

| |
|---|
| 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/m² 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 $\geq 50\%$ 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 ≤ 250 mg/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 agree 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/m² 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 μ U/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 (%) | Sitagli ptin 100 mg N=101 n (%) | Place- bo 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 discontinua- tion | | | | | | | | |
| 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 la- boratory value(s) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Abnormal test procedure re- sult(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 condi- tion no longer requires study drug | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Patient with- drew 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 devia- tion | 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 (%) | Sitaglipt in 100 mg N=101 n (%) | Place- bo 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 (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, Bel- gium, Ger- many) | 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 Ameri- ca (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 Amer- ica (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, Po- land, Slo- vakia) | 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 circumference (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) (bpm) | | | | | | | | |
| 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 |

| | | | | | | | | |
|---|-----------|-----------|-----------|-----------|-----------|-------------|------------------------|-------------------------|
| > 8 | 35 (35.7) | 35 (36.1) | 35 (36.1) | 24 (23.8) | 36 (36.4) | 3 (35.6) | (66.0) 31 (31.0) | (60.5) 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 | 287.5 | 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)

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 ($\mu\text{mol/L}$) | | | | | | | | |
| 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 circumference (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 re-sponse estimate | 95% CI | Percent of baseline | | Relative to Placebo | | p-value |
|-----------------------------------|----|-------------------------|--------------|---------------------|--------------|---------------------|--------------|---------|
| | | | | Estimat-ed me-dian | 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 |

| | | | | | | | | |
|---|---|---|--|---|---|--|--|----------------------------------|
| 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 (%) | LCQ90 8 20 mg N=98 n (%) | Sitaglipti n 100 mg N=101 n (%) | Place- bo 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) |
| Nasopharyngitis | 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 dis- tension | 1 (1.0) | 3 (3.1) | 1 (1.0) | 1 (1.0) | 7 (7.1) | 0 | 0 | 13 (1.9) |
| Upper respira- tory tract infec- tion | 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 dis- comfort | 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) |
| Musculoskele- tal pain | 1 (1.0) | 2 (2.1) | 0 | 0 | 0 | 1 (1.0) | 0 | 4 (0.6) |
| Pain in extremi- ty | 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 conges- tion | 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 brady- cardia | 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 sto- matitis | 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) |

| Hypertriglyceridaemia | 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 (%) | Placebo 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 discontinuation | 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 confirmed by adjudication 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 increase | 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 discontinuation | 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 discontinuation | 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 (%) | LCQ90 8 15 mg N=101 n (%) | LCQ90 8 20 mg N=98 n (%) | Sitaglipti n 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