Sponsor

Novartis

Generic Drug Name

Vildagliptin and metformin

Trial Indication(s)

Type 2 Diabetes

Protocol Number

CLMF237A2302

Protocol Title

A randomized, double-blind, active-controlled, multicenter study to compare the effect of 24 weeks treatment with a fixed combination therapy of vildagliptin and metformin to the individual monotherapy components in drug naïve patients with type 2 diabetes

Clinical Trial Phase

Phase III

Study Start/End Dates

02 Aug 2006 to 03 Jun 2008

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This was a multicenter, randomized, double-blind, active-controlled study. Drug naïve patients with Type 2 Diabetes Mellitus (HbA1c 7.5-11%) were randomized equally across the following treatment groups (maximum possible final doses in parentheses): monotherapy vildagliptin 50 mg qd (50 mg twice a day (bid)), monotherapy metformin 500 mg qd (1000 mg bid), vildagliptin and low dose metformin fixed combination 50/500 mg every day (qd) (50/500 mg bid), and vildagliptin and high dose metformin fixed combination 50/500 mg qd (50/1000 mg bid). Study medication was increased to the next dose level until glycemic control was attained, based on a fasting fingerstick capillary glucose measurement, the maximum dose level was reached (vildagliptin 50 mg bid, monotherapy metformin 1000 mg bid, vildagliptin and low dose metformin fixed combination 50/500 mg bid, and vildagliptin and high dose metformin fixed combination 50/1000 mg bid).

Centers

215 Centers in 13 countries: Canada (7), Hungary (4), Germany (28), Italy (13), Poland (4), India (6), United States (85), United Kingdom (16), Sweden (6), Brazil (8), Argentina (5), Spain (21) and Russia (12)

Objectives:

Primary objective(s)

To demonstrate the efficacy of initial fixed combination treatment with vildagliptin and metformin in drug naïve patients with T2DM by testing the hypotheses that the HbA1c reduction with fixed combination of vildagliptin and (high or low dose) metformin is superior to that of both individual monotherapy components after 24 weeks of treatment.

Secondary objective(s)

- To demonstrate the dose-sparing properties of initial fixed combination treatment with vildagliptin and metformin in drug naïve patients with T2DM by demonstrating that the HbA1c reduction with lower final doses in the fixed combination of vildagliptin and metformin is comparable to (or better
- but not statistically significant) that of both individual monotherapy components with an improved safety and tolerability profile.

- To demonstrate the efficacy of initial fixed combination treatment with vildagliptin and metformin by testing the hypotheses that the fasting plasma glucose (FPG) reduction with the fixed combination of vildagliptin and (high or low dose) metformin is superior to that of both individual monotherapy components.

- To demonstrate the efficacy of initial fixed combination treatment with vildagliptin and metformin by testing the hypotheses that the responder rates with the fixed combination of vildagliptin and (high or low dose) metformin are superior to those of both individual monotherapy components.

- To demonstrate the safety of initial fixed combination treatment with vildagliptin and metformin by demonstrating that fixed combination therapy with vildagliptin and (high or low dose) metformin has at least a comparable adverse event profile including GI tolerability to metformin alone.

- To evaluate the body weight change from baseline of initial fixed combination treatment with vildagliptin and (high or low dose) metformin compared to both individual monotherapy components.

- To evaluate the lipid profile of initial fixed combination treatment with vildagliptin and (high or low dose) metformin compared to both individual monotherapy components.

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

Monotherapy vildagliptin 50 mg tablets taken orally once a day (maximum dose 50 mg twice a day), monotherapy metformin 500 mg tablets taken orally once a day (maximum dose 1000 mg twice a day), vildagliptin and low dose metformin fixed combination 50/500 mg tablets taken orally once a day (maximum dose 50/500 mg twice a day), and vildagliptin and high dose metformin fixed combination 50/500 mg tablets taken orally once a day (maximum dose 50/1000mg twice a day).

Statistical Methods

The primary efficacy variable was change from baseline in Hemoglobin A1c (HbA1c) at Week 24 or at the final post-baseline visit with an HbA1c measurement for those patients for whom the Week 24 HbA1c measurement was missing (last observation carried forward (LOCF)).

The primary analysis was the comparison of change from baseline in HbA1c in the fixed combinations (high dose (HD) and low dose (LD) of vildagliptin and metformin) versus each of the monotherapy components. The tests for simultaneous superiority of each fixed combination to the two monotherapy components was based on the following null hypotheses and two-sided alternative: hypotheses.

High dose fixed combination hypotheses (H0HD):

H01: δHD combination = δmetformin vs. H01a δHD combination ≠ δmetformin and H02: δHD combination = δvildagliptin vs. H02a δHD combination ≠ δvildagliptin Low dose fixed combination hypotheses (H0LD):

H03: δLD combination = δmetformin vs. H03a δLD combination ≠ δmetformin and

H04: δLD combination = δvildagliptin vs. H04a δLD combination ≠ δvildagliptin where δ is the change from baseline in HbA1c in the treatment group indicated by the subscript. The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment pooled center as the classification variables and baseline HbA1c as the covariate. The proportions of responders based on pre-defined reductions in HbA1c in the high and low dose fixed combination arms were compared with each monotherapy component using a Chi-square test (or Fisher's exact test, if Chi-square test was not valid). Secondary efficacy variables such as FPG, fasting lipids and body weights were analyzed using similar ANCOVA models as used for HbA1c.

Safety data were evaluated descriptively.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria

• Drug naïve patients with Type 2 Diabetes Mellitus (T2DM)
• Age in the range of 18-78 years inclusive
• Male and non-fertile female or female of childbearing potential using a medically approved birth control method;
• Diagnosis of T2DM for at least 4 weeks prior to study entry
• Body mass index (BMI) in the range of 22-40 kg/m2 inclusive at visit 1
• HbA1c in the range of 7.5 to 11% inclusive at visit 1; Fasting plasma glucose (FPG)
<270 mg/dL (15 mmol/L) at visit 1 (measurement may be repeated once to confirm FPG value);
• Agreement to maintain prior diet and exercise habits during the full course of the study.

Key Exclusion Criteria

• Pregnant or lactating female

• A history of type 1 diabetes, diabetes that was a result of pancreatic injury, or secondary forms of diabetes, e.g., Cushing's syndrome and acromegaly
• History of acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma) within the past 6 months
• Acute infections which might have affected blood glucose control within 4 weeks prior to Visit 1 and other concurrent medical condition that might have interfered with the interpretation of efficacy and safety data during the study
• Any of the following within the past 6 months: myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention, unstable angina or stroke.
• Congestive heart failure requiring pharmacological treatment
• Any of the following ECG abnormalities: Torsades de pointes, sustained and clinically relevant ventricular tachycardia or ventricular fibrillation, second degree AV block (Mobitz 1 and 2), third degree AV block, prolonged QTc (> 500 msec)
• Liver disease such as cirrhosis or chronic active hepatitis.
• Treatment with class Ia, Ib and Ic or III anti-arrhythmics.
• Any of the following significant laboratory abnormalities:
ALT, AST greater than 2 times the upper limit of the normal range at visit 1, confirmed by a repeat measure within 3 working days.

- Total bilirubin greater than 2 times upper limit of the normal range and/or direct bilirubin greater than the upper limit of the normal range at visit 1, confirmed by a repeat measure within 3 working days.
- A positive Hepatitis B test (surface antigen -HBsAg).
- A positive Hepatitis C test (HCV antibodies).
- Clinically significant renal dysfunction as indicated by serum creatinine levels ≥
- 1.5 mg/dL (132 umol/L) males, ≥ 1.4 mg/dL (123 umol/L) females, or a history of abnormal creatinine clearance.
- Clinically significant TSH values outside of normal range at visit 1.
- Clinically significant laboratory abnormalities, confirmed by repeat measurement, other than hyperglycemia, hyperinsulinemia, and glycosuria at visit 1.
- Fasting triglycerides >700 mg/dL (7.9 mmol/L) at visit 1.

Participant Flow Table

(Randomized Population)

Disposition Reason	Vilda + Low dose Met n (%)	Vilda + High dose Met n (%)	Mono Vilda n (%)	Mono Met n (%)	Total n (%)
All randomized patients	290 (100)	295 (100)	300 (100)	294 (100)	1179 (100)
Completed [1]	245 (84.5)	260 (88.1)	245 (81.7)	245 (83.3)	995 (84.4)
Discontinued	45 (15.5)	35 (11.9)	55 (18.3)	49 (16.7)	184 (15.6)
Adverse event(s)	8 (2.8)	10 (3.4)	7 (2.3)	13 (4.4)	38 (3.2)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.2)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	3 (1.0)	0 (0.0)	12 (4.0)	5 (1.7)	20 (1.7)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	2 (0.7)	1 (0.3)	4 (1.3)	1 (0.3)	8 (0.7)
Subject withdrew consent	20 (6.9)	16 (5.4)	21 (7.0)	22 (7.5)	79 (6.7)
Lost to follow-up	11 (3.8)	7 (2.4)	7 (2.3)	6 (2.0)	31 (2.6)
Administrative problems	1 (0.3)	0 (0.0)	3 (1.0)	1 (0.3)	5 (0.4)
Death	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (<0.1)

Baseline Characteristics

(Randomized Population)

Baseline Characteristic	Statistic	Vilda + Low dose Met N=290	Vilda + High dose Met N=295	Mono Vilda N=300	Mono Met N=294	Total N=1179
Sex						
Male	n (%)	162 (55.9)	171 (58.0)	180 (60.0)	171 (58.2)	684 (58.0)
Female	n (%)	128 (44.1)	124 (42.0)	120 (40.0)	123 (41.8)	495 (42.0)
Race						
Caucasian	n (%)	212 (73.1)	218 (73.9)	225 (75.0)	212 (72.1)	867 (73.5)
Black	n (%)	11 (3.8)	15 (5.1)	8 (2.7)	14 (4.8)	48 (4.1)
Asian (non Indian Subcontinent)	n (%)	5 (1.7)	1 (0.3)	5 (1.7)	4 (1.4)	15 (1.3)
Asian (Indian Subcontinent)	n (%)	27 (9.3)	29 (9.8)	25 (8.3)	26 (8.8)	107 (9.1)
Hispanic or Latino	n (%)	28 (9.7)	27 (9.2)	31 (10.3)	27 (9.2)	113 (9.6)
Japanese	n (%)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.2)
Native American	n (%)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.2)
Pacific Islander	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (<0.1)
Other	n (%)	6 (2.1)	5 (1.7)	5 (1.7)	8 (2.7)	24 (2.0)
Age (years)						
	n	290	295	300	294	1179
	Mean (SD)	52.5 (10.32)	52.8 (10.64)	53.5 (10.95)	52.4 (10.71)	52.8 (10.65)
	Median	53.0	53.0	53.5	53.0	53.0
	(Min, Max)	(20, 77)	(19, 78)	(24, 78)	(25, 78)	(19, 78)
Age Groups						
< 65 years	n (%)	254 (87.6)	255 (86.4)	250 (83.3)	256 (87.1)	1015 (86.1)
≥ 65 years	n (%)	36 (12.4)	40 (13.6)	50 (16.7)	38 (12.9)	164 (13.9)
< 75 years	n (%)	289 (99.7)	289 (98.0)	291 (97.0)	290 (98.6)	1159 (98.3)
≥ 75 years	n (%)	1 (0.3)	6 (2.0)	9 (3.0)	4 (1.4)	20 (1.7)

Summary of Efficacy

Primary Outcome Result(s)

Change from baseline in Hemoglobin A1C (HbA1c) (%) at Week 24 Endpoint (Last observation carried forward)

Treatment	n	Baseline Mean (SE)	Adjusted Mean Change (SE)	Treatments Compared	Difference in Adjusted Mean Change Mean (SE)	95% CI	p-value*
ITT Population							
A. Vilda + Low dose Met	277	8.56 (0.061)	-1.61 (0.063)	(A-C)	-0.52 (0.087)	(-0.69, -0.34)	<0.001*
				(A-D)	-0.25 (0.087)	(-0.42, -0.08)	0.004*
B. Vilda + High dose Met	285	8.71 (0.061)	-1.82 (0.062)	(B-C)	-0.72 (0.086)	(-0.89, -0.56)	<0.001*
				(B-D)	-0.46 (0.086)	(-0.63, -0.29)	<0.001*
C. Mono Vilda	287	8.67 (0.060)	-1.09 (0.061)				
D. Mono Met	285	8.60 (0.055)	-1.36 (0.062)				
Per Protocol Population							
A. Vilda + Low dose Met	244	8.53 (0.064)	-1.68 (0.064)	(A-C)	-0.54 (0.089)	(-0.71, -0.36)	<0.001*
				(A-D)	-0.20 (0.090)	(-0.38, -0.03)	0.025*
B. Vilda + High dose Met	258	8.70 (0.061)	-1.89 (0.062)	(B-C)	-0.75 (0.088)	(-0.92, -0.58)	<0.001*
				(B-D)	-0.41 (0.089)	(-0.59, -0.24)	<0.001*
C. Mono Vilda	254	8.65 (0.063)	-1.14 (0.063)				
D. Mono Met	238	8.56 (0.059)	-1.48 (0.065)				

Baseline is measurement obtained on the day of randomization, or on the sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if the Day 1 (Visit 2) measurement is missing.

Week 24 endpoint is the measurement obtained at the last scheduled or unscheduled post-baseline study visit prior to or at the last scheduled visit (Week 24, Visit 8).

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 obtained from an ANCOVA model containing terms for treatment, pooled study center and baseline HbA_{1c}.

* indicates statistical significance at 5% level according to the Hochberg step-up procedure.

Secondary Outcome Result(s)

Percentage of patients who responded at Week 24 Endpoint

Responder criterion	Vilda + Low dose Met			Vilda + High dose Met			Mono Vilda	Mono Met
	n (%)	p-value#	p-value ##	n (%)	p-value#	p-value ##	n (%)	n (%)
ITT Population	N=277			N=285			N=287	N=285
N [1]	277 (100)			285 (100)			287 (100)	285 (100)
At least one criterion met	231 (83.4)	<0.001*	0.005*	251 (88.1)	<0.001*	<0.001*	193 (67.2)	210 (73.7)
HbA_{1c} < 7% [2]	149/269 (55.4)	<0.001*	0.005*	185/283 (65.4)	<0.001*	<0.001*	114/285 (40.0)	123/283 (43.5)
HbA_{1c} < 7% in patients with baseline HbA_{1c}≤8% [3]	62/90 (68.9)	0.469	0.015*	72/81 (88.9)	<0.001*	<0.001*	60/94 (63.8)	46/90 (51.1)
HbA_{1c}≤6.5% [2]	100/274 (36.5)	0.003*	0.012*	134/283 (47.3)	<0.001*	<0.001*	71/286 (24.8)	76/285 (26.7)
Reduction of HbA_{1c}≥1% [1]	191 (69.0)	<0.001*	0.061	231 (81.1)	<0.001*	<0.001*	158 (55.1)	175 (61.4)
Reduction of HbA_{1c}≥1% in patients with baseline HbA_{1c} >9% [4]	69/84 (82.1)	0.016*	0.631	84/96 (87.5)	<0.001*	0.610	65/98 (66.3)	73/86 (84.9)
Reduction of HbA_{1c}≥0.7% [1]	225 (81.2)	<0.001*	0.009*	244 (85.6)	<0.001*	<0.001*	188 (65.5)	205 (71.9)
Per Protocol Population	N=244			N=258			N=254	N=238
N [1]	244 (100)			258 (100)			254 (100)	238 (100)
At least one criterion met	209 (85.7)	<0.001*	0.024*	232 (89.9)	<0.001*	<0.001*	172 (67.7)	185 (77.7)
HbA_{1c} < 7% [2]	139/236 (58.9)	<0.001*	0.027*	175/258 (67.8)	<0.001*	<0.001*	105/252 (41.7)	115/236 (48.7)
HbA_{1c} < 7% in patients with baseline HbA_{1c}≤8% [3]	57/81 (70.4)	0.406	0.064	65/72 (90.3)	<0.001*	<0.001*	54/84 (64.3)	45/80 (56.3)
HbA_{1c}≤6.5% [2]	95/241 (39.4)	0.002*	0.045*	129/258 (50.0)	<0.001*	<0.001*	67/253 (26.5)	73/238 (30.7)
Reduction of HbA_{1c}≥1% [1]	174 (71.3)	<0.001*	0.120	220 (85.3)	<0.001*	<0.001*	142 (55.9)	154 (64.7)
Reduction of HbA_{1c}≥1% in patients with baseline HbA_{1c} >9% [4]	62/72 (86.1)	0.030*	0.538	80/86 (93.0)	<0.001*	0.446	61/85 (71.8)	60/67 (89.6)
Reduction of HbA_{1c}≥0.7% [1]	204 (83.6)	<0.001*	0.039*	227 (88.0)	<0.001*	<0.001*	168 (66.1)	181 (76.1)

Chi-square test vs. Mono Vilda

Chi-square test vs Mono Met

[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%.

[4] Denominator includes only patients with baseline HbA_{1c} > 9%.

Baseline is measurement obtained on day of randomization, or on the sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if the Day 1 (Visit 2) measurement is missing.

Week 24 endpoint is the final available post-randomization assessment up to the last regular scheduled visit.

* indicates statistical significance at 5% level

Change in fasting plasma glucose (FPG) (mmol/L) from baseline at Week 24 Endpoint (Intent-to-treat Population)

					Difference in Adjusted Mean Change		
Treatment	n	Baseline Mean (SE)	Adjusted Mean Change (SE)	Treatments Compared	Mean (SE)	95% CI	p-value*
A. Vilda + Low dose Met	277	10.19 (0.160)	-2.21 (0.128)	(A-C)	-0.95 (0.177)	(-1.30, -0.61)	<0.001
				(A-D)	-0.29 (0.178)	(-0.64, 0.06)	0.099
B. Vilda + High dose Met	285	10.76 (0.170)	-2.63 (0.126)	(B-C)	-1.37 (0.176)	(-1.72, -1.03)	<0.001*
				(B-D)	-0.71 (0.176)	(-1.06, -0.37)	<0.001*
C. Mono Vilda	287	10.29 (0.178)	-1.26 (0.125)				
D. Mono Met	285	10.48 (0.164)	-1.92 (0.125)				

Baseline is measurement obtained on the day of randomization, or on the sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if the Day 1 (Visit 2) measurement is missing.

Endpoint is the final available post-randomization assessment up to the last regular scheduled visit.

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

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

* indicates statistical significance at 5% level according to the Hochberg step-up procedure.

Percent change in fasting lipid parameters from baseline to Week 24 Endpoint (Intent- to-treat Population)

Treatment	n	Baseline Mean (SE)	Adjusted Mean Percent Change (SE)	Treatments Compared	Difference in Adjusted Mean Percent Change		
					Mean (SE)	95% CI	p-value*
Triglycerides (mmol/L)							
A. Vilda + Low dose Met	253	2.33 (0.106)	0.18 (3.245)	(A-C)	-3.91 (4.471)	(-12.68, 4.86)	0.382
				(A-D)	2.16 (4.495)	(-6.66, 10.98)	0.631
B. Vilda + High dose Met	271	2.17 (0.091)	3.32 (3.139)	(B-C)	-0.77 (4.395)	(-9.40, 7.85)	0.861
				(B-D)	5.29 (4.422)	(-3.38, 13.97)	0.231
C. Mono Vilda	272	2.29 (0.108)	4.09 (3.135)				
D. Mono Met	267	2.52 (0.175)	-1.98 (3.158)				
Total Cholesterol (mmol/L)							
A. Vilda + Low dose Met	248	5.29 (0.072)	-2.67 (1.001)	(A-C)	-2.97 (1.378)	(-5.67, -0.26)	0.032*
				(A-D)	-2.26 (1.387)	(-4.98, 0.46)	0.103
B. Vilda + High dose Met	266	5.23 (0.073)	-4.10 (0.967)	(B-C)	-4.40 (1.355)	(-7.05, -1.74)	0.001*
				(B-D)	-3.69 (1.362)	(-6.36, -1.02)	0.007*
C. Mono Vilda	266	5.30 (0.072)	0.30 (0.968)				
D. Mono Met	260	5.28 (0.076)	-0.41 (0.975)				
LDL Cholesterol (mmol/L)							
A. Vilda + Low dose Met	212	3.13 (0.067)	-2.59 (1.694)	(A-C)	-4.91 (2.310)	(-9.45, -0.38)	0.034*
				(A-D)	-2.30 (2.333)	(-6.88, 2.28)	0.325
B. Vilda + High dose Met	229	3.13 (0.064)	-4.89 (1.624)	(B-C)	-7.21 (2.264)	(-11.65, -2.76)	0.002*
				(B-D)	-4.59 (2.286)	(-9.08, -0.11)	0.045*
C. Mono Vilda	233	3.22 (0.067)	2.32 (1.617)				
D. Mono Met	224	3.09 (0.063)	-0.29 (1.637)				
HDL Cholesterol (mmol/L)							
A. Vilda + Low dose Met	242	1.17 (0.019)	4.81 (1.118)	(A-C)	0.77 (1.542)	(-2.26, 3.79)	0.619
				(A-D)	-2.17 (1.553)	(-5.22, 0.88)	0.162
B. Vilda + High dose Met	255	1.17 (0.019)	3.72 (1.090)	(B-C)	-0.32 (1.524)	(-3.31, 2.67)	0.832
				(B-D)	-3.26 (1.532)	(-6.27, -0.25)	0.034*
C. Mono Vilda	258	1.13 (0.018)	4.04 (1.086)				
D. Mono Met	251	1.15 (0.020)	6.98 (1.094)				
Non-HDL Cholesterol (mmol/L)							
A. Vilda + Low dose Met	241	4.11 (0.074)	-4.06 (1.318)	(A-C)	-3.96 (1.814)	(-7.52, -0.40)	0.029*
				(A-D)	-2.05 (1.828)	(-5.64, 1.53)	0.261
B. Vilda + High dose Met	255	4.07 (0.073)	-6.11 (1.282)	(B-C)	-6.02 (1.790)	(-9.53, -2.51)	<0.001*
				(B-D)	-4.11 (1.801)	(-7.64, -0.57)	0.023*
C. Mono Vilda	258	4.16 (0.072)	-0.10 (1.275)				
D. Mono Met	251	4.12 (0.077)	-2.01 (1.286)				
Calculated VLDL Cholesterol (mmol/L)							
A. Vilda + Low dose Met	217	0.86 (0.024)	-0.42 (2.754)	(A-C)	-1.46 (3.760)	(-8.84, 5.92)	0.698
				(A-D)	1.30 (3.776)	(-6.11, 8.71)	0.731
B. Vilda + High dose Met	237	0.83 (0.024)	0.15 (2.627)	(B-C)	-0.89 (3.682)	(-8.12, 6.34)	0.809
				(B-D)	1.87 (3.694)	(-5.38, 9.12)	0.613
C. Mono Vilda	238	0.89 (0.026)	1.04 (2.636)				
D. Mono Met	234	0.87 (0.025)	-1.72 (2.637)				

Baseline is the measurement obtained on the day of randomization (Day 1, Visit 2).

Endpoint is the final available post-randomization assessment up to the last regularly scheduled 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 obtained from an ANCOVA model containing terms for treatment, pooled study center and baseline measure.

* indicates statistical significance at 5% level

Change in body weight (kg) from baseline to Week 24 Endpoint (Intent-to-treat Population)

Treatment	n	Baseline Mean (SE)	Adjusted Mean Change (SE)	Treatments Compared	Difference in Adjusted Mean Change Mean (SE)	95% CI	p-value*
A. Vilda + Low dose Met	258	87.36 (1.017)	-1.17 (0.225)	(A-C)	-0.58 (0.310)	(-1.19, 0.02)	0.060
				(A-D)	0.45 (0.312)	(-0.16, 1.06)	0.149
B. Vilda + High dose Met	275	90.11 (1.143)	-1.19 (0.218)	(B-C)	-0.60 (0.305)	(-1.20, -0.00)	0.048*
				(B-D)	0.43 (0.307)	(-0.17, 1.03)	0.161
C. Mono Vilda	276	87.66 (1.070)	-0.59 (0.218)				
D. Mono Met	271	88.20 (1.063)	-1.62 (0.219)				

Baseline is the measurement obtained on the day of randomization (Day 1, Visit 2), or the screening measurement (Visit 1) if the Visit 2 assessment is missing.
Endpoint is the final available post-randomization assessment up to the last regular scheduled visit.
n is the number of patients with observations at both baseline and endpoint.
Adjusted means and the associated standard errors (SE), confidence intervals (CI) and p-values were obtained from an ANCOVA model containing terms for treatment, pooled study center and baseline measure.
* indicates statistical significance at 5% level

Summary of Safety

Safety Results

Adverse Events by System Organ Class (Safety Population)

Primary system organ class	Vilda + Low dose Met N=290 n (%)	Vilda + High dose Met N=292 n (%)	Mono Vilda N=297 n (%)	Mono Met N=292 n (%)
Any Primary system organ class	162 (55.9)	168 (57.5)	153 (51.5)	175 (59.9)
Blood and lymphatic system disorders	0 (0.0)	1 (0.3)	3 (1.0)	1 (0.3)
Cardiac disorders	6 (2.1)	10 (3.4)	3 (1.0)	10 (3.4)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ear and labyrinth disorders	8 (2.8)	8 (2.7)	2 (0.7)	4 (1.4)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye disorders	9 (3.1)	8 (2.7)	6 (2.0)	10 (3.4)
Gastrointestinal disorders	57 (19.7)	64 (21.9)	49 (16.5)	73 (25.0)
General disorders and administration site conditions	24 (8.3)	30 (10.3)	21 (7.1)	35 (12.0)
Hepatobiliary disorders	1 (0.3)	0 (0.0)	5 (1.7)	2 (0.7)
Immune system disorders	0 (0.0)	3 (1.0)	2 (0.7)	2 (0.7)
Infections and infestations	57 (19.7)	68 (23.3)	65 (21.9)	57 (19.5)
Injury, poisoning and procedural complications	14 (4.8)	13 (4.5)	16 (5.4)	10 (3.4)
Investigations	2 (0.7)	4 (1.4)	4 (1.3)	8 (2.7)
Metabolism and nutrition disorders	2 (0.7)	5 (1.7)	7 (2.4)	6 (2.1)
Musculoskeletal and connective tissue disorders	32 (11.0)	31 (10.6)	30 (10.1)	35 (12.0)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.4)	1 (0.3)	1 (0.3)	3 (1.0)
Nervous system disorders	44 (15.2)	44 (15.1)	39 (13.1)	40 (13.7)
Psychiatric disorders	13 (4.5)	8 (2.7)	14 (4.7)	7 (2.4)
Renal and urinary disorders	5 (1.7)	2 (0.7)	5 (1.7)	8 (2.7)
Reproductive system and breast disorders	7 (2.4)	3 (1.0)	4 (1.3)	5 (1.7)
Respiratory, thoracic and mediastinal disorders	15 (5.2)	13 (4.5)	18 (6.1)	17 (5.8)
Skin and subcutaneous tissue disorders	23 (7.9)	17 (5.8)	23 (7.7)	16 (5.5)
Surgical and medical procedures	1 (0.3)	4 (1.4)	1 (0.3)	0 (0.0)
Vascular disorders	8 (2.8)	10 (3.4)	12 (4.0)	12 (4.1)

A patient with multiple occurrences of an AE is counted only once in the AE category

Common Adverse Events ≥ 2 % in any group by Preferred Term (Safety Population)

Preferred term	Vilda + Low dose Met N=290 n (%)	Vilda + High dose Met N=292 n (%)	Mono Vilda N=297 n (%)	Mono Met N=292 n (%)
Diarrhea	21 (7.2)	19 (6.5)	7 (2.4)	32 (11.0)
Headache	18 (6.2)	16 (5.5)	16 (5.4)	13 (4.5)
Nasopharyngitis	16 (5.5)	22 (7.5)	11 (3.7)	14 (4.8)
Dizziness	14 (4.8)	15 (5.1)	8 (2.7)	12 (4.1)
Nausea	14 (4.8)	19 (6.5)	7 (2.4)	17 (5.8)
Pain in extremity	9 (3.1)	4 (1.4)	5 (1.7)	7 (2.4)
Upper respiratory tract infection	9 (3.1)	4 (1.4)	10 (3.4)	8 (2.7)
Arthralgia	8 (2.8)	3 (1.0)	5 (1.7)	7 (2.4)
Bronchitis	7 (2.4)	6 (2.1)	6 (2.0)	2 (0.7)
Fatigue	7 (2.4)	7 (2.4)	6 (2.0)	15 (5.1)
Dyspepsia	6 (2.1)	10 (3.4)	3 (1.0)	5 (1.7)
Influenza	6 (2.1)	5 (1.7)	6 (2.0)	4 (1.4)
Tremor	6 (2.1)	5 (1.7)	5 (1.7)	3 (1.0)
Abdominal pain upper	5 (1.7)	8 (2.7)	5 (1.7)	7 (2.4)
Asthenia	4 (1.4)	9 (3.1)	4 (1.3)	4 (1.4)
Cough	4 (1.4)	5 (1.7)	8 (2.7)	9 (3.1)
Flatulence	4 (1.4)	4 (1.4)	4 (1.3)	6 (2.1)
Urinary tract infection	4 (1.4)	7 (2.4)	6 (2.0)	3 (1.0)
Vomiting	4 (1.4)	9 (3.1)	1 (0.3)	7 (2.4)
Abdominal distension	3 (1.0)	2 (0.7)	2 (0.7)	6 (2.1)
Back pain	3 (1.0)	11 (3.8)	6 (2.0)	11 (3.8)
Hyperhidrosis	3 (1.0)	3 (1.0)	6 (2.0)	5 (1.7)
Hypertension	3 (1.0)	6 (2.1)	7 (2.4)	10 (3.4)
Abdominal pain	2 (0.7)	2 (0.7)	6 (2.0)	10 (3.4)
Constipation	2 (0.7)	6 (2.1)	10 (3.4)	5 (1.7)
Neuropathy peripheral	0 (0.0)	0 (0.0)	2 (0.7)	6 (2.1)

A patient with multiple occurrences of an AE is counted only once in the AE category

Serious Adverse Events and Deaths (Safety Population)

Primary system organ class Preferred term	LD Vilda + Met N=290 n (%)	HD Vilda + Met N=292 n (%)	Mono Vilda N=297 n (%)	Mono Met N=292 n (%)
Any primary system organ class				
-Total	7 (2.4)	11 (3.8)	4 (1.3)	12 (4.1)
Cardiac disorders				
-Total	3 (1.0)	2 (0.7)	1 (0.3)	3 (1.0)
Angina unstable	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Atrial fibrillation	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Myocardial infarction	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.7)
Myocardial ischaemia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Sinoatrial block	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Endocrine disorders				
-Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Goitre	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Gastrointestinal disorders				
-Total	2 (0.7)	1 (0.3)	0 (0.0)	2 (0.7)
Anal haemorrhage	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Colitis ischaemic	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Rectal polyp	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Infections and infestations								
-Total	0	(0.0)	3	(1.0)	1	(0.3)	3	(1.0)
Erysipelas	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Gastroenteritis	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Perianal abscess	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Pneumonia primary atypical	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Staphylococcal infection	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Upper respiratory tract infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Injury, poisoning and procedural complications								
-Total	1	(0.3)	1	(0.3)	1	(0.3)	0	(0.0)
Femur fracture	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Head injury	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Joint dislocation	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Metabolism and nutrition disorders								
-Total	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Hypoglycaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
-Total	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.0)
Adenocarcinoma	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Prostate cancer	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)

Neoplasms benign, malignant and unspecified (incl cysts and polyps) (continued)								
Uterine cancer	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Nervous system disorders								
-Total	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Transient ischaemic attack	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Reproductive system and breast disorders								
-Total	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Cystocele	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Uterovaginal prolapse	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders								
-Total	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Cough	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders								
-Total	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Urticaria	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Surgical and medical procedures								
-Total	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Inguinal hernia repair	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Vascular disorders								
-Total	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)
Arterial occlusive disease	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Hypertensive crisis	0	(0.0)	2	(0.7)	0	(0.0)	0	(0.0)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically.
A patient with multiple occurrences of an SAE under one treatment is counted only once in the SAE category for that treatment.
A patient with multiple serious adverse events within a primary system organ class is counted only once in the total row.

Date of Clinical Trial Report

17-Dec-2008