Sponsor

Novartis

Generic Drug Name

LCQ908A

Therapeutic Area of Trial

Type 2 Diabetes Mellitus (T2DM)

Approved Indication

N/A

Study Number

CLCQ908A2203

Title

A 12-week multi-center, randomized, double-blind, placebo-controlled, parallel-group adaptive design study to evaluate the efficacy on blood glucose control and safety of five doses of LCQ908 (2, 5, 10, 15 and 20 mg) or sitagliptin 100 mg on a background therapy of metformin in obese patients with type 2 diabetes.

Phase of Development

Phase IIb

Study Start/End Dates

30 APR 2009 to 21 JUN 2010

Study Design/Methodology

This was a 12 week Phase 2 adaptive design study conducted in centers worldwide. Study included males and females of non-childbearing potential aged 18-75 years, with BMI 28 to 42 kg/m^2 inclusive, and diagnosed with T2DM. These patients were on metformin therapy for 3 months prior to screening, and on a stable dose of at least 1500 mg daily for 4 weeks prior to randomization. No other anti-diabetic agents should have been taken for at least three months prior to screening. Study participants had to have a HbA_{1c} of 7.0 to 10.0% inclusive and fasting blood glucose (FPG) of 250 mg/dl (13.9 mmol/L) or less at screening.

Centers

156 centers in 15 countries; Australia (4), Belgium (8), Canada (9), Colombia (5), France (8), Germany (21), India (5), Italy (10), Mexico (5), Peru (5), Poland (5), Russia (7), Slovakia (10), Spain (7), US (50).

Publication

Ongoing

Objectives

Primary objective

To evaluate the effect of five oral doses of LCQ908 (2 mg, 5 mg, 10 mg, 15 mg or 20 mg) and placebo over 12 weeks on HbA_{1c} in obese patients with T2DM. The patients had been on prior metformin monotherapy for at least 3 months prior to screening and remained on a stable dose of metformin (≥ 1500 mg daily) throughout the study

Secondary objective(s)

- To evaluate the safety and tolerability of LCQ908 (2 mg, 5 mg, 10 mg, 15 mg, 20 mg) vs. placebo
- To evaluate the effect of LCQ908 (2 mg, 5 mg, 10 mg, 15 mg, 20 mg) vs. placebo:
  - As a potential therapy for obesity, assessed by changes in body weight & waist circumference
  - On other measures reflecting short term control of hyperglycemia, assessed by changes in fasting plasma glucose and plasma fructosamine
  - As a potential therapy for dyslipidemia, assessed by changes in fasting plasma lipids
  - On apparent insulin sensitivity assessed by HOMA-IR

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

Investigational drugs:

- LCQ908 2 mg tablets, supplied in bottles
- LCQ908 5 mg tablets, supplied in bottles
- LCQ908 10 mg tablets, supplied in bottles
- Placebo to match LCQ908 2 mg tablets, supplied in bottles
- Placebo to match LCQ908 5 mg tablets, supplied in bottles
- Placebo to match LCQ908 10 mg tablets, supplied in bottles

Active control drug:

- Sitagliptin 100 mg capsules, supplied in bottles
- Placebo to match Sitagliptin 100 mg capsules, supplied in bottles

Patients were to continue to take their own supply of metformin.

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

In order to adequately blind the study during the double-blind active-controlled treatment period, patients were instructed to take 4 tablets and 1 capsule of study medication once daily for the duration of the trial. Each dose was taken with water before 10:00 a.m., except on the morning of every scheduled study visit, when study drug was taken in the office after the completion of all other study procedures.

Placebo matching to LCQ908 and sitagliptin was used as reference therapy. Please see above.

Criteria for Evaluation

Primary variables

The primary efficacy variable was the change from baseline of HbA_{1c} at 12 weeks (or the last available post-randomization value).

Secondary variables

Secondary efficacy variables include

Percent change from baseline at 12 weeks (or the last available post-randomization value) in

- Body weight

Change from baseline at 12 weeks (or the last available post-randomization value) in

- Waist circumference
- Fasting plasma fructosamine
- Fasting plasma glucose

Percent of baseline at 12 weeks (or the last available post-randomization value) in

- Fasting plasma lipids

Change from baseline at 12 weeks (or the last available post-randomization value) in

- Apparent insulin sensitivity assessed by HOMA-IR, determined from fasting insulin and glucose.

Safety and tolerability

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. They included the regular monitoring of hematology, blood chemistry and urine analyses performed at a central laboratory, regular measurement of vital signs, the performance of physical examinations and ECGs.

Statistical Methods

The primary efficacy variable was the change from baseline of HbA1c at 12 weeks (or the last available post-randomization value). The primary analysis was performed for the Full Analysis Set which included all randomized patients except those who were inadvertently randomized and did not take study medication.
Five candidate models to describe the potential dose-response curve were selected based on previous data
as follows:

Linear model, Linear in log-dose model, Emax model with half of maximum effect attained at dose 4.6 mg, Quadratic model with maximum effect attained at dose 14 mg, Sigmoid Emax model with 10% of the maximum effect attained at dose 2 mg and half of maximum effect attained at dose 8 mg (Hill coefficient =1.58496)

The null hypothesis of a constant dose response curve for HbA1c was tested at a one-sided significance level of 2.5% against the alternative hypothesis of a non-constant dose response curve. For each candidate model, a t-statistic based on a linear combination of the mean responses per individual dose, adjusted for baseline HbA1c and using optimal contrast coefficients corresponding to the candidate model was derived. The vector of t-statistics for the candidate models follows a multivariate t-distribution. If the maximum t-statistic exceeded the critical value (determined to control the family-wise error rate), the null hypothesis was rejected and the best dose-response model was selected for further estimation of doses achieving target clinical effects. The Minimum Effective Dose (MED) was determined as the minimum dose which fulfilled: The predicted mean response at MED < least squares (LS) mean for sitagliptin and the upper 95% CI of the predicted mean response at MED < the predicted mean response at placebo. The LS mean for sitagliptin was based on the sitagliptin treatment group only.
Three interim analyses to monitor safety were planned: after 105, 210 and 315 randomized patients had completed at least 4 weeks of treatment or discontinued. There was a fourth DMC meeting to review safety. Treatment arms with ≥ 50% discontinuation due to diarrhea or with an otherwise unacceptable tolerability or safety profile were to be stopped. The remaining patients planned to be randomized to a stopped arm were to be randomized to all other arms in equal proportion. The third interim analysis was used for an assessment of futility. Of the 315 patients in this interim analysis, those completing 12 weeks (200 expected in total) were included in the futility analysis taking into account tolerability and safety in all randomized groups. Arms whose efficacy was considered insufficient using predefined evaluation rules could be stopped. In addition, following the third interim analysis and assuming at least one low dose was dropped due to inadequate efficacy and assuming no higher doses were discontinued due to inadequate safety or tolerability, a higher dose (30 mg) could be added. Patients planned to be randomized to stopped arms were to be equally allocated to the remaining treatment groups.
The primary analysis approach was also applied to secondary variables. As supportive analyses, the primary and secondary variables were analyzed using ANCOVA with treatment and region as classification variables, and the baseline value as covariate. Two-sided Dunnett's tests were performed for the comparison of each active treatment versus placebo. Lipids were log-transformed to account for the non-normality of the distribution of percent of baseline. MED was determined as the minimum dose which fulfilled: The predicted mean response at MED < clinical relevance threshold + predicted mean response at placebo and the upper 95% CI limit of the predicted mean response at MED <the predicted mean response at placebo. The clinical relevance threshold is 3% for reduction from baseline in weight. For the other variables, the

default of 0 was used.
Assuming the maximum effect with a LCQ908 dose was 0.4% (SD=1%), no doses were dropped or changed and 10% of values were not available for analysis, the power (averaged over candidate models) at the one-sided significance level of 2.5% to reject the hypothesis of no dose-response was >85%. If the 20 mg arm was dropped at the first interim analysis, the average power was > 80%. If a 30 mg dose group was added and one or more lower doses were dropped, the expected average power to determine a dose response across dose groups remained at >75%.

Safety analyses were performed for the Safety Set which included all patients who took at least one dose of study medication.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Patients eligible for inclusion in this study had to fulfill all of the following criteria:

1. Written informed consent to participate in the study, before any study related activities are performed, and is likely to comply with all study requirements, including dietary guidelines.
2. Age 18-75 years, inclusive.
3. Males, non-fertile females, and females of non-childbearing potential. Women must be (a) postmenopausal, defined as age >48 with 12 months of natural (i.e. spontaneous) amenorrhea or age >42 with ≥6 months of spontaneous amenorrhea with serum FSH levels > 30 mIU/mL and estradiol <30 pg/ml ; (b) 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or (c) have a **documented** history of tubal ligation at least 1 year prior to screening.
4. Patients with T2DM with HbA_{1c} 7.0 to 10.0%, inclusive, at Visit 1.
5. Fasting plasma glucose ≤250mg/dL (13.9 mmol/L) at Visit 1 assessed by the central laboratory
6. Patients treated with metformin for at least three months prior to Visit 1 (screening) and on a stable dose ≥1500 mg for 4 weeks prior to Visit 3 (randomization). Patients must of agreed to maintain the same dose of metformin from 4 weeks before Visit 3 to the end of the study.
7. Body mass index (BMI) of 28 to 42 kg/m^2 inclusive
8. Body weight at Visit 1 within 5% of their self-reported weight over the past three months and agreement to maintain the study-recommended diet (counseled during screening) and usual exercise habits during the full course of the study.
9. Patients on stable doses of statins or fibrates for 6 weeks prior to Visit 1 must have agreed to maintain those doses during the study period.

Exclusion Criteria

Patients with any of the following at any visit prior to randomization (except as stated) were to be excluded from participation in the study:

1. A history of type 1 diabetes, diabetes that is a result of pancreatic injury, or secondary forms of diabetes, e.g. Cushing's syndrome and acromegaly
2. A history of acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma) within the past 6 months.
3. Evidence of significant diabetic complications, e.g., symptomatic autonomic neuropathy, severe diabetic retinopathy (e.g. associated with retinal hemorrhages or repeated photocoagulation therapy), diabetic gastroparesis or enteropathy.
4. Treatment with any oral antidiabetic agent other than metformin within 12 weeks prior to Visit 1.
5. Chronic insulin treatment (> 1 week of treatment in the absence of concurrent illness) within the 6 months prior to Visit 1.
6. Acute infections which may affect blood glucose control 4 weeks prior to Visit 1 and

other concurrent medical conditions that may interfere with the interpretation of efficacy and safety during the study.

7. Donation of one unit (500 ml) or more of blood, significant blood loss equaling at least one unit of blood within 2 weeks, or a blood transfusion within 8 weeks prior to Visit 1
8. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
9. Severe illness, trauma, or major surgery within 3 months prior to Visit 1.
10. Mean (of the last 2 of 3 consecutive determinations) sitting diastolic blood pressure >100 mmHg and/or mean sitting systolic blood pressure >150 mmHg. (patients may have their blood pressure re-evaluated on one occasion only no sooner than 4 weeks after adjustment of antihypertensive medications)
11. History of Congestive Heart Failure (New York Heart Association (NYHA) Class III-IV) or pacemaker use within the past 5 years.
12. Any of the following within the past 12 months:

a. Myocardial infarction (MI). If the screening ECG reveals patterns consistent with a MI in the absence of clinical signs and symptoms of acute MI and in the absence of elevated troponin and CK-MB enzymes and the date of the event can not be determined, then the patient can enter the trial at the discretion of the investigator and/or local medical monitor
b. Unstable angina
c. Arterial revascularization, coronary artery bypass graft surgery, or percutaneous coronary intervention
d. Cerebrovascular accident or recurrent transient ischemic attacks

13. Any of the following ECG abnormalities:

a. Torsades de pointes, sustained and clinically relevant atrial or ventricular tachycardia, or atrial or ventricular fibrillation
b. Second degree AV block (Mobitz 1 and 2)
c. Third degree AV block
d. Prolonged QTc (>450 ms for males and >470 ms for females) at screening confirmed by visual inspection of the electrocardiogram

14. Liver disease such as cirrhosis or chronic active hepatitis B and C
15. Impaired renal function including a history of dialysis or of nephrotic syndrome and/or estimated creatinine clearance less than 60 ml/min (using the Modification of Diet in Renal Disease (MDRD) formula). Proteinuria <300 mg/gram creatinine was allowed.
16. Any of the following significant laboratory abnormalities at Visit 1:

a. Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) > 2 times the upper limit of normal (ULN), confirmed by a repeat measurement within 3 working days
b. Total bilirubin >2 times ULN and/or direct bilirubin greater than the ULN, confirmed by a repeat measurement within 3 working days
c. Thyroid stimulating hormone (TSH) <0.3 and >5.5 µU/ml. Patients on a stable dose of

L-thyroxine for 2 months prior to Visit 1 can be included if their TSH is within the acceptable range. If the TSH is outside the acceptable range, patients may be re-evaluated on one occasion only no sooner than 2 months after adjustment of their thyroid replacement dose.

d. Platelet count <100,000/ml or white blood cell count <4000/ml
e. Hemoglobin <12 g/L in men, <11 g/L in women
f. Fasting Triglycerides >500 mg/dL (>5.65 mmol/L)
g. Fasting LDL cholesterol >130 mg/dL (>3.4 mmol/L) unless on a statin
h. Self reported positive HIV test, currently treated for HIV, presence of Hepatitis C antibodies or positive Hepatitis B serology indicative of ongoing or latent disease

17. Any of the following concomitant medications:
a. Any anti-diabetic medication other than metformin
b. Any new lipid lowering therapy (stable doses of statins or fibrates for 6 weeks before Visit 1 are allowed)
c. Bile resin binders such as cholestyramine, ezetimibe, or colesevelam
d. Class Ia, Ib, Ic or III antiarrhythmics
e. Warfarin and dicoumadin derivatives
f. Chronic oral or parenteral corticosteroid treatment (> 7 consecutive days of treatment) regardless of the underlying cause for such administration, within the past 8 weeks
g. Growth hormone, synthetic androgens, or similar drugs.
h. Selective Serotonin Reuptake Inhibitors (SSRIs) unless the patient has been on a stable dose for at least 3 months prior to Visit 1 and remains on the same dose for the duration of the study
i. Tricyclic antidepressants
j. Other investigational drugs at the time of enrollment, or within 4 weeks or 5 half-lives of the investigational drug, whichever is longer, prior to Visit 1.

18. Familial or personal event of hypersensitivity or intolerance during participation in a clinical study with investigational compounds directed at DGAT1 or DPP4 inhibitors (i.e. sitagliptin).
19. History of drug or alcohol abuse within the past 2 years.
20. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug including but not limited to the following: History of major gastro-intestinal surgery (other than appendectomy or uncomplicated cholecystectomy) such as gastrectomy, gastroenterostomy, or bowel resection, including previous gastric restrictive surgery (Lap-Banding) or other surgical procedures to induce weight loss.
21. A documented history of inflammatory bowel disease (Crohn's or ulcerative colitis) treated within the previous 5 years. (Patients with Irritable Bowel Syndrome are allowed)
22. Active gastritis (ongoing pain, recent bleeding or related symptoms), ulcers, or gastrointestinal/rectal bleeding.
23. Any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase.

24. Malignancy including leukemia and lymphoma (not including basal cell skin cancer) within the last 5 years.
25. History of significant psychiatric disorder, including, schizophrenia, or psychosis or severe depression requiring hospitalizations. Patients with a history of milder depression, previously or currently treated with SSRI's, are allowed so long as the dose has been stable for at least 3 months and the patient agrees to remain on the same dose during the study period.
26. Any other conditions that, at the discretion of the investigator, place the patient at higher risk from his/her participation to the study, or are likely to prevent compliance with and/or completion of the study

a. Potentially unreliable patients
b. Patients unable to comprehend or comply with the dietary recommendations for this study
c. Patients judged by the investigator to be unsuitable for the study.

Patient disposition by treatment group (Enrolled set)

	LCQ908 2 mg N=98 n (%)	LCQ908 5 mg N=97 n (%)	LCQ908 10 mg N=97 n (%)	LCQ908 15 mg N=101 n (%)	LCQ908 20 mg N=99 n (%)	Sitagliptin 100 mg N=101 n (%)	Placebo N=100 n (%)	Total N=693 n (%)
Enrolled								1582
Randomized								693 (100)
Completed	93 (94.9)	88 (90.7)	83 (85.6)	82 (81.2)	82 (82.8)	95 (94.1)	96 (96.0)	619 (89.3)
Discontinued	5 (5.1)	9 (9.3)	14 (14.4)	19 (18.8)	17 (17.2)	6 (5.9)	4 (4.0)	74 (10.7)
Full Analysis Set	98	97	97	101	98	101	100	693
Safety Set	98	97	97	101	99	101	100	692
Primary reason for discontinuation								
Adverse event(s)	1 (1.0)	4 (4.1)	11 (11.3)	15 (14.9)	9 (9.1)	2 (2.0)	0	42 (6.1)
Abnormal laboratory value(s)	0	0	0	0	0	0	0	0
Abnormal test procedure result(s)	0	0	0	0	0	0	0	0
Unsatisfactory therapeutic effect	0	2 (2.1)	1 (1.0)	0	0	0	0	3 (0.4)
Patient's condition no longer requires study drug	0	0	0	0	0	0	0	0
Patient withdrew consent	1 (1.0)	3 (3.1)	2 (2.1)	2 (2.0)	4 (4.0)	2 (2.0)	0	14 (2.0)
Lost to follow-up	1 (1.0)	0	0	1 (1.0)	4 (4.0)	2 (2.0)	2 (2.0)	10 (1.4)
Administrative problems	1 (1.0)	0	0	0	0	0	2 (2.0)	3 (0.4)
Death	0	0	0	0	0	0	0	0
Protocol deviation	1 (1.0)	0	0	1 (1.0)	0	0	0	2 (0.3)

Demographic and Background Characteristics summary by treatment group (Randomized set)

	LCQ908 2 mg N=98 n (%)	LCQ908 5 mg N=97 n (%)	LCQ908 10 mg N=97 n (%)	LCQ908 15 mg N=101 n (%)	LCQ908 20 mg N=99 n (%)	Sitagliptin 100 mg N=101 n (%)	Placebo N=100 n (%)	Total N=693 n (%)
Age (years)								
n	98	97	97	101	99	101	100	693
Mean	56.0	56.5	55.9	58.0	57.4	57.6	55.6	56.7
SD	9.31	9.51	8.57	9.09	9.00	9.19	9.53	9.18
Median	57.0	56.0	56.0	59.0	58.0	59.0	57.0	58.0
Minimum	29	33	38	24	30	35	32	24
Maximum	73	75	72	75	75	74	75	75
Age group (years) - n (%)								
< 65	78 (79.6)	75 (77.3)	83 (85.6)	75 (74.3)	81 (81.8)	73 (72.3)	85 (85.0)	550 (79.4)
≥ 65	20 (20.4)	22 (22.7)	14 (14.4)	26 (25.7)	18 (18.2)	28 (27.7)	15 (15.0)	143 (20.6)
< 75	98 (100)	96 (99.0)	97 (100)	99 (98.0)	96 (97.0)	101 (100)	99 (9.0)	686 (99.0)
≥ 75	0	1 (1.	0	2 (2.0)	3 (3.0)	0	1 (1.0)	7 (1.0)
Region								
India	9.2)	9 (9.3)	9 (9.3)	9 (8.9)	9 (9.1)	10 (9.9)	9 (9.0)	64 (9.2)
Australia	3 (3.1)	3 (3.1)	4 (4.1)	4 (4.0)	4 (4.0)	4 (4.0)	4 (4.0)	26 (3.8)
Europe North (France, Belgium, Germany)	17 (17.3)	18 (18.6)	19 (19.6)	18 (17.8)	17 (17.2)	19 (18.8)	17 (17.0)	125 (18.0)
Europe South (Italy, Spain)	11 (11.2)	11 (11.3)	11 (11.3)	12 (11.9)	11 (11.1)	11 (10.9)	12 (12.0)	79 (11.4)
Latin America (Columbia, Mexico, Peru)	15 (15.3)	15 (15.5)	13 (13.4)	15 (14.9)	14 (14.1)	14 (13.9)	15 (15.0)	101 (14.6)
North America (USA, Canada)	25 (25.5)	24 (24.7)	25 (25.8)	26 (25.7)	26 (26.3)	25 (24.8)	26 (26.0)	177 (25.5)
Eastern EU (Russia, Poland, Slovakia)	18 (18.4)	17 (17.5)	16 (16.5)	17 (16.8)	18 (18.2)	18 (17.8)	17 (17.0)	121 (17.5)
Gender - n (%)								
Male	55 (56.1)	61 (62.9)	47 (48.5)	47 (46.5)	56 (56.6)	53 (52.5)	60 (60.0)	379 (54.7)
Female	43 (43.9)	36 (37.1)	50 (51.5)	54 (53.5)	43 (43.4)	48 (47.5)	40 (40.0)	314 (45.3)

Race - n (%)								
Caucasian	71 (72.4)	68 (70.1)	71 (73.2)	72 (71.3)	68 (68.7)	74 (73.3)	70 (70.0)	494 (71.3)
Black	4 (4.1)	4 (4.1)	1 (1.0)	3 (3.0)	5 (5.1)	3 (3.0)	2 (2.0)	22 (3.2)
Asian	8 (8.2)	9 (9.3)	12 (12.4)	9 (8.9)	8 (8.1)	8 (7.9)	10 (10.0)	64 (9.2)
Native American	0	0	0	0	0	0	0	0
Pacific Islander	0	0	0	0	0	0	0	0
Other	15 (15.3)	16 (16.5)	13 (13.4)	17 (16.8)	18 (18.2)	16 (15.8)	18 (18.0)	113 (16.3)
Ethnicity - n (%)								
Hispanic/Latino	24 (24.5)	19 (19.6)	21 (21.6)	24 (23.8)	26 (26.3)	23 (22.8)	30 (30.0)	167 (24.1)
Chinese	0	0	0	0	0	0	0	0
Indian (Indian subcontinent)	9 (9.2)	9 (9.3)	11 (11.3)	10 (9.9)	9 (9.1)	10 (9.9)	9 (9.0)	67 (9.7)
Japanese	0	0	0	0	0	0	0	0
Mixed ethnicity	1 (1.0)	0	0	1 (1.0)	0	0	0	2 (0.3)
Other	64 (65.3)	69 (71.1)	65 (67.0)	66 (65.3)	64 (64.6)	68 (67.3)	61 (61.0)	457 (65.9)
Height (cm)								
n	98	97	97	101	98	101	100	692
Mean	165.50	167.28	164.25	166.05	165.63	165.98	165.66	165.77
SD	10.630	9.780	11.289	10.598	11.507	10.995	11.938	10.968
Median	166.50	167.00	163.00	165.10	165.50	165.00	165.00	165.80
Minimum	142.0	145.0	142.0	140.0	143.0	144.0	144.0	140.0
Maximum	189.0	189.0	193.1	193.0	190.5	194.0	194.0	194.0
Weight (kg)								
n	98	97	97	101	98	101	100	692
Mean	90.34	93.13	88.71	91.02	90.12	88.49	88.14	89.98
SD	16.231	16.649	16.929	16.773	18.107	16.789	17.222	16.969
Median	90.90	90.10	86.00	90.20	85.90	88.00	85.40	88.15
Minimum	59.4	61.6	57.0	55.2	56.3	56.0	56.8	55.2
Maximum	143.0	129.2	146.6	138.0	139.0	134.2	149.5	149.5
BMI (kg/m²)								
n	98	97	97	101	98	101	100	692
Mean	32.83	33.14	32.68	32.84	32.57	31.90	31.89	32.54
SD	3.838	4.292	3.795	4.094	3.793	3.685	3.576	3.882
Median	32.30	32.41	31.67	32.34	31.65	31.55	31.10	31.90
Minimum	27.3	26.4	26.9	27.5	26.9	25.0	26.4	25.0
Maximum	42.7	42.1	41.9	41.5	42.1	41.2	43.1	43.1
BMI (kg/m²) group - n (%)								
< 30	29 (29.6)	28 (28.9)	35 (36.1)	34 (33.7)	30 (30.3)	38 (37.6)	33 (33.0)	227 (32.8)
≥ 30	69 (70.4)	69	62 (63.9)	67 (66.3)	68 (68.7)	63 (62.4)	67	465

		(71.1					(67.0)	(67.1)
< 35	69 (70.4)	66 (68.0)	73 (75.3)	74 (73.3)	74 (74.7)	79 (78.2)	82 (82.0)	517 (74.6)
≥ 35	29 (29.6)	31 (32.0)	24 (24.7)	27 (26.7)	24 (24.2)	22 (21.8)	18 (18.0)	75 (25.3)
Waist cir-cumfe ence (cm)								
n	97	97	97	101	97	101	98	688
Mean	107.1	107.5	107.1	107.6	106.7	105.5	105.3	106.7
SD	11.32	12.10	12.51	11.41	12.24	11.34	11.94	11.82
Median	107.0	107.0	106.0	107.0	105.0	104.0	104.0	106.0
Minimum	83	79	84	79	48	81	84	48
Maximum	140	137	153	144	139	131	147	153
Pulse rate (sitting) (bmp)								
n	98	97	97	101	98	101	100	692
Mean	73.5	75.2	75.1	71.2	73.3	73.6	73.3	73.6
SD	9.26	10.35	9.76	8.78	8.32	10.37	8.66	9.43
Median	74.0	76.0	75.0	71.0	75.0	73.0	72.5	73.0
Minimum	51	52	57	51	50	52	55	50
Maximum	94	99	106	99	91	94	96	106
Mean SBP (sitting) (mmHg)								
n	94	95	96	97	97	99	100	678
Mean	130.22	131.76	129.72	131.13	129.72	128.27	129.80	130.08
SD	13.836	14.355	11.990	13.478	10.747	11.988	11.783	12.626
Median	132.75	130.50	130.75	131.00	129.50	128.00	131.00	130.00
Minimum	96.5	103.0	92.5	100.0	100.0	104.0	102.0	92.5
Maximum	161.0	180.5	158.0	170.5	158.0	151.0	156.0	180.5
Mean DBP (sitting) (mmHg)								
n	94	95	96	97	97	99	100	678
Mean	79.63	78.11	77.57	79.36	78.58	77.45	78.67	78.48
SD	9.052	9.481	7.772	8.610	7.299	9.048	8.279	8.529
Median	80.00	78.00	78.00	80.00	80.00	79.00	79.00	79.00
Minimum	58.0	55.5	55.5	57.0	59.0	54.0	59.0	54.0
Maximum	97.5	105.0	96.5	98.0	91.0	97.0	99.0	105.0
HbA1c (%)								
n	91	90	92	92	92	97	97	651
Mean	7.84	7.90	7.88	7.69	7.90	7.74	7.68	7.80
SD	0.824	0.799	0.820	0.851	0.784	0.765	0.762	0.802
Median	7.80	7.70	7.75	7.50	7.75	7.50	7.60	7.60
Minimum	6.5	6.2	6.3	6.4	6.5	6.2	6.3	6.2
Maximum	10.6	10.1	10.0	11.3	9.9	9.6	9.8	11.3
HbA1c (%) group - n (%)								
≤ 8	56 (57.1)	55 (56.7)	57 (58.8)	68 (67.3)	56 (56.6)	61 (60.4)	66	419

							(66.0)	(60.5)
> 8	35 (35.7)	35 (36.1)	35 (36.1)	24 (23.8)	36 (36.4)	3 (35.6)	31 (31.0)	232 (33 5)
≤ 9	83 (84.7)	82 (84.5)	84 (86.6)	84 (83.2)	83 (83.8)	92 (91.1)	92 (92.0)	600 (86.6)
> 9	8 (8.2)	8 (8.2)	8 (8.2)	8 (7.9)	9 (9.1)	5 (5.0)	5 (5.0)	51 (7.4)
Fasting plasma fructosamine (µmol/L)								
n	93	93	92	93	92	8	98	659
Mean	293.0	28 .5	290.7	280.1	288.4	284.2	286.6	287.4
SD	53.24	43.48	42.88	42.50	46.09	42.86	41.70	44.77
Median	294.0	279.0	284.5	274.0	282.5	279.0	282.5	281.0
Minimum	196	211	220	197	197	176	203	176
Maximum	485	400	427	427	478	423	448	485
FPG (mmol/L)								
n	94	94	92	93	93	98	98	662
Mean	8.70	9.08	8.99	8.55	8.71	8.58	8.61	8.74
SD	2.483	2.257	2.126	1.825	2.088	2.017	2.239	2.155
Median	8.25	8.80	8.70	8.20	8.60	8.25	8.25	8.40
Minimum	3.9	4.3	5.3	5.4	4.9	5.5	4.7	3.9
Maximum	22.0	14.1	16.1	15.3	16.4	16.4	19.8	22.0
Triglycerides (mmol/L)								
n	93	94	93	91	92	99	98	660
Mean	2.025	1.937	1.883	1.946	2.001	1.952	1.885	1.946
SD	1.0880	0.8587	0.8144	0.8337	1.0884	1.0910	1.0419	0.9796
Median	1.810	1.830	1.670	1.730	1.685	1.630	1.555	1.690
Minimum	0.73	0.56	0.78	0.75	0.65	0.62	0.59	0.56
Maximum	6.86	5.12	4.67	5.13	6.72	5.89	6.64	6.86
Triglycerides (mmol/L) group - n (%)								
< 1.7145	45 (45.9)	42 (43.3)	49 (50.5)	42 (41.6)	47 (47.5)	54 (53.5)	58 (58.0)	337 (48.6)
≥ 1.7145	48 (49.0)	52 (53.6)	44 (45.4)	49 (48.5)	45 (45.5)	45 (44.6)	40 (40.0)	323 (46.6)
Total cholesterol (mmol/L)								
n	93	94	93	91	92	99	98	660
Mean	4.740	4.607	4.554	4.673	4.589	4.672	4.554	4.627
SD	0.9559	0.8203	0.88 5	0.9388	1.0753	1. 880	1.0281	0.9732
Median	4.590	4.550	4.530	4.600	4.550	4.590	4.415	4.550
Minimum	2.29	2.59	2.85	2.79	2.66	2.47	2.52	2.29
Maximum	7.11	6.60	6.87	6.94	8.24	8.04	6.96	8.24
LDL cholesterol (mmol/L)								
n	90	92	91	90	88	94	95	640

Mean	2.666	2.565	2.538	2.548	2.505	2.543	2.508	2.553
SD	0.7694	0.7122	0.8210	0.7837	0.8470	0.8243	0.8524	0.8007
Median	2.610	2.485	2.420	2.485	2.395	2.495	2.460	2.480
Minimum	0.99	0.92	0.62	1.24	0.66	0.84	0.80	0.62
Maximum	4.86	4.49	4.68	5.08	4.78	4.64	4.76	5.08
HDL cholesterol (mmol/L)								
n	93	94	93	91	92	99	98	660
Mean	1.210	1.168	1.181	1.239	1.167	1.241	1.190	1.200
SD	0.3270	0.3202	0.3187	0.3406	0.2543	0.3507	0.3362	0.3226
Median	1.140	1.130	1.140	1.190	1.115	1.190	1.135	1.140
Minimum	0.72	0.65	0.65	0.60	0.75	0.76	0.58	0.58
Maximum	2.40	2.16	2.17	2.18	2.07	2.18	2.21	2.40
HOMA-IR								
n	83	85	84	82	77	92	88	591
Mean	4.732	4.799	4.307	3.753	4.775	3.802	4.374	4.353
SD	5.1610	4.0886	2.8828	2.1539	4.1221	2.4807	3.6899	3.6337
Median	3.510	3.850	3.410	3.450	3.440	3.205	3.430	3.420
Minimum	1.18	0.57	0.99	1.13	0.99	0.96	1.00	0.57
Maximum	46.18	26.11	16.24	14.65	24.94	17.53	23.56	46.18
eGFR (mL/min/1.73 m²)								
n	97	97	96	101	98	101	99	689
Mean	92.168	91.927	90.557	86.731	90.219	86.378	91.083	89.831
SD	27.1881	21.0774	23.3478	17.0533	19.6621	19.6727	19.6933	21.2966
Median	87.200	88.270	88.590	84.510	86.935	85.230	87.610	87.200
Minimum	50.86	50.10	49.85	54.26	44.16	53.96	48.55	44.16
Maximum	239.50	149.99	173.40	147.05	161.74	140.41	143.80	239.50
eGFR (mL/min/1.73 m²) group - n (%)								
Normal (> 80)	69 (70.4)	67 (69.1)	66 (68.0)	63 (62.4)	70 (70.7)	58 (57.4)	69 (69.0)	462 (66.7)
Mild (≥ 50 to ≤ 80)	28 (28.6)	30 (30.9)	29 (29.9)	38 (37.6)	2 (27.3)	43 (42.6)	29 (29.0)	224 (32.3)
Moderate (≥ 30 to < 50)	0	0	1 (1.0)	0	1 (1.0)	0	1 (1.0)	3 (0.4)
Severe (< 30)	0	0	0	0	0	0	0	0

Primary Objective Result(s)

Evaluation of dose response relationship of the change from baseline in HbA_{1c} (%) at Week 12 with LOCF (Full Analysis Set)

Model	T-statistic	Adjusted p-value	BIC
Quadratic model with maximum at 14 mg	3.07	0.0021	1264.2
Sigmoid E_{max} model with ED_{50} = 8 mg and ED_{10} = 2 mg	3.01	0.0022	1268.3
E_{max} model with ED_{50} = 4.6 mg	2.93	0.0026	1264.8
Linear log dose model (lin-log model)	2.90	0.0028	1258.9^
Linear model	2.70	0.0036	1259.9

Between treatment analysis of the change from baseline in HbA_{1c} (%) at Week 12 with LOCF including dose response estimates (Full Analysis Set)

				Mean change from baseline		Difference to Placebo		
Treatment group	n	DRE (SE)	95% CI	LSmeans (SE)	95% CI	LSmeans	95% CI	p-value
LCQ908 2 mg	90	-0.40 (0.04)	(-0.49, -0.32)	-0.35 (0.08)	(-0.50, -0.20)	-0.01	(-0.28, 0.26)	1.0000
LCQ908 5 mg	89	-0.46 (0.04)	(-0.53, -0.39)	-0.38 (0.08)	(-0.54, -0.23)	-0.04	(-0.31, 0.23)	0.9968
LCQ908 10 mg	91	-0.51 (0.04)	(-0.59, -0.43)	-0.66 (0.08)	(-0.81, -0.51)	-0.33	(-0.59, -0.06)	0.0100
LCQ908 15 mg	90	-0.54 (0.05)	(-0.64, -0.45)	-0.48 (0.08)	(-0.63, -0.33)	-0.14	(-0.41, 0.13)	0.5917
LCQ908 20 mg	89	-0.57 (0.05)	(-0.67, -0.47)	-0.56 (0.08)	(-0.72, -0.41)	-0.22	(-0.49, 0.05)	0.1491
Sitagliptin 100 mg	95	-0.88 (0.07)	(-1.02, -0.75)	-0.87 (0.07)	(-1.02, -0.72)	-0.53	(-0.79, -0.26)	<.0001
Placebo	96	-0.31 (0.06)	(-0.44, -0.18)	-0.34 (0.07)	(-0.49, -0.19)			
MED (mg/d)								

Secondary Objective Result(s)

Between treatment analysis of percent of baseline lipids at Week 12 with LOCF including dose response estimates (Full Analysis Set)

	n	Dose response estimate (SE)	95% CI	Mean change from baseline		Difference to Placebo		p-value
				LS mean (SE)	95% CI	LS means	95% CI	
Fasting plasma fructosamine (µmol/L)								
LCQ908 2 mg	92	-9.75(2.42)	(-14.5,-5.00)	-9.77(4.00)	(-17.6,-1.91)	-3.73	(-17.7,10.24)	0.9624
LCQ908 5 mg	92	-13.1(2.08)	(-17.2,-9.05)	-9.94(4.01)	(-17.8,-2.07)	-3.91	(-17.9,10.05)	0.9535
LCQ908 10 mg	91	-18.8(1.95)	(-22.6,-14.9)	-25.4(4.01)	(-33.3,-17.5)	-19.4	(-33.4,-5.35)	0.0022
LCQ908 15 mg	91	-24.4(2.43)	(-29.2,-19.6)	-25.3(4.00)	(-33.2,-17.5)	-19.3	(-33.3,-5.31)	0.0023
LCQ908 20 mg	89	-30.0(3.25)	(-36.4,-23.6)	-26.4(4.07)	(-34.4,-18.4)	-20.4	(-34.4,-6.28)	0.0012
Sitagliptin 100 mg	96	-20.8(3.70)	(-28.1,-13.4)	-22.4(3.90)	(-30.0,-14.7)	-16.3	(-30.2,-2.53)	0.0127
Placebo	97	-7.50(2.72)	(-12.8,-2.16)	-6.03(3.88)	(-13.6, 1.58)			
MED (mg/d)		3.82						
Fasting plasma glucose (FPG) (mmol/L)								
LCQ908 2 mg	93	-0.22(0.10)	(-0.43,-0.02)	-0.07(0.19)	(-0.45, 0.30)	0.13	(-0.54, 0.79)	0.9928
LCQ908 5 mg	93	-0.30(0.09)	(-0.47,-0.12)	-0.10(0.19)	(-0.48, 0.27)	0.10	(-0.57, 0.77)	0.9980
LCQ908 10 mg	91	-0.36(0.10)	(-0.56,-0.17)	-0.70(0.19)	(-1.08,-0.32)	-0.50	(-1.17, 0.17)	0.2298
LCQ908 15 mg	91	-0.40(0.11)	(-0.62,-0.18)	-0.34(0.19)	(-0.71, 0.04)	-0.14	(-0.81, 0.53)	0.9902
LCQ908 20 mg	90	-0.43(0.13)	(-0.68,-0.18)	-0.37(0.19)	(-0.75, 0.01)	-0.17	(-0.84, 0.50)	0.9713
Sitagliptin 100 mg	96	-0.99(0.19)	(-1.36,-0.62)	-1.02(0.19)	(-1.38,-0.65)	-0.82	(-1.48,-0.16)	0.0082
Placebo	97	-0.11(0.16)	(-0.42, 0.21)	-0.20(0.19)	(-0.56, 0.16)			
MED (mg/d)		4.43						
Homeostasis Model Assessment of insulin resistance (HOMA-IR)								

LCQ908 2 mg	82	-0.30(0.21)	(-0.71, 0.10)	-0.48(0.37)	(-1.20, 0.24)	-0.51	(-1.81, 0.79)	0.8160
LCQ908 5 mg	82	-0.43(0.18)	(-0.78,-0.08)	-0.25(0.37)	(-0.98, 0.47)	-0.29	(-1.59, 1.01)	0.9850
LCQ908 10 mg	80	-0.54(0.20)	(-0.94,-0.15)	-0.92(0.37)	(-1.66,-0.19)	-0.96	(-2.27, 0.35)	0.2422
LCQ908 15 mg	79	-0.61(0.23)	(-1.06,-0.16)	-0.21(0.37)	(-0.95, 0.52)	-0.25	(-1.56, 1.07)	0.9934
LCQ908 20 mg	71	-0.66(0.26)	(-1.17,-0.16)	-0.68(0.39)	(-1.46, 0.09)	-0.72	(-2.07, 0.63)	0.5616
Sitagliptin 100 mg	89	-0.89(0.24)	(-1.38,-0.41)	-0.92(0.35)	(-1.61,-0.22)	-0.95	(-2.23, 0.32)	0.2270
Placebo	84	-0.10(0.32)	(-0.73, 0.53)	0.04 (0.36)	(-0.68, 0.75)			
MED (mg/d)		5.61						
Waist circum-ference (cm)								
LCQ908 2 mg	97	-1.89(0.29)	(-2.46,-1.32)	-1.24(0.51)	(-2.24,-0.24)	0.57	(-1.22, 2.37)	0.9154
LCQ908 5 mg	96	-2.11(0.25)	(-2.60,-1.63)	-2.24(0.51)	(-3.25,-1.24)	-0.43	(-2.23, 1.37)	0.9771
LCQ908 10 mg	95	-2.31(0.27)	(-2.84,-1.78)	-3.42(0.51)	(-4.42,-2.41)	-1.61	(-3.41, 0.20)	0.1027
LCQ908 15 mg	99	-2.43(0.31)	(-3.04,-1.83)	-2.09(0.50)	(-3.08,-1.11)	-0.28	(-2.07, 1.51)	0.9974
LCQ908 20 mg	95	-2.52(0.34)	(-3.20,-1.84)	-2.33(0.51)	(-3.33,-1.32)	-0.51	(-2.32, 1.30)	0.9494
Sitagliptin 100 mg	98	-1.96(0.40)	(-2.77,-1.16)	-1.68(0.50)	(-2.68,-0.69)	0.13	(-1.66, 1.92)	1.0000
Placebo	97	-1.53(0.44)	(-2.40,-0.66)	-1.81(0.51)	(-2.81,-0.82)			
MED (mg/d)		3.66						
Body weight (kg) #								
LCQ908 2 mg	98	-2.40(0.19)	(-2.76,-2.03)	-2.15(0.34)	(-2.82,-1.48)	-0.04	(-1.24, 1.16)	1.0000
LCQ908 5 mg	96	-2.67(0.16)	(-2.98,-2.35)	-2.81(0.34)	(-3.49,-2.14)	-0.71	(-1.92, 0.50)	0.4654
LCQ908 10 mg	95	-2.91(0.18)	(-3.25,-2.56)	-2.98(0.35)	(-3.66,-2.31)	-0.87	(-2.08, 0.33)	0.2520
LCQ908 15 mg	100	-3.05(0.20)	(-3.45,-2.66)	-2.79(0.34)	(-3.45,-2.13)	-0.68	(-1.87, 0.51)	0.4918
LCQ908 20 mg	97	-3.16(0.22)	(-3.60,-2.72)	-3.41(0.34)	(-4.08,-2.74)	-1.30	(-2.50,-0.10)	0.0281
Sitagliptin 100 mg	100	-1.84(0.35)	(-2.54,-1.14)	-1.78(0.34)	(-2.44,-1.12)	0.33	(-0.86, 1.52)	0.9536
Placebo	100	-1.97(0.29)	(-2.53,-1.40)	-2.11(0.34)	(-2.77,-1.45)			
MED (mg/d)								

Between treatment analysis of percent of baseline lipids at Week 12 with LOCF including dose response estimates (Full Analysis Set)

Treatment group	n	Dose response estimate	95% CI	Percent of baseline		Relative to Placebo		p-value
				Estimated median	95% CI	Relative median	95% CI	
High-density lipoprotein (mmol/L)								
LCQ908 2 mg	92	1.00	(0.99, 1.02)	1.01	(0.98, 1.04)	0.99	(0.94, 1.04)	0.9945
LCQ908 5 mg	93	0.99	(0.98, 1.01)	1.00	(0.97, 1.03)	0.98	(0.93, 1.04)	0.9009
LCQ908 10 mg	92	0.98	(0.97, 0.99)	0.98	(0.95, 1.01)	0.97	(0.92, 1.02)	0.3647
LCQ908 15 mg	89	0.96	(0.95, 0.98)	0.95	(0.92, 0.98)	0.93	(0.88, 0.99)	0.0057
LCQ908 20 mg	89	0.95	(0.93, 0.97)	0.96	(0.93, 0.99)	0.95	(0.90, 1.00)	0.0614
Sitagliptin 100 mg	97	1.00	(0.97, 1.04)	1.00	(0.97, 1.03)	0.98	(0.93, 1.04)	0.8947
Placebo	97	1.01	(0.99, 1.03)	1.01	(0.99, 1.04)			
MED (mg/d)								
Low-density lipoprotein (mmol/L)								
LCQ908 2 mg	88	1.01	(0.98, 1.03)	1.04	(0.99, 1.09)	1.00	(0.92, 1.09)	1.0000
LCQ908 5 mg	90	0.99	(0.97, 1.01)	0.98	(0.94, 1.03)	0.95	(0.87, 1.04)	0.4804
LCQ908 10 mg	90	0.97	(0.95, 1.00)	0.95	(0.91, 1.00)	0.92	(0.84, 1.00)	0.0481
LCQ908 15 mg	87	0.96	(0.93, 0.99)	0.97	(0.92, 1.02)	0.94	(0.86, 1.02)	0.1922
LCQ908 20 mg	86	0.95	(0.92, 0.99)	0.97	(0.93, 1.02)	0.94	(0.86, 1.02)	0.2613
Sitagliptin 100 mg	91	1.03	(0.98, 1.09)	1.01	(0.97, 1.06)	0.98	(0.90, 1.07)	0.9832
Placebo	94	1.04	(1.00, 1.08)	1.03	(0.99, 1.08)			
MED (mg/d)								
Total cholesterol (mmol/L)								
LCQ908 2 mg	92	1.02	(1.00, 1.03)	1.04	(1.01, 1.07)	1.00	(0.94, 1.05)	1.0000
LCQ908 5 mg	93	0.99	(0.98, 1.01)	1.00	(0.97, 1.03)	0.96	(0.91, 1.02)	0.3009
LCQ908 10 mg	92	0.98	(0.96, 0.99)	0.96	(0.93, 0.99)	0.92	(0.87, 0.97)	0.0007
LCQ908 15 mg	89	0.96	(0.95, 0.98)	0.96	(0.93, 0.99)	0.92	(0.87, 0.98)	0.0018

LCQ908 20 mg	89	0.96	(0.94, 0.98)	0.96	(0.93, 0.99)	0.93	(0.88, 0.98)	0.0022
Sitagliptin 100 mg	97	1.00	(0.97, 1.03)	1.00	(0.97, 1.03)	0.96	(0.91, 1.01)	0.1683
Placebo	97	1.05	(1.02, 1.08)	1.04	(1.01, 1.07)			
MED (mg/d)								
Triglycerides (TG) (mmol/L)								
LCQ908 2 mg	92	1.04	(1.00, 1.09)	1.06	(0.99, 1.14)	1.01	(0.89, 1.14)	0.9999
LCQ908 5 mg	93	1.02	(0.99, 1.06)	1.02	(0.95, 1.09)	0.97	(0.86, 1.10)	0.9778
LCQ908 10 mg	92	0.99	(0.96, 1.03)	0.95	(0.89, 1.02)	0.90	(0.80, 1.02)	0.1639
LCQ908 15 mg	89	0.96	(0.93, 1.01)	0.96	(0.90, 1.03)	0.92	(0.81, 1.04)	0.2693
LCQ908 20 mg	89	0.94	(0.89, 0.99)	0.95	(0.89, 1.02)	0.90	(0.80, 1.02)	0.1679
Sitagliptin 100 mg	97	0.92	(0.86, 0.98)	0.93	(0.87, 1.00)	0.89	(0.79, 1.00)	0.0623
Placebo	97	1.05	(1.01, 1.11)	1.05	(0.98, 1.13)			
MED (mg/d)		17.80						

Safety Results

Adverse events during the randomized double-blind treatment period by primary SOC and treatment group (Safety Set)

	LCQ908 2 mg N=98 n (%)	**LCQ908 5 mg N=97 n (%)**	**LCQ908 10 mg N=97 n (%)**	**LCQ908 15 mg N=101 n (%)**	**LCQ908 20 mg N=98 n (%)**	**Sitagliptin 100 mg N=101 n (%)**	**Placebo N=100 n (%)**	**Total N=692 n (%)**
Any primary SOC	51 (52.0)	49 (50.5)	70 (72.2)	67 (66.3)	78 (79.6)	50 (49.5)	42 (42.0)	407 (58.8
Blood and lymphatic system disorders	1 (1.0)	1 (1.0)	1 (1.0)	2 (2.0)	3 (3.1)	0	0	8 (1.2)
Cardiac disorders	3 (3.1)	2 (2.1)	1 (1.0)	2 (2.0)	4 (4.1)	2 (2.0)	5 (5.0)	19 (2.7)
Ear and labyrinth disorders	1 (1.0)	1 (1.0)	0	2 (2.0)	0	0	1 (1.0)	5 (0.7)
Eye disorders	1 (1.0)	3 (3.1)	2 (2.1)	0	0	0	1 (1.0)	7 (1.0)
Gastrointestinal disorders	26 (26.5)	36 (37.1)	49 (50.5)	57 (56.4)	65 (66.3)	17 (16.8)	22 (22.0)	272 (39.3
General disorders and administration site conditions	3 (3.1)	4 (4.1)	8 (8.2)	2 (2.0)	7 (7.1)	3 (3.0)	4 (4.0)	31 (4.5)
Hepatobiliary disorders	0	0	0	0	0	0	1 (1.0)	1 (0.1)

Infections and infestations	17 (17.3)	12 (12.4)	23 (23.7)	17 (16.8)	15 (15.3)	22 (21.8)	15 (15.0)	121 (17.5)
Injury, poisoning and procedural complications	1 (1.0)	2 (2.1)	4 (4.1)	1 (1.0)	3 (3.1)	2 (2.0)	1 (1.0)	14 (2.0)
Investigations	2 (2.0)	1 (1.0)	2 (2.1)	1 (1.0)	3 (3.1)	1 (1.0)	0	10 (1.4)
Metabolism and nutrition disorders	4 (4.1)	1 (1.0)	4 (4.1)	1 (1.0)	2 (2.0)	2 (2.0)	0	14 (2.0)
Musculoskeletal and connective tissue disorders	7 (7.1)	5 (5.2)	3 (3.1)	4 (4.0)	4 (4.1)	11 (10.9)	11 (11.0)	45 (6.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.0)	0	0	0	1 (1.0)	0	2 (0.3)
Nervous system disorders	5 (5.1)	8 (8.2)	7 (7.2)	5 (5.0)	6 (6.1)	9 (8.9)	6 (6.0)	46 (6.6)
Psychiatric disorders	0	0	1 (1.0)	1 (1.0)	3 (3.1)	1 (1.0)	2 (2.0)	8 (1.2)
Renal and urinary disorders	2 (2.0)	1 (1.0)	0	1 (1.0)	1 (1.0)	4 (4.0)	0	9 (1.3)
Reproductive system and breast disorders	0	2 (2.1)	1 (1.0)	2 (2.0)	0	0	1 (1.0)	6 (0.9)
Respiratory, thoracic and mediastinal disorders	3 (3.1)	2 (2.1)	6 (6.2)	1 (1.0)	3 (3.1)	5 (5.0)	4 (4.0)	24 (3.5)
Skin and subcutaneous tissue disorders	3 (3.1)	2 (2.1)	2 (2.1)	4 (4.0)	2 (2.0)	2 (2.0)	3 (3.0)	18 (2.6)
Surgical and medical procedures	0	0	0	0	0	1 (1.0)	0	1 (0.1)
Vascular disorders	2 (2.0)	2 (2.1)	0	0	4 (4.1)	1 (1.0)	4 (4.0)	13 (1.9)

Adverse events during the randomized double-blind treatment period (at least 2% in any treatment group) by preferred term and treatment group (Safety Set)

	LCQ908 2 mg N=98 n (%)	**LCQ908 5 mg N=97 n (%)**	**LCQ908 10 mg N=97 n (%)**	**LCQ908 15 mg N=101 n (%)**	**LCQ908 20 mg N=98 n (%)**	**Sitagliptin 100 mg N=101 n (%)**	**Placebo N=100 n (%)**	**Total N=692 n (%)**
Patients with any AEs	51 (52.0)	49 (50.5)	70 (72.2)	67 (66.3)	78 (79.6)	50 (49.5)	42 (42.0)	407 (58.8
Diarrhoea	11 (11.2)	26 (26.8)	35 (36.1)	43 (42.6)	54 (55.1)	8 (7.9)	13 (13.0)	190 (27.5
Nausea	4 (4.1)	9 (9.3)	13 (13.4)	16 (15.8)	16 (16.3)	1 (1.0)	3 (3.0)	62 (9.0)
Vomiting	3 (3.1)	6 (6.2)	10 (10.3)	15 (14.9)	13 (13.3)	1 (1.0)	2 (2.0)	50 (7.2)
Abdominal pain	4 (4.1)	3 (3.1)	12 (12.4)	12 (11.9)	11 (11.2)	1 (1.0)	2 (2.0)	45 (6.5)
Nasophayrngitis	4 (4.1)	2 (2.1)	6 (6.2)	4 (4.0)	5 (5.1)	10 (9.9)	7 (7.0)	38 (5.5)
Headache	3 (3.1)	4 (4.1)	4 (4.1)	2 (2.0)	2 (2.0)	2 (2.0)	3 (3.0)	20 (2.9)
Dyspepsia	0	1 (1.0)	6 (6.2)	3 (3.0)	3 (3.1)	2 (2.0)	1 (1.0)	16 (2.3)

Flatulence	1 (1.0)	3 (3.1)	2 (2.1)	5 (5.0)	2 (2.0)	1 (1.0)	2 (2.0)	16 (2.3)
Dizziness	1 (1.0)	2 (2.1)	3 (3.1)	2 (2.0)	1 (1.0)	3 (3.0)	2 (2.0)	14 (2.0)
Abdominal distension	1 (1.0)	3 (3.1)	1 (1.0)	1 (1.0)	7 (7.1)	0	0	13 (1.9)
Upper respiratory tract infection	3 (3.1)	1 (1.0)	0	1 (1.0)	4 (4.1)	3 (3.0)	1 (1.0)	13 (1.9)
Abdominal pain upper	2 (2.0)	2 (2.1)	1 (1.0)	3 (3.0)	1 (1.0)	1 (1.0)	2 (2.0)	12 (1.7)
Gastroenteritis	4 (4.1)	0	2 (2.1)	2 (2.0)	2 (2.0)	0	2 (2.0)	12 (1.7)
Fatigue	0	2 (2.1)	5 (5.2)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	11 (1.6)
Abdominal discomfort	1 (1.0)	4 (4.1)	2 (2.1)	0	3 (3.1)	0	0	10 (1.4)
Arthralgia	1 (1.0)	1 (1.0)	2 (2.1)	0	0	2 (2.0)	4 (4.0)	10 (1.4)
Back pain	2 (2.0)	2 (2.1)	0	1 (1.0)	0	2 (2.0)	3 (3.0)	10 (1.4)
Bronchitis	1 (1.0)	1 (1.0)	5 (5.2)	1 (1.0)	0	1 (1.0)	1 (1.0)	10 (1.4)
Constipation	2 (2.0)	0	2 (2.1)	1 (1.0)	1 (1.0)	2 (2.0)	2 (2.0)	10 (1.4)
Urinary tract infection	1 (1.0)	3 (3.1)	1 (1.0)	2 (2.0)	0	2 (2.0)	1 (1.0)	10 (1.4)
Cough	0	1 (1.0)	3 (3.1)	1 (1.0)	2 (2.0)	2 (2.0)	0	9 (1.3)
Influenza	2 (2.0)	0	3 (3.1)	2 (2.0)	1 (1.0)	0	1 (1.0)	9 (1.3)
Hypertension	1 (1.0)	2 (2.1)	0	0	2 (2.0)	0	3 (3.0)	8 (1.2)
Asthenia	0	2 (2.1)	1 (1.0)	1 (1.0)	2 (2.0)	1 (1.0)	0	7 (1.0)
Eructation	0	0	3 (3.1)	2 (2.0)	1 (1.0)	0	1 (1.0)	7 (1.0)
Frequent bowel movements	1 (1.0)	0	3 (3.1)	2 (2.0)	1 (1.0)	0	0	7 (1.0)
Anaemia	0	0	0	2 (2.0)	3 (3.1)	0	0	5 (0.7)
Hyperhidrosis	0	1 (1.0)	1 (1.0)	0	1 (1.0)	0	2 (2.0)	5 (0.7)
Gastritis	0	0	2 (2.1)	0	1 (1.0)	1 (1.0)	0	4 (0.6)
Musculoskeletal pain	1 (1.0)	2 (2.1)	0	0	0	1 (1.0)	0	4 (0.6)
Pain in extremity	0	0	0	1 (1.0)	2 (2.0)	1 (1.0)	0	4 (0.6)
Pyrexia	0	0	1 (1.0)	0	2 (2.0)	0	1 (1.0)	4 (0.6)
Toothache	2 (2.0)	2 (2.1)	0	0	0	0	0	4 (0.6)
Tracheitis	0	0	1 (1.0)	0	0	3 (3.0)	0	4 (0.6)
Gastroenteritis viral	0	0	2 (2.1)	1 (1.0)	0	0	0	3 (0.4)
Irritable bowel syndrome	0	0	0	2 (2.0)	0	1 (1.0)	0	3 (0.4)
Laryngitis	0	0	2 (2.1)	0	0	1 (1.0)	0	3 (0.4)
Nasal congestion	0	0	0	0	0	2 (2.0)	1 (1.0)	3 (0.4)
Respiratory tract infection	0	2 (2.1)	1 (1.0)	0	0	0	0	3 (0.4)
Sinus bradycardia	0	2 (2.1)	0	0	1 (1.0)	0	0	3 (0.4)
Somnolence	0	0	1 (1.0)	2 (2.0)	0	0	0	3 (0.4)
Vertigo	1 (1.0)	0	0	2 (2.0)	0	0	0	3 (0.4)
Aphthous stomatitis	2 (2.0)	0	0	0	0	0	0	2 (0.3)
Chills	0	0	0	0	2 (2.0)	0	0	2 (0.3)

Hypertriglycer-idaemia	0	0	0	0	0	2 (2.0)	0	2 (0.3)
Insomnia	0	0	0	0	2 (2.0)	0	0	2 (0.3)
Rhinitis	0	0	0	0	0	2 (2.0)	0	2 (0.3)

Deaths, other serious or clinically significant adverse events or related discontinuations during the randomized double-blind treatment period by treatment group (Safety Set)

	LCQ908 2 mg N=98 n (%)	**LCQ908 5 mg N=97 n (%)**	**LCQ908 10 mg N=97 n (%)**	**LCQ908 15 mg N=101 n (%)**	**LCQ908 20 mg N=98 n (%)**	**Sitagliptin 100 mg N=101 n (%)**	**Place-bo N=100 n (%)**	**Total N=692 n (%)**
Deaths	0	0	0	0	0	0	0	0
SAEs	3 (3.1)	2 (2.1)	4 (4.1)	2 (2.0)	1 (1.0)	2 (2.0)	4 (4.0)	18 (2.6)
AEs leading to dis-continuation	1 (1.0)	4 (4.1)	11 (11.3)	15 (14.9)	9 (9.2)	2 (2.0)	0	42 (6.1)
AEs requiring dose adjustment or study drug interruption	5 (5.1)	3 (3.1)	9 (9.3)	2 (2.0)	8 (8.2)	1 (1.0)	2 (2.0)	30 (4.3)
Other pre-defined clinically significant AEs	29 (29.6)	36 (37.1)	51 (52.6)	57 (56.4)	66 (67.3)	18 (17.8)	24 (24.0)	281 (40.6)
CCV events con-firmed by adjudica-tion committee	1 (1.0)	0	0	0	0	0	0	1 (0.1)
Diarrhea	11 (11.2)	26 (26.8)	35 (36.1)	43 (42.6)	54 (55.1)	8 (7.9)	13 (13.0)	190 (27.5)
GI other	19 (19.4)	28 (28.9)	32 (33.0)	33 (32.7)	41 (41.8)	10 (9.9)	13 (13.0)	176 (25.4)
Skin events	1 (1.0)	0	0	1 (1.0)	0	0	0	2 (0.3)
Hepatic disorders	2 (2.0)	0	0	0	0	0	1 (1.0)	3 (0.4)
Phototoxicity	1 (1.0)	0	0	1 (1.0)	0	0	0	2 (0.3)
Reticulocyte in-crease	1 (1.0)	0	4 (4.1)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	9 (1.3)
SAEs leading to dis-continuation	1 (1.0)	0	2 (2.1)	1 (1.0)	0	1 (1.0)	0	5 (0.7)
Other pre-defined clinically significant AEs leading to dis-continuation	1 (1.0)	1 (1.0)	9 (9.3)	11 (10.9)	9 (9.2)	0	0	31 (4.5)

Other Relevant Findings

Other clinically significant adverse events during the randomized double-blind treatment period by primary SOC, severity and treatment group (Safety Set)

	LCQ908 2 mg N=98 n (%)	LCQ908 5 mg N=97 n (%)	LCQ908 10 mg N=97 n (%)	LCQ908 15 mg N=101 n (%)	LCQ908 20 mg N=98 n (%)	Sitagliptin 100 mg N=101 n (%)	Placebo N=100 n (%)	Total N=692 n (%)
Any primary SOC	28 (28.6)	36 (37.1)	49 (50.5)	57 (56.4)	65 (66.3)	17 (16.8)	23 (23.0)	275 (39.7
Mild	25 (25.5)	32 (33.0)	38 (39.2)	43 (42.6)	45 (45.9)	11 (10.9)	17 (17.0)	211 (30.5
Moderate	7 (7.1)	9 (9.3)	16 (16.5)	24 (23.8)	28 (28.6)	7 (6.9)	7 (7.0)	98 (14.2)
Severe	1 (1.0)	2 (2.1)	6 (6.2)	7 (6.9)	2 (2.0)	1 (1.0)	1 (1.0)	20 (2.9)
Gastrointestinal disorders	26 (26.5)	36 (37.1)	49 (50.5)	57 (56.4)	65 (66.3)	17 (16.8)	22 (22.0)	272 (39.3
Mild	23 (23.5)	32 (33.0)	38 (39.2)	43 (42.6)	45 (45.9)	11 (10.9)	17 (17.0)	209 (30.2
Moderate	7 (7.1)	9 (9.3)	16 (16.5)	24 (23.8)	28 (28.6)	7 (6.9)	6 (6.0)	97 (14.0)
Severe	0	2 (2.1)	6 (6.2)	7 (6.9)	2 (2.0)	1 (1.0)	1 (1.0)	19 (2.7)
Hepatobiliary disorders	0	0	0	0	0	0	1 (1.0)	1 (0.1)
Mild	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	1 (1.0)	1 (0.1)
Severe	0	0	0	0	0	0	0	0
Investigations	2 (2.0)	0	0	0	0	0	0	2 (0.3)
Mild	2 (2.0)	0	0	0	0	0	0	2 (0.3)
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Nervous system disorders	1 (1.0)	0	0	0	0	0	0	1 (0.1)
Mild	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Severe	1 (1.0)	0	0	0	0	0	0	1 (0.1)
Skin and subcutaneous tissue disorders	1 (1.0)	0	0	1 (1.0)	0	0	0	2 (0.3)
Mild	1 (1.0)	0	0	1 (1.0)	0	0	0	2 (0.3)
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0

Date of Clinical Trial Report 27-May-2011
Date Inclusion on Novartis Clinical Trial Results Database 17-June-2011
Date of Latest Update 17-June-2011