NOVARTIS

Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

LCQ908

Therapeutic Area of Trial

Chylomicronemia

Approved Indication

Investigational

Protocol Number

CLCQ908A2212

Title

A multiple-dose, parallel group study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of LCQ908 in patients with severe hypertriglyceridemia and chylomicronemia (phenotypes I and V)

Phase of Development

Phase I/II

Study Start/End Dates

20-May-2010 to 12-Oct-2011

Study Design/Methodology

This was a multiple-dose, outpatient study to assess the safety, tolerability, pharmacokinetics and triglyceride-lowering effects of LCQ908 in patients with chylomicronemia. The study involved patients with complete lipoprotein lipase (LPL) deficiency (a.k.a. familial chylomicronemia syndrome, FCS) and patients with partial LPL deficiency.

FCS patients (n=6) underwent three consecutive treatment periods in an open label manner where patients were treated with 20 mg, 40 mg and 10 mg LCQ908 once a day (q.d.), respectively, during each of the three 21-day treatment periods. Patients were advised on a low fat diet throughout and were provided with low fat meals on study days -3 to -1 before baseline.

Chylomicronemia patients with partial LPL deficiency (n=6) underwent a single open label 21-day treatment period with 20 mg LCQ908 q.d.

Protocol Amendment Number 3 allowed enrolling up to 30 patients with partial LPL deficiency in treatment period 2. Patients were treated with placebo, 10 mg or 40 mg LCQ908 in a randomized, double-blinded 28-day treatment period.

Centers

1 center in Canada

Publication

None

Outcome measures

Primary outcome measures

- Fasting and postprandial plasma triglycerides at baseline and end of the 21-day treatment period (a test meal was served at baseline and on Day 21 of treatment) and fasting plasma triglycerides at baselines and end of the 28-day treatment period.

Secondary outcome measures(s)

- LCQ908 blood concentration to characterize pharmacokinetics. Serial blood samples collected from all patients enrolled in the 21-day treatment periods and trough samples collected weekly during the 28-day treatment period.

- Blood lipid biomarkers (such as phospholipids, apolipoproteins, and free fatty acids) at baseline and end of treatment.

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

LCQ908 20 mg, 40 mg, 10 mg and placebo (once daily oral administration).

Statistical Methods

Analysis was performed separately for both FCS and partial LPL deficient patients. For FCS patients, and Period 1 of partial LPL deficient patients, the fasting triglyceride (TG) endpoint was defined as the mean of Day 21 and 22 fasting values. The peak and AUC0-9 were calculated for postprandial triglycerides on Day 21. The linear trapezoidal rule was used to calculate the area under the curve using actual times.

For partial LPL deficient patients, Period 2, the fasting TG was defined as Day 28. Some patients participated in Period 1 and then later participated in Period 2; these patients were treated as independent subjects for simplicity.

Absolute and percent change from baseline (dietary controlled) in fasting; peak and AUC of postprandial TG were summarized using descriptive statistics, including mean, median, geometric mean, SD, CV, minimum and maximum. The summary for change from baseline was provided for fasting TG.

Fasting TG were analyzed using a linear mixed effect model for repeated measurements. The model included treatment, time and treatment by time interaction and baseline as fixed effects, and subject as a random effect. Day 21 peak and AUC were analyzed by a linear mixed effect model with treatment and baseline values as fixed effects and subject as random effect for FCS patients. For partial LPL deficient patients in period 2, the primary endpoint was analyzed by an analysis of covariance (ANCOVA) with treatment and covariate baseline value as effects. The point estimate and 90% CI for the difference between LCQ (10 mg or 40 mg) and placebo were calculated from the ANCOVA model.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Male or female 18 to 75 years old (inclusive) with hyperchylomicronemia phenotypes I (FCS,

complete LPL deficiency) and V (partial LPL deficiency).

- Willing and medically able to discontinue lipid lowering treatment for up to 8 weeks prior to the first dose of the study drug and for the duration of the study.
- For randomized patients in treatment period 2, statins were allowed as long as patients were on a stable dose during the 8 weeks prior to treatment and the dose was not to be modified until study completion.
- Women of child bearing potential practicing appropriate contraception with a negative pregnancy test before dosing.

Exclusion criteria:

- Pregnant or nursing women.
- Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing.
- Participation in any clinical investigation within four (4) weeks prior to initial dosing.

And patients with:

- uncontrolled type 1 or type 2 diabetes mellitus,
- active pancreatitis (the month prior to study start),
- history of drug or alcohol abuse within the 12 months prior to dosing,
- any surgical or medical condition, acute or unstable chronic disease which may, based on the investigator's opinion, jeopardize the patient in case of participation in the study.
- or evidence of liver disease or liver injury as indicated by abnormal liver function tests

Participant Flow

FCS patients' disposition - (n %) of patients

	T Period 1 (N=6) LCQ908 20 mg	T Period 2 (N=6) LCQ908 40 mg	T Period 3 (N=4*) LCQ908 10 mg	All Treatment Periods (N=6)
Completed	6 (100%)	6 (100%)	4 (100%)	4 (66.7%)
Discontinued	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)*
Main cause of discontinuation				
Withdrawal of consent*				2 (33.3%)*

T Period = Treatment Period. Treatment periods were separated with at least 4 weeks of washout.
6 FCS patients completed treatment periods 1 and 2.
*2 of the 6 patients could not participate in treatment period 3 due to personal scheduling conflict. Therefore only 4 FCS were enrolled in, and completed treatment period 3.

Partial LPL deficient patients' disposition - (n %) of patients

	Period 1 Open-label, non randomized 21-day treatment	Period 2 Randomized, double-blinded 28-day treatment			All Treatment Periods
	LCQ908 20 mg (N=6)	Placebo (N=9)	LCQ908 10 mg (N=11)	LCQ908 40 mg (N=10)	Total (N=31)*
Completed	6 (100%)	9 (100%)	9 (81.8%)	7 (70%)	26 (83.9%)*
Discontinued	0 (0.0%)	0 (0.0%)	2 (18.2%)	3 (30%)	5 (16.1%)*
Main cause of discontinuation					
Withdrawal of consent			1 (9.1%)	1 (10%)	2 (6.4%)*
Adverse event(s)			1 (9.1%)	2 (20%)	3 (9.7%)*

Five patients from Period 1 were also enrolled in Period 2 (1 in placebo, 1 in 10 mg, and 3 in 40 mg).
*These 5 patients have only been counted once for the Total column.
Treatment periods were separated with at least 4 weeks of washout.

Baseline Characteristics

	FCS	Partial LPL deficiency			
	All T Periods	T Period 1	T Period 2		
	LCQ908 20, 40 & 10 mg N=6	LCQ908 20 mg N=6	LCQ908 10 mg N=11	LCQ908 40 mg N=10	Placebo N=9
Age (years)					
Mean	51.5	58.3	62.4	52.7	51.2
SD	12.69	9.14	5.22	9.09	8.42
Range	35-66	46-72	51-70	33-64	35-61
Weight (kg)					
Mean	59.37	81.63	84.80	89.38	74.70
SD	15.80	9.06	9.92	14.62	13.52
Range	36.5-77.7	65.4-93.4	65.3-103.7	61.7-116.7	46.1-95.4
Height (cm)					

Mean	165.0	164.3	164.9	167.7	164.0
SD	8.83	7.42	8.96	12.56	9.77
Range	153-175	154-175	153-181	154-190	148-178
BMI (kg/m^2)					
Mean	21.50	30.21	31.32	31.72	27.70
SD	3.91	2.57	4.41	3.59	4.31
Range	14.4-25.4	26.2-34.3	26.8-42.1	26.0-37.7	21.1-34.3
Gender					
Male	2 (33.3%)	4 (66.7%)	7 (63.6%)	7 (70%)	5 (55.6%)
Female	4 (66.7%)	2 (33.3%)	4 (36.4%)	3 (30%)	4 (44.4%)
Race					
Caucasian	6 (100%)	6 (100%)	11 (100%)	10 (100%)	9 (100%)

BMI = body mass index. SD = standard deviation.
T Period = Treatment Period.

Outcome measures

Primary Outcome Result(s):

Change in fasting and postprandial triglycerides (TG) from baseline in FCS patients:

	T Period 1	T Period 2	T Period 3
	LCQ908	LCQ908	LCQ908
	20 mg	40 mg	10 mg
Baseline			
N	6	6	4
Fasting TG; Mean ± SD (mg/dL)	1968 ± 582.5	5072 ± 3868	3552 ± 2210
Peak Postprandial TG; Mean ± SD (mg/dL)	1913 ± 469.8	-	-
AUC Postprandial TG; Mean ± SD (h* mg/dL)	15045 ± 4154	-	-
Change at end of treatment (Day 21)			
N	6	6	4
Change in Fasting TG; Mean ± SD (mg/dL)*	-625.8 ± 510.0	-256.8 ± 642.5	911.3 ± 687.2
N	6	6	3
Change in Peak Postprandial TG; Mean ± SD (mg/dL)	-720.2 ± 420.5	-302.3 ± 996.0	1606 ± 1245
Change in AUC of Postprandial TG; Mean ± SD (h* mg/dL)	-5657 ± 3352	-2384 ± 7438	12074 ± 9943

*Fasting TG was measured on both Day 21 and Day 22. The mean of the 2 measurements was used for the "end of treatment" evaluation.

T Period = Treatment Period.

Change in fasting and postprandial triglycerides (TG) from baseline in patients with partial LPL deficiency:

	T Period 1	T Period 2		
	LCQ908	LCQ908	LCQ908	Placebo
	20 mg	40 mg	10 mg	
Baseline				
N	6	10	11	8
Fasting TG**; Mean ± SD (mg/dL)	745.5 ± 312.3	825.6 ± 780.8	921.9 ± 1242	969.9 ± 817.37
Peak Postprandial TG; Mean ± SD (mg/dL)	835.7 ± 316.5	-	-	-
AUC Postprandial TG; Mean ± SD (h* mg/dL)	6873 ± 2791	-	-	-
Change at Day 21*				
N	6	7	9	8
Change in Fasting TG**; Mean ± SD (mg/dL)	-175.0 ± 148.7**	-240.6 ± 511.24	307.0 ± 1201	-39.9 ± 644.7

Change in Peak Postprandial TG; Mean ± SD (mg/dL)	-217.2 ± 160.7	-	-	-
Change in AUC of Postprandial TG; Mean ± SD (h* mg/dL)	-1879 ± 1194	-	-	-
Change at Day 28*				
Change in Fasting TG; Mean ± SD (mg/dL)	-	-258.3 ± 413.7	-446.9 ± 1014	-52.0 ± 614.3

*Day 21 is end of treatment for the 20 mg dose cohort while Day 28 is the end of treatment for the other treatment arms (placebo, 10 and 40 mg doses).

**Fasting TG was measured on both Day 21 and Day 22 during the 20 mg treatment period. The mean of the 2 measurements was used for this evaluation.

T Period = Treatment Period.

Secondary Outcome Result(s):

Change in free fatty acids (FFA) from baseline in FCS patients:

	T Period 1	T Period 2	T Period 3
	LCQ908	LCQ908	LCQ908
	20 mg	40 mg	10 mg
Baseline			
N	6	6	4
Fasting FFA; Mean ± SD (mmol/L)	0.5060 ± 0.1469	-	-
Peak Postprandial FFA; Mean ± SD (mmol/L)	0.5233 ± 0.1890	-	-
AUC Postprandial FFA; Mean ± SD (h* mmol/L)	2.6583 ± 0.7702	-	-
Change at end of treatment; Day 21			
N	6	6	4
Change in Fasting FFA; Mean ± SD (mmol/L)*	-0.1000 ± 0.1172	-0.0150 ± 0.0456	-0.0488 ± 0.1330
N	6	6	3
Change in Peak Postprandial FFA; Mean ± SD (mmol/L)	-0.0983 ± 0.2607	-0.0100 ± 0.1441	-0.1967 ± 0.2001
Change in AUC of Postprandial FFA; Mean ± SD (h* mmol/L)	-0.8300 ± 0.6178	-0.1850 ± 0.6996	-1.0933 ± 0.71600

* Fasting FFA was not measured at the beginning of treatment periods 2 or 3, so the baseline value from period 1 is used for these periods. Fasting FFA was measured on both Day 21 and Day 22. The mean of the 2 measurements was used for the “end of treatment” evaluation.

T Period = Treatment Period.

Change in free fatty acids (FFA) from baseline in patients with partial LPL deficiency:

	T Period 1	T Period 2		
	LCQ908	LCQ908	LCQ908	Placebo
	20 mg	40 mg	10 mg	
Baseline				
N	6	10	11	8
Fasting FFA**; Mean ± SD (mmol/L)	0.6467 ± 0.1844	0.4676 ± 0.1264	0.5531 ± 0.1992	0.4374 ± 0.0656
Peak Postprandial FFA; Mean ± SD (mmol/L)	0.8250 ± 0.1783	-	-	-
AUC Postprandial FFA; Mean ± SD (h* mmol/L)	3.583 ± 0.1498	-	-	-
Change at Day 21*				
N	6	7	9	8
Change in Fasting FFA**; Mean ± SD (mmol/L)	-0.0208 ± 0.0971**	-0.0933 ± 0.1104	-0.1234 ± 0.1047	-0.0183 ± 0.1092

Change in Peak Postprandial FFA; Mean ± SD (mmol/L)	-0.0450 ± 0.3379	-	-	-
Change in AUC of Postprandial FFA; Mean ± SD (h* mmol/L)	-0.2275 ± 0.6707	-	-	-
Change at Day 28*				
Change in Fasting FFA; Mean ± SD (mmol/L)	-	-0.1209 ± 0.1106	-0.1589 ± 0.1848	0.0551 ± 0.1439

*Day 21 is end of treatment for the 20 mg dose cohort while Day 28 is the end of treatment for the other treatment arms (placebo, 10 and 40 mg doses).
**Fasting FFA was measured on both Day 21 and Day 22 during the 20 mg treatment period. The mean of the 2 measurements was used for this evaluation.

T Period = Treatment Period.

Change in phospholipids (PL) from baseline in FCS patients:

	T Period 1	T Period 2	T Period 3
	LCQ908	LCQ908	LCQ908
	20 mg	40 mg	10 mg
Baseline			
N	6	6	4
Fasting PL; Mean ± SD (mmol/L)	3.886 ± 0.8973	-	-
N	6	6	3
Peak Postprandial PL; Mean ± SD (mmol/L)	3.697 ± 0.8228	-	-
AUC Postprandial PL; Mean ± SD (h* mmol/L)	31.11 ± 7.654	-	-
Change at end of treatment; Day 21			
N	6	6	4
Change in Fasting PL; Mean ± SD (mmol/L)*	-0.228 ± 0.3189	-0.0156 ± 0.7488	0.641 ± 0.8577
N	6	6	3
Change in Peak Postprandial PL; Mean ± SD (mmol/L)	-0.338 ± 0.1888	-0.172 ± 0.9381	0.950 ± 0.3205
Change in AUC of Postprandial PL; Mean ± SD (h* mmol/L)	-2.851 ± 3.574	-1.078 ± 8.154	4.395 ± 7.137

* Fasting phospholipids were not measured at the beginning of treatment periods 2 or 3, so the baseline value from period 1 is used for these periods. Fasting phospholipids was measured on both Day 21 and Day 22. The mean of the 2 measurements was used for the “end of treatment” evaluation.

T Period = Treatment Period.

Change in phospholipids (PL) from baseline in patients with partial LPL deficiency:

	T Period 1	T Period 2		
	LCQ908	LCQ908	LCQ908	Placebo

	20 mg	40 mg	10 mg	
Baseline				
N	6	10	11	8
Fasting PL**; Mean ± SD (mmol/L)	4.355 ± 0.6647	3.899 ± 1.602	3.782 ± 1.447	3.974 ± 0.998
Peak Postprandial PL; Mean ± SD (mmol/L)	4.512 ± 0.7270	-	-	-
AUC Postprandial PL; Mean ± SD (h* mmol/L)	38.744 ± 6.081	-	-	-
Change at Day 21*				
N	6	7	9	8
Change in Fasting PL**; Mean ± SD (mmol/L)	-0.688 ± 0.5584**	-0.816 ± 1.055	0.087 ± 1.269	0.233 ± 1.182
Change in Peak Postprandial PL; Mean ± SD (mmol/L)	-0.772 ± 0.6429	-	-	-
Change in AUC of Postprandial PL; Mean ± SD (h* mmol/L)	-7.050 ± 4.601	-	-	-
Change at Day 28*				
Change in Fasting PL; Mean ± SD (mmol/L)	-	-0.729 ± 0.7315	-0.431 ± 0.3820	0.185 ± 0.8399

*Day 21 is end of treatment for the 20 mg dose cohort while Day 28 is the end of treatment for the other treatment arms (placebo, 10 and 40 mg doses).
**Fasting phospholipids (PL) was measured on both Day 21 and Day 22 during the 20 mg treatment period. The mean of the 2 measurements was used for this evaluation

T Period = Treatment Period.

Change in apolipoprotein B48 (APB48) from baseline in FCS patients:

	T Period 1	T Period 2	T Period 3
	LCQ908	LCQ908	LCQ908
	20 mg	40 mg	10 mg
Baseline			
N	6	6	4
Fasting APB48**; Mean ± SD (ng/mL)	83109 ± 37804	-	-
N	6	6	3
Peak Postprandial APB48; Mean ± SD (ng/mL)	83055 ± 30178	-	-
AUC Postprandial APB48; Mean ± SD (h* ng/mL)	666051 ± 242454	-	-
Change at end of treatment; Day 21			
N	6	6	4
Change in Fasting APB48**; Mean ± SD (ng/mL)*	-10685 ± 15670	-26618 ± 14437	30247 ± 26496
N	6	6	3
Change in Peak Postprandial APB48; Mean ± SD (ng/mL)	-11904 ± 15162	-27646 ± 12686	52447 ± 23154
Change in AUC of Postprandial APB48; Mean ± SD (h* ng/mL)	-103609 ± 122447	-221241 ± 135100	483370 ± 199273

*Day 21 is end of treatment for the 20 mg dose cohort while Day 28 is the end of treatment for the other treatment arms (placebo, 10 and 40 mg doses).
** Fasting APB48 was not measured at the beginning of treatment periods 2 or 3, so the baseline value from period 1 is used for these periods. Fasting APB48 was measured on both Day 21 and Day 22 during the 20 mg treatment period. The mean of the 2 measurements was used for this evaluation

T Period = Treatment Period.

Change in apolipoprotein B48 (APB48) from baseline patients with partial LPL deficiency:

	T Period 1	T Period 2		
	*LCQ908	LCQ908	LCQ908	Placebo
	20 mg	40 mg	10 mg	
Baseline				
N	6	10	11	8
Fasting APB48**; Mean ± SD (ng/mL)	27484 ± 8193	26381 ± 16674	39973 ± 35813	39485 ± 25138
Peak Postprandial APB48; Mean ± SD (ng/mL)	33424 ± 8465	-	-	-
AUC Postprandial APB48; Mean ± SD (h* ng/mL)	257491 ± 49628	-	-	-
Change at Day 21*				
N	6	7	8	8
Change in Fasting APB48**; Mean ± SD (ng/mL)	-2921 ± 6929**	-4227 ± 14477	16467 ± 27883	8716 ± 14470
Change in Peak Postprandial APB48; Mean ± SD (ng/mL)	-2715 ± 13600	-	-	-
Change in AUC of Postprandial APB48; Mean ± SD (h* ng/mL)	-32210 ± 69567	-	-	-
Change at Day 28*		7	9	8
Change in Fasting APB48; Mean ± SD (ng/mL)		-4294 ± 8433	-458.8 ± 14729	-892.7 ± 21698

*Day 21 is end of treatment for the 20 mg dose cohort while Day 28 is the end of treatment for the other treatment arms (placebo, 10 and 40 mg doses).
**Fasting APB48 was measured on both Day 21 and Day 22 during the 20 mg treatment period. The mean of the 2 measurements was used for this evaluation

T Period = Treatment Period.

Summary of LCQ908 trough concentration in FCS and partial LPL deficient patients:

Patient group	Dose (mg)		Study Day				
			7	14	21	22	28
FCS	10	N	4	4	4	4	-
		Mean	348	476	502	506	-
		SD	211	393	481	519	-
FCS	20	N	6	6	6	6	-
		Mean	668	738	736	684	-

Patient group	Dose (mg)		Study Day				
			7	14	21	22	28
		SD	305	457	497	340	-
FCS	40	N	6	6	6	5	-
		Mean	1230	1210	1620	1210	-
		SD	683	600	1080	656	-
Partial LPL deficiency	10	N	10	9	9	-	9
		Mean	332	450	464	-	474
		SD	122	166	119	-	168
Partial LPL deficiency	20	N	6	6	6	6	-
		Mean	790	870	883	740	-
		SD	394	405	351	334	-
Partial LPL deficiency	40	N	9	8	7	-	7
		Mean	684	756	585	-	610
		SD	372	487	174	-	238

LCQ908 Pharmacokinetic parameters for FCS and partial LPL deficient patients

Patient group	Dose (mg)	Study day		Tmax,ss* (hr)	Cmax,ss (ng/mL)	AUCtau (hr*ng/mL)
FCS	10	21	N	3	3	3
			Mean	10*	296	6190
			SD	-	111	2660
FCS	20	21	N	6	6	5
			Mean	5.5*	950	18000
			SD	-	572	10600
FCS	40	21	N	6	6	4
			Mean	1*	2170	39900
			SD	-	1300	24100
Partial LPL deficiency	20	21	N	6	6	6
			Mean	10*	1050	19700
			SD	-	377	7740

*Median is reported for Tmax

Safety Results

Adverse Events by System Organ Class – FCS Patients

	LCQ908 20 mg N=6 n (%)	LCQ908 40 mg N=6 n (%)	LCQ908 10 mg N=4 n (%)	Total N=6 N (%)
Patients with AE(s)	6 (100.0)	6 (100.0)	4 (100)	6 (100.0)
System organ class				
Gastrointestinal disorders	6 (100.0)	6 (100.0)	4 (100.0)	6 (100.0)
Nervous system disorders	0 (0.0)	2 (33.3)	1 (25.0)	2 (33.3)
Eye disorders	2 (33.3)	1 (16.7)	0 (0.0)	3 (50.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	1 (16.7)	2 (33.3)	0 (0.0)	3 (50.0)
Musculoskeletal and connective tissue disorders	1 (16.7)	2 (33.3)	0 (0.0)	3 (50.0)
Psychiatric disorders	1 (16.7)	1 (16.7)	0 (0.0)	1 (16.7)
Renal and urinary disorders	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (16.7)	1 (25.0)	2 (33.3)
Vascular disorders	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse Events by System Organ Class – Partial LPL Deficient Patients

	LCQ908 20 mg N=6 n (%)	LCQ908 40 mg N=10 n (%)	LCQ908 10 mg N=11 N (%)	Placebo N=9 n (%)	Total N=31 n (%)
Patients with AE(s)	6 (100.0)	10 (100.0)	10 (90.9)	6 (66.7)	27 (87.1)
System organ class					
Gastrointestinal disorders	6 (100.0)	9 (90.0)	9 (81.8)	4 (44.4)	24 (77.4)
Nervous system disorders	1 (16.7)	3 (30.0)	3 (27.3)	3 (33.3)	9 (29.0)
Eye disorders	0 (0.0)	3 (30.0)	3 (27.3)	1 (11.1)	7 (22.6)
General disorders and administration site conditions	1 (16.7)	5 (50.0)	4 (36.4)	1 (11.1)	10 (32.3)
Metabolism and nutrition disorders	3 (50.0)	5 (50.0)	0 (0.0)	0 (0.0)	8 (25.8)
Infections and infestations	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)
Musculoskeletal and connective tissue disorders	1 (16.7)	2 (20.0)	0 (0.0)	0 (0.0)	2 (6.5)
Psychiatric disorders	2 (33.3)	0 (0.0)	1 (9.1)	1 (11.1)	4 (12.9)
Renal and urinary disorders	2 (33.3)	1 (10.0)	0 (0.0)	0 (0.0)	3 (9.7)
Injury, poisoning and procedural complications	1 (16.7)	1 (10.0)	0 (0.0)	1 (11.1)	3 (9.7)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (10.0)	0 (0.0)	1 (11.1)	2 (6.5)
Cardiac disorders	1 (16.7)	0 (0.0)	0 (0.0)	1 (11.1)	2 (6.5)
Reproductive system and breast disorders	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (3.2)
Blood and lymphatic system disorders	1 (16.7)	1 (10.0)	0 (0.0)	0 (0.0)	1 (3.2)
Ear and labyrinth disorders	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
Investigations	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (3.2)

Most Frequently Reported AEs Overall by Preferred Term n (%)

	FCS patients				Partial LPL deficient patients				
	T Period 1	T Period 2	T Period 3		T Period 1	T Period 2 (randomized, 28-day)*			
	LCQ908 20 mg N=6 n (%)	LCQ908 40 mg N=6 n (%)	LCQ908 10 mg N=4 n (%)	Total N=6 n (%)	LCQ908 20 mg N=6 n (%)	LCQ908 40 mg N=10 n (%)	LCQ908 10 mg N=11 n (%)	Placebo N=9 n (%)	Total N=31* n (%)
Patients with AE(s)	6 (100.0)	6 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	10 (100.0)	10 (90.9)	6 (66.7)	27 (87.1)
Preferred term									
Diarrhea	4 (66.7)	5 (83.3)	3 (75.0)	6 (100.0)	4 (66.7)	7 (70.0)	8 (72.7)	3 (33.3)	20 (64.5)
Abdominal pain	3 (50.0)	2 (33.3)	1 (25.0)	4 (66.7)	1 (16.7)	5 (50.0)	5 (45.5)	1 (11.1)	11 (35.5)
Nausea	0 (0.0)	2 (33.3)	1 (25.0)	2 (33.3)	1 (16.7)	7 (70.0)	2 (18.2)	1 (11.1)	10 (32.3)
Flatulence	2 (33.3)	2 (33.3)	3 (75.0)	4 (66.7)	4 (66.7)	3 (30.0)	0 (0.0)	1 (11.1)	6 (19.4)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	5 (50.0)	0 (0.0)	0 (0.0)	8 (25.8)
Lipaemia retinalis	1 (16.7)	1 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)	2 (20.0)	3 (27.3)	1 (11.1)	6 (19.4)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	3 (30.0)	3 (27.3)	0 (0.0)	6 (19.4)
Abdominal pain upper	2 (33.3)	2 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	2 (20.0)	0 (0.0)	1 (11.1)	3 (9.7)
Faecal incontinence	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	3 (30.0)	1 (9.1)	0 (0.0)	4 (12.9)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	2 (18.2)	1 (11.1)	5 (16.1)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (20.0)	2 (18.2)	0 (0.0)	5 (16.1)

*Five partial LPL deficient patients from Period 1 were also enrolled in Period 2 (1 in placebo, 1 in 10 mg, and 3 in 40 mg). The 5 patients have only been counted once for the Total column.

Treatment periods were separated with at least 4 weeks of washout. An AE starting in one period and continuing into the next period is counted in the first period only.

A patient with multiple occurrences of an AE is counted only once in the AE category during each treatment period.

T Period = Treatment Period.

Serious Adverse Events and Deaths

No. of subjects studied	37
No. (%) of subjects with AE(s)	33 (89%)
Number (%) of subjects with serious or other significant events	n (%)
Death	0 (0.0%)
SAE(s)	1 (2.7%)
Discontinued due to SAE(s)	0 (0%)
Discontinued due to other significant events	3 (8.1%)

Other Relevant Findings

None

Date of Clinical Trial Report
12 OCT 2012

Date Inclusion on Novartis Clinical Trial Results Database
12 OCT 2012

Date of Latest Update
10 OCT 2012