The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: DPB100925

Title: A 12-Week, Parallel-Group, Double-Blind, Randomised, Placebo-Controlled, Multicentre, Dose Ranging Study to Evaluate the Efficacy, Safety and Tolerability of GW823093 (2.5mg, 7.5mg, 15mg, 30mg and 45mg), Administered Orally, Once Daily, as Monotherapy in Subjects With Type 2 Diabetes Mellitus followed by a 12-week Active Treatment Extension

Rationale: This study was conducted to evaluate the dose-response, efficacy, safety and tolerability of a range of doses of denagliptin (DEN) compared to placebo over a 12 week period in subjects with type 2 diabetes mellitus (T2DM). A subsequent 12 week Extension Phase evaluated the safety and tolerability and time course for glycaemic effects after an additional 12 weeks of dosing.

Phase: IIb

Study Period: 28Apr2005 - 21Jul2006

Study Design: Parallel group, double-blind, randomized, placebo-controlled, multicenter, dose-ranging study.

Centres: 94 centres from 9 countries: Canada 10, Czech Republic 7, Finland 3, Germany 25, Greece 7, Latvia 6, Romania 3, Sweden 3, US 30.

Indication: Type 2 diabetes mellitus (T2DM).

Treatment: Eligible subjects were stratified by gender and prior therapy (diet and exercise; monotherapy) and randomly assigned (1:1:1:1:1:1 ratio) to one of 5 doses of DEN od or placebo for 12 weeks within each stratum. Subjects randomised to placebo in the Main Phase received 2.5mg of DEN in the Extension Phase and subjects randomised to DEN in the Main Phase remained at their randomised dose and dosing regimen in the Extension Phase.

Objectives: To evaluate the dose response and efficacy of GW823093 (2.5mg, 7.5mg, 15mg, 30mg and 45mg), versus placebo on the change in HbA1c after 12 weeks of dosing in subjects with T2DM.

Primary Outcome/Efficacy Variable: Change from baseline (Week 0) in HbA1c at Week 12.

Secondary Outcome/Efficacy Variables:

Main Phase:

- Change from baseline in FPG at week 12;
- Proportion of subjects who achieve various HbA1c (≤6.5%, <7% and ≤8%) and FPG (<126mg/dL [7.0mmol/L] and <140mg/dL [7.8mmol/L]) targets, and/or achieve a clinically meaningful decrease in HbA1c (≥0.7%) and FPG (≥30mg/dL [1.7mmol/L]) at week 12
- Change from baseline (week 0) in fructosamine and fasting serum insulin at Week 12;
- Population PK parameters of DEN
- Percent change from baseline (Week 0) in fasting lipids (triglycerides [TGs], free fatty acids [FFAs], total cholesterol [TC], LDL-c, HDL-c) at week 24

Extension Phase:

- Change from baseline in FPG at week 24;
- Proportion of subjects who achieve various HbA1c (≤6.5%, <7% and ≤8%) and FPG (<126mg/dL [7.0mmol/L] and <140mg/dL [7.8mmol/L]) targets, and/or achieve a clinically meaningful decrease in HbA1c (≥0.7%) and FPG (≥30mg/dL [1.7mmol/L]) at week 24
- Change from baseline (week 0) in fructosamine and fasting serum insulin at Week 24;
- Population PK parameters of DEN
- Percent change from baseline (Week 0) in fasting lipids (triglycerides [TGs], free fatty acids [FFAs], total cholesterol [TC], LDL-c, HDL-c) at week 24

Statistical Methods:

Main Phase: The Intent-to-treat (ITT) Population was used to assess efficacy and consisted of all randomised subjects who received at least one dose of randomised study medication, had a baseline assessment and had at least one corresponding on-therapy (scheduled or unscheduled) efficacy assessment. The Safety Population was used to assess the safety data and consisted of all subjects who received at least one dose of study medication.
Comparison of the change in HbA1c, FPG, fructosamine, fasting insulin, from baseline at Week 12 between each of the five DEN treatment groups and placebo was assessed using an analysis of covariance model based on terms for gender, prior therapy (diet and exercise/monotherapy), treatment, region and baseline measurement. Point estimates

and corresponding 95% confidence intervals (CI) were calculated. To address the issue of multiplicity, inferences from the study were based on a closed testing procedure. The highest dose, DEN 45mg, was to be assessed first, in comparison to placebo (5% level, 2-sided). If this comparison was significant, then the comparison of the DEN 30mg dose to placebo was to be interpreted at the 5% level. This process continued, going down through all the doses, until the first non-significant test was reached. With this approach, no adjustment to the significance level at each step was needed.

The primary comparison of interest was based on analysis of the ITT Population with last observation carried forward (LOCF).

Differences between treatment groups in the proportion of subjects who achieved HbA1c (≤6.5%, <7%) and FPG (<126mg/dL [7.0mmol/L]) targets, and/or achieved a decrease in HbA1c ≥0.7% and FPG ≥30mg/dL [1.7mmol/L]) at Week 12, were assessed based on a logistic regression model with terms for treatment, gender, prior therapy, and baseline measurement.

For all lipid (triglycerides [TGs], free fatty acids [FFAs], total cholesterol [TC], LDL-c, HDL-c) assessments, the percentage change from baseline (log-transformed data) were summarised at each treatment week where data were collected. Statistical analysis for lipids was performed at Week 12, using an analysis of covariance with terms for gender, prior therapy, treatment, region and log-transformed baseline. The point estimates and corresponding 95% CI for treatment ratios were calculated.

Extension Phase: The ITT Population was used to assess efficacy and consisted of all randomised subjects who received at least one dose of randomised study medication, had a baseline assessment and had at least one corresponding on-therapy (scheduled or unscheduled) efficacy assessment. The Safety Population was used to assess the safety data and consisted of all subjects who received at least one dose of study medication.

The primary population of interest for efficacy was the ITT Population without LOCF. Summary statistics for HbA1c, FPG, fructosamine and fasting insulin were produced.

For all lipid (TGs, FFAs, TC, LDL-c, HDL-c) assessments, the percentage change from baseline (log-transformed data) were summarised.

Study Population: Men and women aged 18 to 75 years with T2DM and Body Mass Index (BMI) ≥24kg/m^2 and ≤40kg/m^2 receiving diet and exercise therapy or taking only one oral anti-diabetic agent, and willing to stop treatment at Screening (Visit 2). HbA1c level at Pre-Screen (Visit 1) ≥7.0% and ≤8.5% for subjects treated with monotherapy; ≥7.5% and ≤10.0% for subjects treated with diet and exercise only. FPG level at Screen (Visit 2) ≥140mg/dL (7.8 mmol/L) and ≤240mg/dL (13.3mmol/L) for all subjects and at baseline (Visit 5) ≤240mg/dL (13.3mmol/L).

Number of subjects	Placebo to 2.5mg	Denagliptin					Total
		2.5mg	7.5mg	15mg	30mg	45mg	
Planned, n	61	61	61	61	61	61	366
Entered run-in, n							476
Randomised, n	64	61	62	63	59	62	371
Safety Population[1]	64	61	63	66	60	61	375
Completed Main Phase, n (%)	49 (77)	47 (77)	54 (87)	60 (95)	55 (93)	56 (90)	321 (87)
Withdrawn from Main Phase, n (%)	15 (23)	14 (23)	9 (15)	6 (10)	5 (8)	5 (8)	54 (15)
Entered Extension Phase, n (%)	48 (75)	47 (77)	54 (87)	59 (94)	55 (93)	55 (89)	318 (86)
Completed Extension Phase, n (%)	46 (72)	40 (66)	47 (76)	54 (86)	51 (93)	53 (85)	291 (78)
Withdrawn from Extension Phase, n (%)	2 (3)	7 (11)	7 (11)	5 (8)	4 (7)	2 (3)	27 (7)
Withdrawn due to adverse events n (%)	0	2 (3)	1 (2)	3 (5)	0	0	6 (2)
Withdrawn due to lack of efficacy n (%)	2 (3)	2 (3)	1 (2)	2 (3)	1 (2)	2 (3)	10 (3)
Withdrawn for other reasons n (%)	0	3 (5)	5 (8)	0	3 (5)	0	11 (3)
TOTAL Withdrawn from whole study, n (%)	17 (27)	21 (34)	16 (26)	11 (17)	9 (15)	7 (11)	81 (22)
Total WD due to AEs, n (%)	5 (8)	6 (10)	1 (2)	3 (5)	1 (2)	0	16 (4)
Total WD due to lack of efficacy, n (%)	7 (11)	3 (5)	1 (2)	3 (5)	2 (3)	2 (3)	18 (5)
Total WD due to other reasons, n (%)	5 (8)	12 (20)	14 (23)	5 (8)	6 (10)	5 (8)	47 (13)

[1] Includes 4 subjects who erroneously received double-blind medication during the run-in

NOTE: percentage values represent proportion of randomised subjects

Demographics	Placebo	Denagliptin					Total
		2.5mg	7.5mg	15mg	30mg	45mg	
N (Safety)	64	61	63	66	60	61	375
Females:Males, n:n	32:32	30:31	31:32	33:33	29:31	29:32	184:191

Age (years), mean±SD	60.8±10.9	58.6±9.5	60.4±12.4	59.9±8.0	58.8±10.0	59.2±7.9	59.6±9.9
White, n (%)	57 (89)	58 (95)	57 (90)	60 (91)	53 (88)	55 (90)	340 (91)
Number of years with diabetes, mean±SD	5.4±4.6	5.3±4.6	5.7±6.0	5.1±4.8	5.3±5.1	5.1±4.2	5.3±4.9
Pre-study diabetes treatment, n (%):							
Diet and Exercise	28 (44)	24 (39)	27 (43)	24 (36)	25 (42)	25 (41)	153 (41)
Monotherapy	36 (56)	37 (61)	36 (57)	42 (64)	35 (58)	36 (59)	222 (59)

Primary Efficacy Results:

Change from baseline at Week 12 in HbA1c (%)	Placebo	Denagliptin 2.5mg	Denagliptin 7.5mg	Denagliptin 15mg	Denagliptin 30mg	Denagliptin 45mg
n	59	56	59	62	56	58
Baseline: mean±SD	7.76±0.68	8.02±0.93	7.97±0.76	7.88±0.65	7.77±0.66	8.07±0.75
Week 12: mean±SD	8.18±1.33	8.20±1.28	7.93±1.16	7.92±0.92	7.43±0.86	7.68±0.96
Adjusted change from baseline: mean±SE	0.46±0.105	0.18±0.873	-0.07±0.104	0.01±0.102	-0.34±0.107	-0.38±0.105
Adjusted mean difference vs PBO:						
Mean	-	-0.28	-0.53	-0.45	-0.80	-0.84
[95% CI]	-	[-0.58, 0.01]	[-0.82, -0.24]	[-0.74, -0.16]	[-1.09, -0.50]	[-1.13, -0.55]
P-value	-	0.061	<0.001	0.002	<0.001	<0.001

Secondary Outcome Variables:

MAIN PHASE

Change from baseline at Week 12 in FPG (mmol/L)

	Placebo	Denagliptin 2.5mg	Denagliptin 7.5mg	Denagliptin 15mg	Denagliptin 30mg	Denagliptin 45mg
n	62	58	62	63	58	60
Baseline: mean±SD	9.64±1.97	9.64±2.41	9.89±2.02	9.93±1.59	9.94±2.24	9.98±1.74
Week 12: mean±SD	10.21±2.88	9.83±2.68	9.58±3.09	9.86±2.14	8.94±2.20	9.23±2.27
Adjusted change from baseline: mean±SE	0.52±0.273	0.11±0.282	-0.28±0.272	0.07±0.270	-0.95±0.281	-0.71±0.276
Adjusted mean difference vs PBO:						
Mean	-	-0.40	-0.80	-0.58	-1.46	-1.22
95% CI	-	-1.18, 0.37	-1.56, -0.04	-1.34, 0.17	-2.23, -0.69	-1.99, -0.46

HbA1c/FPG responders at Week 12

	Placebo	Denagliptin 2.5mg	Denagliptin 7.5mg	Denagliptin 15mg	Denagliptin 30mg	Denagliptin 45mg
HbA1c, n	59	56	59	62	56	58
HbA1c ≤6.5%, n (%)	6 (10%)	4 (7%)	4 (7%)	5 (8%)	9 (16%)	8 (14%)
Odds ratio vs PBO	-	0.92	1.15	1.20	2.68	3.24
95% CI	-	0.21, 3.95	0.27, 4.92	0.30, 4.83	0.74, 9.77	0.85, 12.37
HbA1c <7%, n (%)	11 (19%)	9 (16%)	12 (20%)	9 (15%)	14 (25%)	14 (24%)
Odds ratio vs PBO	-	1.10	1.99	1.04	2.15	3.24
95% CI	-	0.36, 3.36	0.69, 5.76	0.35, 3.13	0.76, 6.13	1.11, 9.52
Reduction ≥0.7%, n (%)	10 (17%)	6 (11%)	14 (24%)	10 (16%)	21 (38%)	17 (29%)
Odds ratio vs PBO	-	0.46	1.43	1.01	3.65	2.00
95% CI	-	0.14, 1.50	0.53, 3.85	0.36, 2.78	1.41, 9.48	0.76, 5.24
FPG, n	62	58	62	63	58	60
FPG <7mmol/L, n (%)	5 (8%)	8 (14%)	9 (15%)	4 (6%)	6 (10%)	9 (15%)
Odds ratio vs PBO	-	1.77	2.57	1.09	1.56	3.14
95% CI	-	0.50, 6.30	0.72, 9.11	0.26, 4.62	0.41, 5.91	0.89, 11.14
Reduction ≥1.7mmol/L, n (%)	8 (13%)	12 (21%)	13 (21%)	10 (16%)	18 (31%)	18 (30%)
Odds ratio vs PBO	-	1.90	1.59	1.35	3.24	3.00
95% CI	-	0.63, 5.72	0.55, 4.62	0.45, 4.00	1.15, 9.13	1.08, 8.30

Change from baseline at Week 12 in fasting insulin (pmol/L)

	Placebo (N=62)	Denagliptin 2.5mg (N=59)	7.5mg (N=62)	15mg (N=63)	30mg (N=58)	45mg (N=60)
n	56	52	58	62	52	54
Baseline: mean±SD	87.8±52.4	104.1±82.8	113.9±109.4	104.0±65.5	87.5±47.2	109.5±73.5
Week 12: mean±SD	87.9±52.1	92.0±56.3	125.6±171.0	109.1±77.4	92.7±54.7	118.2±77.1
Adjusted change from baseline: mean±SE	-2.04±8.51	-10.55±8.81	12.14±8.36	5.27±8.06	3.23±8.73	10.71±8.64
Adjusted mean difference vs PBO:						
Mean	-	-8.51	14.81	7.31	5.27	12.74
95% CI	-	-32.66, 15.65	-9.37, 37.72	-15.79, 30.42	-18.64, 29.17	-18.18, 36.65
Change from baseline at Week 12 in fructosamine (umol/L)						
		Denagliptin				
	Placebo	2.5mg	7.5mg	15mg	30mg	45mg
	(N=62)	(N=59)	(N=62)	(N=63)	(N=58)	(N=60)
n	55	53	61	62	57	58
Baseline: mean±SD	306.5±39.25	312.8±53.53	311.0±53.11	308.6±48.8	312.3±55.74	316.3±55.08
Week 12: mean±SD	325.9±67.96	317.6±70.50	309.5±63.36	300.7±50.20	292.2±60.45	295.8±47.62
Adjusted change from baseline: mean±SE	19.9±5.44	5.0±5.55	-2.5±5.16	-9.3±5.12	-19.7±5.34	-19.0±5.29
Adjusted mean difference vs PBO:						
Mean	-	-14.9	-22.4	-29.2	-39.6	-38.9
95% CI	-	-30. 2,0.5	-37.1,-7.6	-43.9,-14.5	-54.6,-24.6	-53.8,-23.9
Change from baseline at Week 12 in lipid parameters						
TGs (mmol/L), n	58	58	60	62	56	58
Baseline: GM	2.01	1.90	1.82	1.92	2.00	1.99
CV%	38.36	54.15	55.86	47.61	49.87	54.80
Week 12: GM	1.96	1.82	1.66	1.87	1.63	1.76
-SE, +SE§	1.86, 2.07	1.71, 1.94	1.56, 1.77	1.77, 1.99	1.56, 1.71	1.66, 1.86
Adjusted ratio to baseline:						
GM	-1.42	-4.62	-11.02	-2.82	-17.46	-10.37
-SE, +SE§	-5.61, 2.96	-8.67, -0.39	-14.73, -7.14	-6.80, 1.33	-21.02, -13.74	-14.17, -6.40
Adjusted percent difference vs PBO:						
GM	-	-3.25	-9.74	-1.42	-16.27	-9.08
95% CI	-	-14.03, 9.22	-19.93, 1.75	-12.46, 11.01	-25.85, -5.46	-19.42, 2.58
FFAs (mmol/L), n	57	52	61	62	56	57
Baseline: GM	0.49	0.55	0.52	0.48	0.54	0.47
CV%	41.72	44.60	48.02	49.13	41.29	42.16
Week 12: GM	0.47	0.50	0.46	0.48	0.46	0.47
-SE, +SE§	0.44, 0.51	0.47, 0.53	0.44, 0.49	0.46, 0.51	0.43, 0.50	0.44, 0.50
Adjusted ratio to baseline:						
GM	-4.14	-4.61	-10.11	-2.82	-11.35	-4.25
-SE, +SE§	-9.09, 1.08	-9.78, 0.86	-14.60, -5.39	-7.64, 2.24	-15.97, -6.48	-9.19, 0.97
Adjusted percent difference vs PBO:						
GM	-	-0.48	-6.23	1.38	-7.52	-0.11
95% CI	-	-14.49, 15.82	-18.89, 8.42	-12.27, 17.15	-20.26, 7.24	-13.80, 15.77
TC (mmol/L), n	58	58	60	62	56	58
Baseline: GM	5.13	5.24	5.21	5.09	5.42	5.28
CV%	19.69	23.68	19.75	21.13	19.98	17.95

Week 12: GM	5.17	5.36	5.22	5.13	5.29	5.16
-SE, +SE§	5.05, 5.29	5.23, 5.49	5.09, 5.37	4.99, 5.28	5.15, 5.43	5.03, 5.29
Adjusted ratio to baseline:						
GM	0.17	2.63	-0.14	0.04	-1.42	-1.70
-SE, +SE§	-1.70, 2.07	0.72, 4.58	-1.97, 1.72	-1.76, 1.88	-3.29, 0.49	-3.52, 0.17
Adjusted percent difference vs PBO:						
GM	-	2.46	-0.31	-0.13	-1.59	-1.86
95% CI	-	-2.79, 7.99	-5.35, 5.00	-5.14, 5.15	-6.65, 3.75	-6.87, 3.41
HDL-c (mmol/L), n	58	58	60	62	56	58
Baseline: GM	1.17	1.26	1.24	1.21	1.23	1.23
CV%	20.95	26.66	26.61	27.57	22.63	26.07
Week 12: GM	1.23	1.26	1.30	1.22	1.27	1.27
-SE, +SE§	1.20, 1.27	1.23, 1.30	1.25, 1.34	1.18, 1.26	1.23, 1.30	1.22, 1.31
Adjusted ratio to baseline:						
GM	4.36	1.03	4.81	0.50	3.02	3.42
-SE, +SE§	2.71, 6.04	-0.59, 2.65	3.18, 6.46	-1.04, 2.06	1.37, 4.71	1.78, 5.07
Adjusted percent difference vs PBO:						
GM	-	-3.20	0.43	-3.70	-1.28	-0.91
95% CI	-	-7.42, 1.23	-3.89, 4.95	-7.81, 0.60	-5.60, 3.23	-5.21, 3.59
LDL-c (mmol/L), n	58	55	56	59	55	55
Baseline: GM	2.92	2.95	3.03	2.85	3.18	2.97
CV%	31.25	34.71	31.19	38.82	28.86	33.17
Week 12: GM	2.89	3.14	3.03	2.85	3.19	2.96
-SE, +SE§	2.79, 3.00	3.02, 3.25	2.90, 3.16	2.69, 3.01	3.07, 3.32	2.84, 3.08
Adjusted ratio to baseline:						
GM	-1.25	6.18	0.44	-1.47	1.70	-0.26
-SE, +SE§	-4.09, 1.68	3.03, 9.41	-2.49, 3.46	-4.28, 1.42	-1.31, 4.80	-3.20, 2.76
Adjusted percent difference vs PBO:						
GM	-	7.52	1.71	-0.23	2.98	1.00
95% CI	-	-1.02, 16.79	-6.29, 10.38	-7.97, 8.17	-5.15, 11.82	-6.97, 9.64
§ GM-SE, GM+SE						
EXTENSION PHASE						
	Placebo	Denagliptin				
	to 2.5mg	2.5mg	7.5mg	15mg	30mg	45mg
	(N=62)	(N=59)	(N=62)	(N=63)	(N=58)	(N=60)
Change from baseline at Week 24 in HbA1c (%)						
n	46	37	46	54	49	50
Baseline: mean±SD	7.81±0.65	7.92±0.87	7.87±0.71	7.81±0.63	7.72±0.67	8.14±0.73
Week 24: mean±SD	8.07±1.41	8.06±1.51	7.79±1.09	7.95±1.09	7.38±0.88	7.76±1.14
Change from baseline:						
mean±SE	0.26±0.192	0.14±0.207	-0.08±0.158	0.14±0.132	-0.34±0.144	-0.38±0.123
Change from baseline at Week 24 in FPG (mmol/L)						
n	46	39	48	54	48	52
Baseline: mean±SD	9.51±1.96	9.27±1.76	9.82±1.97	9.90±1.67	9.67±2.23	9.92±1.66
Week 24: mean±SD	10.03±2.92	9.41±2.69	9.14±2.80	10.04±2.45	8.55±1.87	9.23±2.34
Change from baseline:						
mean±SE	0.52±0.400	0.14±0.444	-0.68±0.416	0.14±0.283	-1.12±0.309	-0.69±0.328
Change from baseline at Week 24 in fasting insulin (pmol/L)						
n	44	36	44	54	45	45
Baseline: mean±SD	91.8±55.87	111.5±93.72	122.1±120.88	103.7±66.01	91.9±49.12	106.4±66.77
Week 24: mean±SD	98.2±71.79	97.0±51.22	147.2±280.18	116.8±107.03	95.4±57.35	107.5±60.76
Change from baseline:						
mean±SE	6.44±8.74	-14.51±15.23	25.14±27.15	13.12±10.32	3.47±4.83	1.11±8.38
Change from baseline at Week 24 in fructosamine (umol/L)						
n	43	37	48	52	50	47

Baseline: mean±SD	307.5±37.3	308.6±53.8	303.9±46.9	305.3±46.5	305.2±54.2	316.5±57.7
Week 24: mean±SD	314.0±64.1	306.7±73.6	310.9±69.2	309.3±50.5	289.6±56.3	302.4±48.6
Change from baseline:						
mean±SE	6.6±8.77	-1.9±8.73	7.0±7.08	4.0±6.46	-15.6±6.75	-14.1±6.25
Change from baseline at Week 24 in lipid parameters:						
TGs (mmol/L), n	43	40	46	54	47	51
Baseline: GM (CV%)	2.03 (38.52)	1.95 (48.84)	1.81 (49.68)	1.87 (46.75)	2.04 (51.77)	1.96 (51.96)
Week 24: GM [-SE, SE] §	1.81 [1.69, 1.94]	1.74 [1.65, 1.84]	1.63 [1.53, 1.74]	1.80 [1.67, 1.93]	1.79 [1.69, 1.90]	1.89 [1.77, 2.02]
Ratio to baseline: GM [-SE, SE] §	-10.75 [-15.33, -5.92]	-10.94 [-17.52, -3.83]	-9.65 [-14.75, -4.24]	-3.82 [-9.08, 1.74]	-12.33 [-17.69, -6.62]	-3.67 [-8.35, 1.25]
FFAs (mmol/L), n	45	37	48	52	48	47
Baseline: GM (CV%)	0.52 (37.65)	0.57 (47.03)	0.53 (49.02)	0.48 (48.93)	0.54 (43.61)	0.48 (42.01)
Week 24: GM [-SE, SE] §	0.47 [0.44, 0.51]	0.53 [0.50, 0.56]	0.47 [0.44, 0.50]	0.50 [0.46, 0.53]	0.46 [0.43, 0.49]	0.51 [0.48, 0.54]
Ratio to baseline: GM [-SE, SE] §	-10.14 [-15.74, -4.16]	-6.83 [-12.37, -0.94]	-11.42 [-17.47, -4.92]	2.96 [-3.50, 9.85]	-14.61 [-21.40, -7.24]	5.91 [-0.40, 12.62]
TC (mmol/L), n	43	40	46	54	47	51
Baseline: GM (CV%)	5.26 (19.09)	5.22 (24.01)	5.22 (20.24)	5.12 (21.97)	5.37 (19.99)	5.20 (17.99)
Week 24: GM [-SE, SE] §	5.23 [5.06, 5.39]	5.26 [5.09, 5.44]	5.16 [5.00, 5.32]	5.24 [5.10, 5.38]	5.32 [5.19, 5.46]	5.07 [4.95, 5.20]
Ratio to baseline: GM [-SE, SE] §	-0.70 [-2.57, 1.21]	0.71 [-1.86, 3.33]	-1.11 [-3.47, 1.31]	2.37 [-0.13, 4.93]	-0.91 [-3.79, 2.06]	-2.48 [-4.95, 0.05]
HDL-c (mmol/L), n	43	40	46	54	47	51
Baseline: GM (CV%)	1.17 (21.36)	1.27 (25.18)	1.28 (26.03)	1.22 (25.22)	1.20 (22.80)	1.24 (24.13)
Week 24: GM [-SE, SE] §	1.23 [1.19, 1.28]	1.31 [1.26, 1.35]	1.32 [1.27, 1.37]	1.28 [1.23, 1.32]	1.27 [1.23, 1.32]	1.28 [1.24, 1.32]
Ratio to baseline: GM [-SE, SE] §	4.83 [1.64, 8.11]	3.02 [0.21, 5.91]	2.80 [0.29, 5.37]	4.28 [2.78, 5.81]	6.46 [3.30, 9.72]	2.86 [0.86, 4.89]
LDL-c (mmol/L), n	43	39	44	48	46	49
Baseline: GM (CV%)	3.05 (28.44)	2.87 (36.72)	2.98 (31.74)	2.95 (38.93)	3.16 (28.43)2	2.90 (34.35)
Week 24: GM [-SE, SE] §	3.02 [2.88, 3.17]	2.99 [2.83, 3.16]	2.96 [2.82, 3.11]	3.04 [2.89, 3.19]	3.11 [2.99, 3.23]	2.77 [2.64, 2.90]
Ratio to baseline: GM [-SE, SE] §	-0.98 [-3.51, 1.62]	4.22 [-0.20, 8.84]	-0.60 [-4.31, 3.25]	2.85 [-1.09, 6.94]	-1.54 [-5.39, 2.48]	-4.76 [-8.41, -0.97]
§ [GM-SE, GM+SE]						

Most frequent On-therapy AEs, i.e. those AEs occurring on or after the start of the first dose of study medication and ending one day after the last dose of study medication						
AE by Preferred Term, n (%)	Placebo to 2.5mg (N=64)	Denagliptin				
		2.5mg (N=61)	7.5mg (N=63)	15mg (N=66)	30mg (N=60)	45mg (N=61)
Subjects with at least 1 AE	28 (44%)	26 (43%)	31 (49%)	36 (55%)	29 (48%)	30 (49%)
Nasopharyngitis	4 (6%)	6 (10%)	10 (16%)	6 (9%)	5 (8%)	3 (5%)
Headache	1 (2%)	2 (3%)	3 (5%)	4 (6%)	3 (5%)	3 (5%)
Back pain	2 (3%)	1 (2%)	1 (2%)	4 (6%)	1 (2%)	3 (5%)
Dizziness	1 (2%)	1 (2%)	3 (5%)	0	1 (2%)	3 (5%)
Upper respiratory tract infection	1 (2%)	2 (3%)	3 (5%)	2 (3%)	1 (2%)	2 (3%)
Constipation	3 (5%)	0	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Diarrhoea	2 (3%)	2 (3%)	0	1 (2%)	3 (5%)	1 (2%)
Cough	3 (5%)	0	0	1 (2%)	1 (2%)	1 (2%)
Sinusitis	0	0	3 (5%)	0	1 (2%)	1 (2%)
Nausea	1 (2%)	3 (5%)	3 (5%)	4 (6%)	1 (2%)	0
Hyperglycaemia	0	3 (5%)	0	0	0	0
Serious On-therapy AEs, i.e. those SAEs occurring on or after the start of the first dose of study medication and ending one day after the last dose of study medication; n (%) [n considered by the investigator to be related to study medication]						
AE by Preferred Term, n (%)	Placebo to 2.5mg (N=64)	Denagliptin				
		2.5mg (N=61)	7.5mg (N=63)	15mg (N=66)	30mg (N=60)	45mg (N=61)
Subjects with at least 1 SAE	1 (2%) [1]	1 (2%) [0]	2 (3%) [1]	0	4 (7%) [0]	3 (5%) [0]
Dehydration	0	0	0	0	0	1 (2%) [0]
Diverticular perforation	0	0	0	0	0	1 (2%) [0]
Vertigo	0	0	0	0	0	1 (2%) [0]
Acute MI	0	0	0	0	1 (2%) [0]	0
Cardiac failure congestive	0	0	0	0	1 (2%) [0]	0
Cerebrovascular accident	0	0	1 (2%) [1]	0	1 (2%) [0]	0
Hemiparesis	0	0	0	0	1 (2%) [0]	0
Ischaemic stroke	0	0	0	0	1 (2%) [0]	0
Sepsis	0	0	1 (2%) [0]	0	0	0
Laryngitis	0	1 (2%) [0]	0	0	0	0
Gastroenteritis	1 (2%) [1]	0	0	0	0	0

Conclusion:
Statistically significant reductions from baseline in HbA1c compared to placebo occurred at week 12 at the 7.5mg, 15mg, 30mg and 45mg doses of DEN (-0.53%, -0.45%, -0.80% and -0.84%, respectively). Decreases in mean HbA1c observed at week 12 were sustained to week 24 in the 30mg and 45mg DEN groups, only.
Statistically significant reductions from baseline in FPG compared to placebo occurred at week 12 at the 30mg and 45mg doses of DEN (-1.46mmol/L and -1.22mmol/L, respectively). Decreases in mean FPG observed at week 12 were sustained to week 24 in the 7.5mg, 30mg and 45mg DEN groups, only.
Statistically significant reductions from baseline in fructosamine compared to placebo occurred at week 12 at the 7.5mg, 15mg, 30mg and 45mg doses of DEN (-22.4μmol/L, -29.2μmol/L, -39.6μmol/L and -38.9μmol/L, respectively). Decreases in mean fructosamine observed at week 12 waned over the subsequent 12 weeks, however the reductions were still clinically relevant in the 30mg and 45mg DEN groups, only.
The incidence of on-therapy AEs for the treatment groups during the 12 week main phase were as follows: 38% reported in the placebo group and 36%, 32%, 42%, 32% and 38% reported for the 2.5mg, 7.5mg, 15mg, 30mg and 45mg DEN groups, respectively. The incidence of on-therapy AEs in the treatment groups during the 24 week study (main and extension phases) were 44% reported in the placebo/2.5mg DEN group and 43%, 49%, 55%, 48% and 49% reported for the 2.5mg, 7.5mg, 15mg, 30mg and 45mg DEN groups, respectively.
Five subjects reported 6 on-therapy SAEs in the 12 week main phase: 1 subject in each of the placebo, 2.5mg DEN and 45mg DEN groups and 2 subjects in the 30mg DEN group. Six further subjects reported on-therapy SAEs during the extension phase: 2 subjects each in the 7.5mg, 30mg and 45mg DEN groups. The overall incidence of on-therapy SAEs for the 24 week study (main and extension phases) were as follows: 2% for the placebo/2.5mg DEN group and 2%, 3%, 0%, 7% and 5% for the 2.5mg, 7.5mg, 15mg, 30mg and 45mg DEN groups, respectively.

Publications: -

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