was to be rejected and non-inferiority established if the lower limit of the 95% CI for the difference in the mean change in LVEF (vilda – placebo) obtained from the ANCOVA model is not smaller than 3.5 (i.e. the deterioration in LVEF with vildagliptin is no worse than 3.5 as compared to placebo).

The primary variable was analyzed for the PPS, FAS, and PPS48weeks using an analysis of covariance (ANCOVA) model with treatment, region (pooled center), NYHA class as the classification variable and baseline LVEF as the covariate. The primary analysis population was the Per protocol Set; analyses using the FAS and PPSwk48 were performed to assess the robustness of the results. The least squares mean (adjusted mean) change from baseline for each treatment group and associated standard error, the differences in the least squares mean changes between the two treatment groups, associated two-sided 95% confidence interval for the differences and p-values were obtained from the primary analysis model. If non-inferiority was demonstrated, superiority could be tested.

As one of the secondary objectives, the efficacy was assessed in change from baseline to 16 week in HbA1c (%) using an analysis of covariance (ANCOVA) model with treatment, region (pooled center) as the classification variable and baseline HbA1c as the covariate in the FAS. Efficacy data were censored at the start of rescue medication use.

The number and percentage of patients with treatment emergent adverse events (AEs) 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), AEs leading to discontinuation were tabulated separately. The number and percentage of patients with AEs confirmed by the CCV adjudication committee, with AEs confirmed by the Hepatic Safety Committee and with AEs confirmed by the SVEM Safety Committee, with program-wise predefined events of special interest and with hypoglycemic events were summarized by treatment and event category.

Hematology and biochemistry data were summarized for absolute values, changes from baseline, treatment emergent notable abnormalities and specified relevant percent changes from baseline. Changes in GFR MDRD from study entry value to endpoint value were summarized by treatment. Vital signs, body weight and ECG findings by category were evaluated descriptively.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Males and females (non-fertile or of childbearing potential using a medically approved form of birth control)
- T2DM (HbA1c 6.5%-10% inclusive)
- CHF (NYHA Class I – III, LVEF <40%)
- Age from 18 to 85 years (inclusive)
- Untreated (defined as not taking anti-diabetic therapy for at least 8 weeks prior to Visit 1) or treated with anti-diabetic therapy (defined as taking anti-diabetic therapy for at least 8 weeks and on a stable dose for at least 4 weeks prior to Visit 1)
- Acceptable background anti-diabetic therapy included metformin, sulfonylurea, insulin, alpha-glucosidase inhibitors, or glinides as monotherapy or combination therapy. Patients not taking anti-diabetic medication were also allowed.

Exclusion criteria:

- Fasting Plasma Glucose (FPG) ≥ 270 mg/dL (15 mmol/L) at Visit 1.
- A history of Type 1 Diabetes or secondary forms of diabetes or acute metabolic diabetic complications within the past 6 months.
- Patients taking thiazolidinediones (TZDs).
- Myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, unstable angina or stroke within the past 6 months.
- ECG abnormalities: Torsades de pointes, ventricular tachycardia or ventricular fibrillation, second or third degree AV block, prolonged QTc.
- GFR < 30 mL/min.
- treatment with any medication that is contraindicated in the CHF (NYHA class I-III) population
- treatment with any drug with a known and frequent toxicity to a major organ system within the past 3 months
- Elevated fasting triglycerides > 500 mg/dL at Visit 1
- ALT and/or AST > 2 x ULN at Visit 1 Total bilirubin > 2 x ULN and/or direct bilirubin > 1 x ULN at Visit 1
- Any medical condition that causes heart failure in which there was an indication for either a surgical intervention or a medical intervention that would result in the resolution of the heart failure.

The other protocol defined inclusion/exclusion criteria applied.

Participant Flow

Disposition Reason	Vilda* N=128 n (%)	Placebo N=126 n (%)	Total N=254 n (%)
Completed	101 (78.9)	100 (79.4)	201 (79.1)
Discontinued	27 (21.1)	26 (20.6)	53 (20.9)
Administrative problems	1 (0.8)	3 (2.4)	4 (1.6)
Adverse Event (s)	5 (3.9)	4 (3.2)	9 (3.5)
Death	11 (8.6)	4 (3.2)	15 (5.9)
Lost to follow-up	2 (1.6)	2 (1.6)	4 (1.6)

Disposition Reason	Vilda* N=128 n (%)	Placebo N=126 n (%)	Total N=254 n (%)
Patient withdrew consent	3 (2.3)	10 (7.9)	13 (5.1)
Protocol deviation	3 (2.3)	2 (1.6)	5 (2.0)
Unsatisfactory therapeutic effect	2 (1.6)	1 (0.8)	3 (1.2)

* Vilda-Vildagliptin

Baseline Characteristics (Randomized set)

Demographic Variable	Vilda N=128	Placebo N=126	Total N=254
Age (years)			
N	128	126	254
Mean	62.9	63.4	63.1
SD	8.48	10.17	9.34
Min	41.0	36.0	36.0
Median	63.5	64.0	64.0
Max	83.0	83.0	83.0
Age group			
< 65 yrs	70 (54.7%)	66 (52.4%)	136 (53.5%)
≥ 65 yrs	58 (45.3%)	60 (47.6%)	118 (46.5%)
< 75 yrs	120 (93.8%)	109 (86.5%)	229 (90.2%)
≥ 75 yrs	8 (6.3%)	17 (13.5%)	25 (9.8%)
Sex			
Male	99 (77.3%)	96 (76.2%)	195 (76.8%)
Female	29 (22.7%)	30 (23.8%)	59 (23.2%)
Predominant Race			
Caucasian	85 (66.4%)	81 (64.3%)	166 (65.4%)
Asian (non-Indian subcontinent)	2 (1.6%)	1 (0.8%)	3 (1.2%)
Asian (Indian subcontinent)	29 (22.7%)	31 (24.6%)	60 (23.6%)
Hispanic or Latino	10 (7.8%)	9 (7.1%)	19 (7.5%)
Other	2 (1.6%)	4 (3.2%)	6 (2.4%)
Height (cm)			
N	128	126	254
Mean	168.3	166.8	167.6
SD	9.51	9.29	9.41
Min	140.0	140.0	140.0
Median	168.5	167.5	168.0
Max	192.0	188.0	192.0
Body weight (kg)			
N	128	126	254
Mean	84.4	81.9	83.2
SD	17.38	16.68	17.05
Min	48.4	47.0	47.0
Median	82.0	79.6	81.0
Max	136.0	133.7	136.0
BMI (kg/m^2)			
N	128	126	254
Mean	29.6	29.3	29.4
SD	4.58	4.65	4.61
Min	21.8	22.0	21.8

Demographic Variable	Vilda N=128	Placebo N=126	Total N=254
Median	29.1	28.7	28.7
Max	40.8	41.7	41.7
BMI group			
<30 (kg/m^2)	74 (57.8%)	76 (60.3%)	150 (59.1%)
≥ 30(kg/m^2)	54 (42.2%)	50 (39.7%)	104 (40.9%)
≥ 35(kg/m^2)	17 (13.3%)	15 (11.9%)	32 (12.6%)
Demography information is collected on the day of the screening measurement (Week -2/-4, Visit 1). Body Mass Index: BMI (kg/m^2) = weight[kg] / (height[m]^2).			

Background Characteristic	**Vilda N=128**	**Placebo N=126**	**Total N=254**
HbA_{1c} (%)			
N	128	126	254
Mean	7.8	7.8	7.8
SD	0.95	1.07	1.01
Min	4.8	5.5	4.8
Median	7.7	7.6	7.6
Max	10.2	10.7	10.7
HbA_{1c} (%) - n (%)			
≤ 8%	79 (61.7%)	82 (65.1%)	161 (63.4%)
> 8%	49 (38.3%)	44 (34.9%)	93 (36.6%)
≤ 9%	118 (92.2%)	110 (87.3%)	228 (89.8%)
> 9%	10 (7.8%)	16 (12.7%)	26 (10.2%)
FPG (mmol/L)			
n	128	126	254
Mean	8.7	9.1	8.9
SD	3.10	2.93	3.02
Min	3.1	3.9	3.1
Median	8.4	8.4	8.4
Max	24.2	21.3	24.2
Duration of Type 2 Diabetes (years)			
n	128	126	254
Mean	9.5	9.1	9.3
SD	8.12	7.76	7.93
Min	0.3	0.1	0.1
Median	6.6	6.9	6.8
Max	30.9	33.8	33.8
Duration of CHF (years)			
n	123	121	244
Mean	4.4	5.4	4.9
SD	4.30	5.56	4.98
Min	0.0	0.0	0.0
Median	3.1	3.9	3.3
Max	18.9	29.5	29.5
GFR (MDRD) (mL/min/1.73 m^2) - n (%)			
Normal (>80)	32 (25.0%)	28 (22.2%)	60 (23.6%)
Mild (≥ 50 - ≤ 80)	64 (50.0%)	61 (48.4%)	125 (49.2%)
Moderate (≥ 30 - <50)	30 (23.4%)	33 (26.2%)	63 (24.8%)
Severe (<30)	2 (1.6%)	4 (3.2%)	6 (2.4%)
Is patient a current smoker - n (%)			
Yes	21 (16.4%)	9 (7.1%)	30 (11.8%)
No	107 (83.6%)	117 (92.9%)	224 (88.2%)
LVEF (%) at Visit 1 - n (%)			
≤ 35%	91 (71.1%)	96 (76.2%)	187 (73.6%)
> 35%	36 (28.1%)	30 (23.8%)	66 (26.0%)
Not recorded	1 (0.8%)	0 (0.0%)	1 (0.4%)

Background Characteristic	**Vilda N=128**	**Placebo N=126**	**Total N=254**
Background anti-diabetic therapy - n (%)			
None	16 (12.5%)	9 (7.1%)	25 (9.8%)
Any medication	112 (87.5%)	117 (92.9%)	229 (90.2%)
Sulfonylurea	29 (22.7%)	37 (29.4%)	66 (26.0%)
Metformin	12 (9.4%)	13 (10.3%)	25 (9.8%)
Metformin + Sulfonylurea	25 (19.5%)	21 (16.7%)	46 (18.1%)
AGI	0 (0.0%)	1 (0.8%)	1 (0.4%)
AGI + Glinide	0 (0.0%)	1 (0.8%)	1 (0.4%)
AGI + Insulin + Sulfonylurea	1 (0.8%)	0 (0.0%)	1 (0.4%)
AGI + Metformin + Sulfonylurea	0 (0.0%)	2 (1.6%)	2 (0.8%)
Glinide + Metformin	1 (0.8%)	0 (0.0%)	1 (0.4%)
Glinide + Insulin + Metformin	1 (0.8%)	0 (0.0%)	1 (0.4%)
Insulin	31 (24.2%)	31 (24.6%)	62 (24.4%)
Insulin + Metformin	7 (5.5%)	4 (3.2%)	11 (4.3%)
Insulin + Sulfonylurea	4 (3.1%)	6 (4.8%)	10 (3.9%)
Insulin + Metformin + Sulfonylurea	1 (0.8%)	1 (0.8%)	2 (0.8%)
NYHA class - n (%)			
Class I	13 (10.2%)	12 (9.5%)	25 (9.8%)
Class II	68 (53.1%)	66 (52.4%)	134 (52.8%)
Class III	47 (36.7%)	48 (38.1%)	95 (37.4%)

Duration of type 2 diabetes is collected on the day of the screening visit (Week -2/-4, Visit 1).

Baseline HbA_{1c}, FPG and NYHA class are the samples/assessment obtained/performed on Day 1(visit 2), or the samples/assessment obtained/performed at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement/assessment is missing.

LVEF (Left ventricular ejection fraction) is the measurement performed at the screening visit (visit 1) or on an unscheduled visit prior to visit 2 (randomization), if visit 1 measurement is missing.

eGFR (MDRD) = eGFR estimated using the Modification of Diet in Renal Disease (MDRD) formula.

AGI = Alpha-Glucosidase Inhibitor.

Outcome Measures

Primary Outcome Result(s)

ANCOVA results for change in LVEF (%) from screening to Week 52 endpoint by treatment (FAS, PP and PP 48 weeks set)

				Difference in adjusted mean change (Vilda-Placebo)	
Treatment	**n**	**Screening mean (SE)**	**Adjusted mean change (SE)**	**mean (SE)**	**95% CI p-value**
Full Analysis Set (FAS)					
Vilda*	114	30.64 (0.61)	4.06 (1.11)	0.54 (1.28)	(-1.97, 3.06)** 0.670
Placebo	111	29.79 (0.71)	3.51 (1.12)		
Per Protocol Set (PPS)					
Vilda	89	30.48 (0.67)	4.95 (1.25)	0.62 (1.43)	(-2.21, 3.44)* 0.667
Placebo	90	29.83 (0.78)	4.33 (1.23)		
Per Protocol Set 48 weeks duration					
Vilda	88	30.60 (0.67)	5.02 (1.29)	0.66 (1.45)	(-2.20, 3.51)* 0.651
Placebo	89	29.74 (0.78)	4.36 (1.25)		

Screening is the measurement performed at visit 1 or on a day (unscheduled) prior to visit 2 (randomization), if visit 1 measurement is missing. Endpoint is defined as the final available post-randomization assessment regardless of whether it is obtained at a scheduled or unscheduled visit up to the last regular scheduled visit (i.e. visit 12 week 52). 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, NYHA class, pooled centers and screening LVEF value as covariate.

* Vilda-Vildagliptin

** indicates non-inferiority to comparator at the 2.5% alpha level. Non-inferiority margin is -3.5.

Primary analysis is based on Per Protocol Set.

LVEF: Left ventricular ejection fraction

Secondary Outcome Result(s)

ANCOVA results for change in HbA_{1c} (%) from baseline to rescue-censored Week 16 endpoint by treatment (FAS)

				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 (FAS)					
Vilda	112	7.77 (0.09)	-0.45 (0.12)	-0.62 (0.16)	(-0.93, -0.30) <0.001*
Placebo	107	7.77 (0.10))	0.17 (0.12)		

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 last available post-baseline measurement regardless of whether it is obtained at a scheduled or unscheduled visit prior to or at the start of rescue medication use up to the last regular scheduled visit (i.e. Visit 6 Week 16).

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, pooled centers and baseline HbA_{1c} value as covariate.

* indicates statistical significance at 5% level.

Primary analysis is based on Full Analysis Set.

ANCOVA results for change in HbA_{1c} (%) from baseline to rescue-censored Week 52 endpoint by treatment (FAS and PPS 48 weeks)

				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 (FAS)					
Vilda	115	7.77 (0.09)	-0.21 (0.13)	-0.36 (0.18)	(-0.71 , -0.02) 0.040*
Placebo	107	7.77 (0.10)	0.15 (0.13)		
Per Protocol Set 48 weeks duration (PPS)					
Vilda	88	7.79 (0.11)	-0.38 (0.12)	-0.40 (0.17)	(-0.73 , -0.06) 0.020*
Placebo	87	7.74 (0.11)	0.02 (0.12)		

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 last available post-baseline measurement regardless of whether it is obtained at a scheduled or unscheduled visit prior to or at the start of rescue medication use up to the last regular scheduled visit (i.e. Visit 12 Week 52).

Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p values were from an ANCOVA model containing terms for treatment, pooled centers and baseline HbA_{1c} value as covariate.

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

* indicates statistical significance at 5% level. Primary analysis is based on Full Analysis Set.

Changes in HbA_{1c} at Week 16 and Week 52 endpoint by NYHA subgroup (FAS)

NYHA category	Treatment	n	Baseline mean (SE)	Mean change from baseline	Median change from baseline
Week 16 endpoint					
NYHA class III	Vilda	44	8.03 (0.13)	-0.26 (0.14)	-0.25
	Placebo	39	7.90 (0.19)	0.08 (0.16)	0.10
NYHA class I/II	Vilda	68	7.60 (0.12)	-0.55 (0.15)	-0.60
	Placebo	68	7.69 (0.12)	0.25 (0.17)	0.10
Week 52 endpoint					
NYHA class III	Vilda	45	8.05 (0.13)	0.12 (0.23)	-0.30
	Placebo	39	7.90 (0.19)	0.06 (0.16)	0.20
NYHA class I/II	Vilda	70	7.58 (0.11)	-0.44 (0.15)	-0.40
	Placebo	68	7.69 (0.12)	0.20 (0.17)	0.05

Safety Results

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

Primary system organ class	Vilda* N=128 n (%)	Placebo N=125 n (%)
Any primary system organ class	96 (75.0)	92 (73.6)
Blood and lymphatic system disorders	6 (4.7)	5 (4.0)
Cardiac disorders	40 (31.3)	38 (30.4)
Ear and labyrinth disorders	8 (6.3)	1 (0.8)
Endocrine disorders	2 (1.6)	0 (0.0)
Eye disorders	6 (4.7)	2 (1.6)
Gastrointestinal disorders	26 (20.3)	22 (17.6)
General disorders and administration site conditions	43 (33.6)	40 (32.0)
Hepatobiliary disorders	9 (7.0)	0 (0.0)
Infections and infestations	31 (24.2)	29 (23.2)
Injury, poisoning and procedural complications	6 (4.7)	8 (6.4)
Investigations	15 (11.7)	15 (12.0)
Metabolism and nutrition disorders	20 (15.6)	24 (19.2)
Musculoskeletal and connective tissue disorders	15 (11.7)	11 (8.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (3.9)	1 (0.8)
Nervous system disorders	26 (20.3)	22 (17.6)
Psychiatric disorders	8 (6.3)	4 (3.2)
Renal and urinary disorders	11 (8.6)	13 (10.4)
Reproductive system and breast disorders	1 (0.8)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	32 (25.0)	19 (15.2)
Skin and subcutaneous tissue disorders	19 (14.8)	10 (8.0)
Surgical and medical procedures	0 (0.0)	1 (0.8)
Vascular disorders	17 (13.3)	12 (9.6)

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 each row.

Coded using MedDRA version 15.0

* Vilda-Vildagliptin

Number (%) of patients reporting common AEs (5% or more in any group) by preferred term (Safety set)

Preferred term	Vilda N=128 n (%)	Placebo N=125 n (%)
-Any preferred term	96 (75.0)	92 (73.6)
Oedema peripheral	21 (16.4)	12 (9.6)
Cardiac failure	19 (14.8)	21 (16.8)
Dyspnoea	16 (12.5)	10 (8.0)
Fatigue	14 (10.9)	15 (12.0)
Asthenia	9 (7.0)	10 (8.0)
Cough	9 (7.0)	2 (1.6)
Hyperhidrosis	9 (7.0)	7 (5.6)
Dizziness	8 (6.3)	9 (7.2)
Nasopharyngitis	7 (5.5)	5 (4.0)

Preferred term	Vilda N=128 n (%)	Placebo N=125 n (%)
Urinary tract infection	7 (5.5)	3 (2.4)
Hypoglycaemia	6 (4.7)	7 (5.6)
Renal impairment	4 (3.1)	7 (5.6)
Diarrhoea	2 (1.6)	7 (5.6)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. Preferred terms are sorted by descending order of incidence in the Vilda group.

Coded using MedDRA version 15.0

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

Event category	Vilda N=128 n (%)	Placebo N=125 n (%)
Deaths	11 (8.6)	4 (3.2)[a]
Cardiovascular death confirmed by CCV committee	7 (5.5)	4 (3.2)
SAEs	40 (31.3)	28 (22.4)
Discontinuation due to AEs	16 (12.5)	8 (6.4)
AEs causing dose adjustment or study drug interruption	15 (11.7)	7 (5.6)
Clinically significant CCV AEs*	35(27.3)	31(24.8)
Clinically significant hepatic AEs**	2(1.6)	0(0.0)
Clinically significant SVEM AEs***	3 (2.3)	0 (0.0)
Clinically significant Breast cancer AEs****	0	0
AEs of predefined risk	38 (29.7)	30 (24.0)

* Patients with events confirmed by the Cardiovascular and Cerebrovascular adjudication committee
** Patients with events confirmed by the Hepatic adjudication committee
*** Patients with events confirmed by the Skin, Vascular, Edema and Muscle adjudication committee
**** Patients with events confirmed by the Breast cancer adjudication committee

[a] One additional patient in the placebo group died due to osteolytic metastases more than 30 days after last study drug dose,

Other relevant findings

(Exploratory efficacy results)

ANCOVA results for change in BNP (pg/mL) from baseline to Week 52 endpoint by treatment (FAS)

Vilda N=115		Placebo N=112		Vilda vs. Placebo	
n	Ratio: E/B Geometric Mean (95% CI)	n	Ratio: E/B Geometric Mean (95% CI)	Ratio: Vilda/Placebo (95% CI)	p-value
75	0.72 (0.56, 0.93)	81	0.86 (0.67, 1.12)	0.84 (0.62, 1.14)	0.252

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 last available post-baseline measurement regardless of whether it is obtained at a scheduled or unscheduled visit up to the last regular scheduled visit (i.e. Visit 12 Week 52).

n is the number of patients with observations at both baseline and endpoint. Geometric means, Confidence intervals (CI), and p values were from an ANCOVA model on log(endpoint)-log(baseline) containing terms for treatment, NYHA class, pooled centers and log (baseline BNP) as covariate. Ratio: E/B = Endpoint / Baseline; CI = Confidence interval.

Geometric means and confidence intervals were exponentially back-transformed to obtain results in terms of the ratio of endpoint/baseline.

Date of Clinical Trial Report

12 DECEMBER 2012

Date Inclusion on Novartis Clinical Trial Results Database

12 AUGUST 2013

Date of Latest Update

11 JANUARY 2013