Sponsor

Novartis

Generic Drug Name

Pradigastat (LCQ908)

Trial Indication(s)

Investigational

Protocol Number

CLCQ908C2201

Protocol Title

A multicenter, randomized, active comparator, placebo controlled, double-blind pilot study to assess the efficacy and safety of LCQ908 alone and in combination with fenofibrate or Lovaza® in patients with severe hypertriglyceridemia

Clinical Trial Phase

II

Phase of Drug Development

II

Study Start/End Dates

18-Jun-2012 to 13-Jul-2013

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multi-center, randomized, active comparator, double-blind, placebo-controlled, parallel-group, pilot phase 2 study to evaluate the efficacy and safety of pradigastat (5 mg, 20 mg, and 40 mg) once daily compared to placebo at 6 and 12 weeks of treatment, as well as the efficacy and safety of adding pradigastat 20 mg to

Lovaza® 4 gm or fenofibrate 145 mg in patients with multifactorial chylomicronemia (severe hypertriglyceridemia ≥750 mg/dL).

Centers

29 centers in 3 countries: Canada (2), Russia (2) and United States (25).

Publication

None

Objectives:

Primary objective

- To evaluate a dose response signal of 3 dose regimens of pradigastat (5 mg, 20 mg, 40 mg) in patients at risk for non-FCS chylomicronemia as measured by change from baseline in triglycerides (TG) relative to placebo at 6 weeks.

Secondary objectives

- To evaluate changes in TG after adding pradigastat 20 mg to background therapy of fenofibrate 145 mg or Lovaza® 4 gm at 12 weeks.
- To evaluate TG changes from baseline after treatment with pradigastat monotherapy (5 mg, 20 mg, 40 mg) relative to fenofibrate 145 mg or Lovaza® 4 gm at 6 weeks.
- To evaluate TG changes from baseline after treatment with pradigastat monotherapy (5 mg, 20 mg, and 40 mg) relative to placebo at 12 weeks.
- To evaluate TG changes from baseline after treatment with pradigastat monotherapy (5 mg, 20 mg, 40 mg) relative to the combination of pradigastat 20 mg with fenofibrate 145 mg and pradigastat 20 mg with Lovaza® 4 gm at 12 weeks.
- To assess the safety and tolerability of pradigastat monotherapy (5 mg, 20 mg, 40 mg) relative to placebo.
- To assess the safety and tolerability of pradigastat 20 mg added to background therapy of fenofibrate 145 mg or Lovaza® 4 gm relative to pradigastat 20 mg monotherapy and placebo.
- To determine change in lipids and lipoprotein profiles in the pradigastat monotherapy doses as well as when pradigastat 20 mg was added to background therapy of either fenofibrate 145 mg or Lovaza® 4 gm.
- To characterize the pharmacokinetics of pradigastat alone and in combination with fenofibrate 145 mg or Lovaza® 4 gm.

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

The test drug, pradigastat, was given in the form of 5 mg, 20 mg or 40 mg film coated tablets.

Patients in the pradigastat groups received oral doses of pradigastat (5 mg, 20 mg or 40 mg) once daily for 12 weeks.

Patients in the fenofibrate group received oral doses of fenofibrate (145 mg) once daily for first 6 weeks following which they received additional 20 mg pradigastat for the next 6 weeks. Similarly, patients in the Lovaza® group received oral doses of Lovaza® (4000 mg) once daily for first 6 weeks following which they received additional 20 mg pradigastat for the next 6 weeks. Fenofibrate (Tricor®) was given in the form of 145 mg hard gelatin capsules. Lovaza® was given in the form of 1000 mg soft gelatin capsules.

Patients in the placebo group received matching placebo tablets and capsules for entire 12 weeks.

Statistical Methods

Efficacy

Primary Endpoint

The primary endpoint was analyzed using Multiple Comparison Procedure-Modeling (MCPMod) in order to provide adequate multiplicity adjustment for the number of response models considered. The effects of baseline and region were taken into account in the model.

There were five candidate models to capture the shape of the dose response relationship for pradigastat at Week 6 endpoint. The candidate models generated a set of five contrasts which were evaluated using the data.

- Model 1: Emax with ED85 at 20 mg
- Model 2: Quadratic with maximum at 36 mg
- Model 3: Linear
- Model 4: Linear in log(dose) with offset 1.1
- Model 5: Exponential with ED50 = 30 mg

All tests were derived from an Analysis of Covariance (ANCOVA) model fitted to the log transformed ratios to baseline, including all treatment groups, with log transformed TG levels at baseline fitted as a covariate and treatment and region fitted as factors.

Secondary analysis of triglycerides

Change from baseline log-transformed TG at Week 12 endpoint was calculated. If the Week 12 value was missing, then the last value collected at Week 8 or later (i.e. in Epoch IV) was used for the analysis. The following comparisons were evaluated using analysis methods same as those for the primary endpoint (including the sensitivity analyses):

- Pradigastat 5 mg vs. placebo
- Pradigastat 20 mg vs. placebo
- Pradigastat 40 mg vs. placebo
- Fenofibrate + pradigastat 20 mg vs. placebo
- Lovaza® + pradigastat 20 mg vs. placebo
- Pradigastat 20 mg vs. fenofibrate + pradigastat 20 mg
- Pradigastat 40 mg vs. fenofibrate + pradigastat 20 mg
- Pradigastat 20 mg vs. Lovaza® + pradigastat 20 mg
- Pradigastat 40 mg vs. Lovaza® + pradigastat 20 mg

In order to estimate the additional efficacy of pradigastat when added to background therapy, the following analyses were carried out.

Change from baseline log transformed TG at Week 6 and Week 12 for the treatment groups (i) placebo, (ii) Lovaza® + pradigastat and (iii) Fenofibrate + pradigastat were analyzed using a mixed effects model. Factors for week and treatment were fitted as fixed effects in the model. Patients were fitted as a random effect. The compound symmetry variance-covariance structure was used.

Using the model treatment comparisons were estimated and 90% confidence intervals were presented for fenofibrate + pradigastat 20 mg vs fenofibrate and Lovaza® + pradigastat 20 mg vs Lovaza®

Analysis of other fasting lipids (Total cholesterol, HDL-C, nonHDL-C)

The % change from baseline and the log-transformed ratio to baseline were calculated for each of the other fasting lipids for each post-dose time point (Weeks 2, 4, 6, 8, 10 and 12) and also for Week 6 endpoint and Week 12 endpoint (using the same definition as for the primary endpoint).

Percentage changes from baseline in total cholesterol and HDL-C at Week 6 endpoint and at Week 12 endpoint were analyzed using ANCOVA with treatment, region and baseline included in the model. The same treatment comparisons were provided as for the analysis of fasting TGs. Log-transformed ratios to baseline for total cholesterol, HDL-C, and non-HDL-C at Week 6 and 12 were analyzed using the same method as described above but including log-transformed baseline as a covariate in the model.

Analysis of fasting lipoproteins and separated fractions from ultracentrifugation

The % change from baseline and the log-transformed ratio to baseline were calculated for each of the variables for each post-dose time point (Weeks 6 and 12).

Log-transformed ratios to baseline for ApoB48, ApoB100, CM-TG, and VLDL-TG at Week 6 and 12 were analyzed using the same method as described for log-transformed fasting lipids:

Safety

The number (and proportion) of patients with treatment emergent AEs were summarized in the following ways:

- by primary system organ class, preferred term, maximum severity and treatment
- by Standardized MedDRA Query (SMQ), preferred term and treatment

Separate summaries were provided for study medication related AEs, death, SAE, other significant AEs leading to discontinuation and AEs leading to dose adjustment. Specialized analyses were performed for diarrhea related AEs and pancreatitis Summary statistics of change from baseline laboratory results were provided over time by treatment. Shift tables based on the normal laboratory ranges were also provided. The number and percentage of subjects with clinically notable laboratory results after baseline were presented. Summary statistics of change from baseline were presented for Vitamin D and Vitamin E over time by treatment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

Male and female non-fertile patients aged more than 18 years, who had plasma TG ≥750 mg/dL after 3-4 weeks on an American Heart Association (AHA) diet, and provided written informed consent. They had a history of plasma TG concentration ≥890 mg/dl or history of lactescent plasma in the fasting state.

Exclusion Criteria:

- Treatment with omega-3 fatty acids or niacin or fibrates within 4 weeks of screening
- Treatment with antiretrovirals, cyclophosphamide, isotretinoin, bile acid binding resins (i.e., colesevelam, etc.), systemic steroids or pharmacologic doses of oral glucocorticosteroids within 4 weeks of screening.
- Patients with confirmed FCS with hyperlipoproteinemia (HLP) Type-I diagnosis or known to be homozygotes or compound heterozygotes for mutations in HLP Type I-causing genes (such as LPL, apoCII, GPIHBP1, or LMF1) prior to screening

- Pancreatitis within 3 months prior to screening,
- Uncontrolled T2DM (as defined by an hemoglobin A1c [HbA1c] value of ≥9.0% at screening),
- Inflammatory bowel disease, Crohn's disease or ulcerative colitis, any GI surgery within 12 weeks of screening,
- History of known allergy to fish/shellfish or any of the ingredients of Lovaza®, as per the Unites States (US) Lovaza® prescribing information

Participant Flow Table

Patient disposition – n (%) of patients (Full analysis set)

Disposition/Reason	LCQ908 5 mg N=11 n (%)	LCQ908 20 mg N=9 n (%)	LCQ908 40 mg N=9 n (%)	Fenofibrate (from Week 6 + LCQ908 20 mg) N=10 n (%)	Lovaza (from Week 6 + LCQ908 20 mg) N=10 n (%)	Placebo N=9 n (%)	Total N=58 n (%)
Completed phase	9 (81.8)	6 (66.7)	4 (44.4)	8 (80.0)	7 (70.0)	4 (44.4)	38 (65.5)
Discontinued prior to phase completion	2 (18.2)	3 (33.3)	5 (55.6)	2 (20.0)	3 (30.0)	5 (55.6)	20 (34.5)
Primary reason for not completing study phase							
Adverse event	0	2 (22.2)	5 (55.6)	0	3 (30.0)	3 (33.3)	13 (22.4)
Lost to follow-up	0	0	0	0	0	1 (11.1)	1 (1.7)
Protocol deviation	0	0	0	0	0	1 (11.1)	1 (1.7)
Subject/Guardian decision	2 (18.2)	0	0	2 (20.0)	0	0	4 (6.9)
Technical problems	0	1 (11.1)	0	0	0	0	1 (1.7)

Baseline Characteristics

Demographic and baseline characteristics by treatment group (Full analysis set)

Demographic variable	LCQ908 5 mg N=11	LCQ908 20 mg N=9	LCQ908 40 mg N=9	Fenofibrate (from Week 6 + LCQ908 20 mg) N=10	Lovaza (from Week 6 + LCQ908 20 mg) N=10	Placebo N=9	Total N=58
Sex, n (%)							
Male	10 (90.9)	6 (66.7)	6 (66.7)	9 (90.0)	9 (90.0)	7 (77.8)	47 (81.0)
Female	1 (9.1)	3 (33.3)	3 (33.3)	1 (10.0)	1 (10.0)	2 (22.2)	11 (19.0)
Age (years)							
n	11	9	9	10	10	9	58
Mean	48.5	46.3	51.2	51.2	49.2	49.9	49.4
SD	9.61	12.36	8.48	11.37	12.12	12.10	10.71
Min	36	31	32	37	27	33	27
Median	47.0	43.0	52.0	49.0	50.0	47.0	49.0
Max	66	65	61	77	63	70	77
Age category, n (%)							
< 65 years	10 (90.9)	8 (88.9)	9 (100)	9 (90.0)	10 (100)	7 (77.8)	53 (91.4)
≥ 65 years	1 (9.1)	1 (11.1)	0	1 (10.0)	0	2 (22.2)	5 (8.6)
Race, n (%)							
Caucasian	11 (100)	9 (100)	8 (88.9)	9 (90.0)	8 (80.0)	7 (77.8)	52 (89.7)
Black	0	0	0	0	1 (10.0)	0	1 (1.7)
Asian	0	0	0	1 (10.0)	0	0	1 (1.7)
Pacific Islander	0	0	0	0	0	1 (11.1)	1 (1.7)
Other	0	0	1 (11.1)	0	1 (10.0)	1 (11.1)	3 (5.2)
Ethnicity, n (%)							
Hispanic or Latino	1 (9.1)	2 (22.2)	1 (11.1)	2 (20.0)	1 (10.0)	4 (44.4)	11 (19.0)
Southeast Asian	0	0	0	1 (10.0)	0	0	1 (1.7)
Russian	3 (27.3)	2 (22.2)	2 (22.2)	2 (20.0)	2 (20.0)	2 (22.2)	13 (22.4)
Mixed ethnicity	0	1 (11.1)	1 (11.1)	1 (10.0)	0	0	3 (5.2)
Not reported	1 (9.1)	0	2 (22.2)	0	1 (10.0)	0	4 (6.9)
Unknown	2 (18.2)	0	0	0	1 (10.0)	1 (11.1)	4 (6.9)
Other	4 (36.4)	4 (44.4)	3 (33.3)	4 (40.0)	5 (50.0)	2 (22.2)	22 (37.9)
Height (cm)							
n	11	9	9	10	10	9	58
Mean	175.40	169.41	169.85	170.27	176.92	169.81	172.12
SD	7.098	15.800	9.315	7.255	9.579	11.727	10.378
Weight (kg)							
n	11	9	9	10	10	9	58
Mean	96.61	97.86	90.13	82.10	104.00	83.64	92.56
SD	15.921	23.357	18.560	10.893	19.631	19.958	19.188
BMI (kg/m^2)							
n	11	9	9	10	10	9	58
Mean	31.31	33.69	31.13	28.35	33.06	28.73	31.04
SD	4.068	3.782	5.710	3.785	4.392	4.533	4.651
BMI category, n (%)							
<30 kg/m^2	4 (36.4)	2 (22.2)	4 (44.4)	7 (70.0)	2 (20.0)	5 (55.6)	24 (41.4)
≥30 kg/m^2	7 (63.6)	7 (77.8)	5 (55.6)	3 (30.0)	8 (80.0)	4 (44.4)	34 (58.6)
Waist circumference (cm)							
n	11	9	9	10	10	9	58
Mean	107.13	107.92	103.10	97.37	110.19	100.56	104.45
SD	10.651	15.667	14.869	7.997	10.973	12.307	12.502
Systolic BP (mmHg)							
n	11	9	9	10	10	9	58
Mean	135.7	127.3	127.0	126.9	140.0	136.0	132.3
SD	12.26	7.40	16.64	11.75	8.45	14.20	12.75

Demographic variable	LCQ908 5 mg N=11	LCQ908 20 mg N=9	LCQ908 40 mg N=9	Fenofibrate (from Week 6 + LCQ908 20 mg) N=10	Lovaza (from Week 6 + LCQ908 20 mg) N=10	Placebo N=9	Total N=58
Diastolic BP (mmHg)							
n	11	9	9	10	10	9	58
Mean	84.1	76.7	80.0	85.3	81.6	79.1	81.3
SD	5.92	5.34	11.14	9.13	7.01	9.14	8.30
Heart rate (beats/min)							
n	11	9	9	10	10	9	58
Mean	69.1	72.7	66.9	68.3	69.0	67.6	68.9
SD	11.38	8.83	12.13	7.18	10.55	12.51	10.26
Type II diabetes, n (%)							
Yes	3 (27.3)	4 (44.4)	3 (33.3)	3 (30.0)	4 (40.0)	4 (44.4)	21 (36.2)
No	8 (72.7)	5 (55.6)	6 (66.7)	7 (70.0)	6 (60.0)	5 (55.6)	37 (63.8)
Statin use, n (%)							
Yes	2 (18.2)	4 (44.4)	1 (11.1)	2 (20.0)	3 (30.0)	1 (11.1)	13 (22.4)
No	9 (81.8)	5 (55.6)	8 (88.9)	8 (80.0)	7 (70.0)	8 (88.9)	45 (77.6)
eGFR (mL/min/1.73 m^2)							
n	11	9	9	10	10	9	58
Mean	94.7	85.0	89.3	88.7	83.8	91.3	88.9
SD	26.54	13.03	26.44	14.91	13.94	24.16	20.19

Demography information is collected on the day of the screening measurement (Visit 1, screening).
Body Mass Index: BMI (kg/m^2) = weight (kg) / height $(m)^2$

Summary of Efficacy

Primary Outcome Result(s)

Evaluation of significant contrasts using MCPMod from analysis of percent change from baseline in fasting triglycerides at Week 6 endpoint (Full Analysis Set)

Model	T-statistic	Adjusted 1-sided P-value	Adjusted 2-sided P-value	AIC
Exponential	0.77	0.333	0.657	71.3
Linear	0.69	0.365	0.716	69.4
Quadratic	0.47	0.453	0.862	71.1
Linear in log-dose	0.03	0.636	1.000	69.8
Emax	-0.30	0.756	0.950	71.5

Ordered by decreasing magnitude of t-statistic. Multiple Comparison procedure-modeling (MCPMod) was used for analysis. Log transformed ratio to baseline fasting triglycerides were analyzed.

- The t-statistic with the largest value establishes proof of efficacy.

- AIC: Akaike information criterion.

Note: Statistical significance is established if the one-sided p-value is ≤ 0.05 (2-sided p-value ≤ 0.1)

Between treatment analysis of percent change from baseline in fasting triglycerides derived from MCPMod analysis at Week 6 endpoint (Full Analysis Set)

					%change from reference Treatment		
Treatment	n	Baseline Geometric Mean	%Change from Baseline Geometric Adjusted mean	Reference Treatment	Estimate	(90% CI)	1-sided p-value
LCQ908 5 mg[1]	11	1450.6	-9.3	vs. Placebo[1]	-2.8	(-19.5, 14.4)	0.289
LCQ908 20 mg[1]	9	1127.4	-13.6	vs. Placebo[1]	-9.0	(-33.0, 30.7)	0.288
LCQ908 40 mg[1]	9	1064.5	-19.0	vs. Placebo[1]	-14.8	(-38.3, 24.8)	0.241
Fenofibrate[2]	10	1247.0	-66.3	vs. Placebo[1]	-64.2	(-74.2, -50.4)	<.001
Lovaza[2]	10	971.7	-31.8	vs. Placebo[1]	-27.6	(-47.7, 1.0)	0.056
Placebo[1]	9	1053.0	-5.7				
LCQ908 5 mg[1]	11	1450.6	-9.3	vs. Fenofibrate[2]	169.2	(104.1, 255.7)	1.000
LCQ908 20 mg[1]	9	1127.4	-13.6	vs. Fenofibrate[2]	156.7	(89.8, 249.9)	1.000
LCQ908 40 mg[1]	9	1064.5	-19.0	vs. Fenofibrate[2]	140.5	(72.3, 237.9)	1.000
LCQ908 5 mg[1]	11	1450.6	-9.3	vs. Lovaza[2]	32.9	(0.1, 76.2)	0.951
LCQ908 20 mg[1]	9	1127.4	-13.6	vs. Lovaza[2]	26.7	(-6.8, 72.9)	0.899
LCQ908 40 mg[1]	9	1064.5	-19.0	vs. Lovaza[2]	18.8	(-15.2, 66.6)	0.800

					%change from reference Treatment		
Treatment	**n**	**Baseline Geometric Mean**	**%Change from Baseline Geometric Adjusted mean**	**Reference Treatment**	**Estimate**	**(90% CI)**	**1-sided p-value**

- Baseline mean shown only for subjects with baseline and post-baseline measurements.
- Baseline was the average of the values taken at day -7 (or the repeat measurement if the patient required an additional week of dietary lead-in) and randomization.
- Week 6 endpoint was the last non-missing post-baseline value collected on or prior to Week 6.
- p-values not adjusted for multiple comparisons.
CI = confidence intervals.
[1]Derived from dose response analysis, using MCPMod methodology. [2]Derived from ANCOVA Models were fitted to the log-transformed ratio to baseline values, with baseline log-transformed baseline as a covariate, treatment and region as factors.
- Adjusted geometric means were calculated by back-transforming the adjusted means from the model and expressed as a percentage change from baseline. The % change from Reference Treatment was calculated by back-transforming the difference in adjusted means from the model and presenting as a percentage..

Secondary Outcome Result(s)

Evaluation of significant contrasts using MCPMod from analysis of percent change from baseline in fasting triglycerides at Week 12 endpoint (Full Analysis Set)

Model	**T-statistic**	**Adjusted 1-sided P-value**	**Adjusted 2-sided P-value**	**AIC**
Exponential	1.42	0.137	0.273	46.0
Linear	1.19	0.198	0.395	46.1
Quadratic	0.78	0.336	0.662	45.1
Linear in log-dose	0.66	0.382	0.745	47.5
Emax	0.39	0.496	0.916	48.7

Ordered by decreasing magnitude of t-statistic. Multiple comparison procedure-modeling (MCPMod) is used for analysis. Log transformed ratio to baseline fasting triglycerides are analyzed.

- The t-statistic with the largest value establishes proof of efficacy.

- AIC: Akaike information criterion.

Between treatment analysis of percent change from baseline in fasting triglycerides derived from MCPMod analysis at Week 12 endpoint (Full Analysis Set)

				%change from reference Treatment			
Treatment	**n**	**Baseline Geometric Mean**	**%Change from Baseline Geometric Adjusted mean**	**Reference Treatment**	**Estimate**	**(90% CI)**	**1-sided p-value**
LCQ908 5 mg[1]	10	1545.7	8.1	vs Placebo[1]	-0.0	(-17.8, 33.9)	0.462
LCQ908 20 mg[1]	8	960.6	5.3	vs Placebo[1]	-1.8	(-35.1, 85.5)	0.453
LCQ908 40 mg[1]	6	1169.2	-25.3	vs. Placebo[1]	-28.5	(-54.8, 21.3)	0.127
Fenofibrate+ LCQ908 20 mg[1]	9	1335.7	-60.6	vs. Placebo[1]	-62.1	(-75.6, -39.7)	<.001
Lovaza+ LCQ908 20 mg[2]	10	971.7	-17.6	vs. Placebo[1]	-21.0	(-49.1, 26.2)	0.205
Placebo[1]	4	980.3	4.5				
LCQ908 20 mg[1]	8	960.6	5.3	vs. Fenofibrate+ LCQ908 20 mg[2]	171.3	(83.7, 320.0)	1.000
LCQ908 40 mg[1]	6	1169.2	-25.3	vs. Fenofibrate+ LCQ908 20 mg[2]	89.8	(20.1, 198.6)	0.990
LCQ908 20 mg[1]	8	960.6	5.3	vs. Lovaza+ LCQ908 20 mg[2]	29.8	(-11.2, 97.8)	0.865
LCQ908 40 mg[1]	6	1169.2	-25.3	vs. Lovaza+ LCQ908 20 mg[2]	-9.3	(-42.1, 42.1)	0.362

- Baseline mean shown only for subjects with baseline and post-baseline measurements.
- Baseline was the average of the values taken at day -7 (or the repeat measurement if the patient required an additional week of dietary lead-in) and randomization.
- Week 12 endpoint was the last non-missing post-baseline value collected on or prior to Week 12.
- p-values not adjusted for multiple comparisons.

CI = confidence intervals.

[1]Derived from dose response analysis, using MCPMod methodology. [2]Derived from ANCOVA Models were fitted to the log-transformed ratio to baseline values, with baseline log-transformed baseline as a covariate, treatment and region as factors.

- Adjusted geometric means were calculated by back-transforming the adjusted means from the model and expressed as a percentage change from baseline. The % change from Reference Treatment was calculated by back-transforming the difference in adjusted means from the model and presenting as a percentage.

Between treatment analysis of percent change from baseline for secondary efficacy variables (fasting lipids) at Week 12 endpoint (Full Analysis Set)

					%change from Placebo			
Parameter	Treatment	n	Baseline Median (mg/dL)	% Change from BL Adjusted mean (%)*	Reference treatment	Estimate	(90% CI)	2-sided p-value
LDL-C	LCQ908 5 mg	10	46.0	-31.5	vs. Placebo	-49.8	(-126.1, 26.6)	0.279
	LCQ908 20 mg	7	62.0	7.8	vs. Placebo	-10.4	(-89.8, 69.0)	0.827
	LCQ908 40 mg	6	39.0	-7.2	vs. Placebo	-25.4	(-107.7, 56.9)	0.606
	Fenofibrate + LCQ908 20 mg	9	53.0	133.6	vs. Placebo	115.4	(39.8, 191.0)	0.014
	Lovaza + LCQ908 20 mg	10	47.0	11.4	vs. Placebo	-6.8	(-83.1, 69.5)	0.881
	Placebo	4	72.0	18.2				
HDL-C	LCQ908 5 mg	10	24.5	7.2	vs. Placebo	5.2	(-16.3, 26.7)	0.687
	LCQ908 20 mg	8	31.5	17.2	vs. Placebo	15.2	(-7.0, 37.3)	0.256
	LCQ908 40 mg	6	26.5	13.3	vs. Placebo	11.3	(-11.7, 34.3)	0.412
	Fenofibrate + LCQ908 20 mg	9	27.0	40.0	vs. Placebo	38.0	(16.6, 59.5)	0.005
	Lovaza + LCQ908 20 mg	10	25.5	13.6	vs. Placebo	11.6	(-9.7, 32.9)	0.364
	Placebo	4	27.0	2.0				
Total cholesterol	LCQ908 5 mg	10	365.0	18.2	vs. Placebo	-28.1	(-57.1, 1.0)	0.111
	LCQ908 20 mg	8	236.0	17.9	vs. Placebo	-28.3	(-57.9, 1.2)	0.114
	LCQ908 40 mg	6	242.8	9.2	vs. Placebo	-37.0	(-67.2, -6.8)	0.046
	Fenofibrate + LCQ908 20 mg	9	314.0	-11.0	vs. Placebo	-57.2	(-86.0, -28.3)	0.002
	Lovaza + LCQ908 20 mg	10	236.5	-4.6	vs. Placebo	-50.9	(-78.6, -23.1)	0.004
	Placebo	4	208.5	46.2				
Non-HDL-C	LCQ908 5 mg	10	336.0	11.4	vs. Placebo	-15.3	(-37.9, 15.4)	0.371
	LCQ908 20 mg	8	199.5	8.3	vs. Placebo	-17.7	(-39.7, 12.4)	0.299
	LCQ908 40 mg	6	214.5	-0.9	vs. Placebo	-24.7	(-45.3, 3.7)	0.143
	Fenofibrate + LCQ908 20 mg	9	288.0	-23.6	vs. Placebo	-41.9	(-57.5, -20.6)	0.006
	Lovaza + LCQ908 20 mg	10	207.5	-15.2	vs. Placebo	-35.5	(-51.9, -13.6)	0.016
	Placebo	4	176.5	31.5				

Baseline median shown only for subjects with baseline and post-baseline measurements.
- Week 12 endpoint was the last non-missing post-baseline value collected on or after week 8 or on or prior to Week 12
- p-values not adjusted for multiple comparisons. SE= standard error, CI= confidence intervals
* For non-HDL-C, the mean % change from baseline was calculated by back-transforming the adjusted mean from the analysis of the log-transformed ratio to baseline values
$ For total cholesterol, HDL-C, and LDL-C the treatment comparison presented is the difference between the Adjusted Means from an analysis of % change from baseline. For non-HDL-C the treatment comparison presented is the relative % change from the reference group derived by back-transformation of the difference between Adjusted Means from an analysis of the log-transformed ratio to baseline.
All statistical models contained treatment and region as factors and baseline as a covariate (log-transformed as appropriate).

Between treatment analysis of percent change from baseline for secondary efficacy variables (relevant lipoprotein fractions) at Week 6 endpoint (Full Analysis Set)

Parameter	Treatment	n	Baseline Median (mg/dL)	% Change from BL Adjusted mean (%)*	%change from Reference Treatment: Reference treatment	Estim-ate	(90% CI)	2-sided p-value
ApoB48	LCQ908 5 mg	11	6.5	62.7	vs. Placebo	79.0	(7.5, 198.0)	0.062
	LCQ908 20 mg	9	4.4	33.1	vs. Placebo	46.5	(-13.1, 146.9)	0.226
	LCQ908 40 mg	8	5.0	-15.0	vs. Placebo	-6.5	(-45.7, 60.9)	0.836
	Fenofibrate	9	10.5	-57.7	vs. Placebo	-53.5	(-73.3, -19.0)	0.025
	Lovaza	10	4.5	-23.9	vs. Placebo	-16.2	(-49.8, 39.6)	0.563
	Placebo	9	4.4	-9.1				
ApoB100	LCQ908 5 mg	11	88.2	4.4	vs. Placebo	6.2	(-8.0, 22.5)	0.487
	LCQ908 20 mg	9	96.4	5.7	vs. Placebo	7.6	(-7.4, 24.9)	0.418
	LCQ908 40 mg	8	92.6	-5.4	vs. Placebo	-3.7	(-17.5, 12.3)	0.682
	Fenofibrate	9	114.6	5.5	vs. Placebo	7.3	(-7.7, 24.8)	0.437
	Lovaza	10	95.7	-6.1	vs. Placebo	-4.5	(-17.5, 10.5)	0.598
	Placebo	9	87.2	-1.7				
CM-TG	LCQ908 5 mg	11	594.0	52.4	vs. Placebo	117.3	(20.3, 292.7)	0.033
	LCQ908 20 mg	9	251.0	-5.8	vs. Placebo	34.3	(-27.9, 150.0)	0.430
	LCQ908 40 mg	8	586.0	-40.4	vs. Placebo	-15.0	(-55.1, 61.0)	0.672
	Fenofibrate	9	588.0	-78.3	vs. Placebo	-69.0	(-83.3, -42.4)	0.003
	Lovaza	10	286.5	-46.2	vs. Placebo	-23.3	(-58.1, 40.4)	0.465
	Placebo	9	643.0	-29.9				
VLDL-TG	LCQ908 5 mg	11	514.0	21.2	vs. Placebo	26.9	(-2.7, 65.5)	0.139
	LCQ908 20 mg	9	439.0	6.3	vs. Placebo	11.3	(-15.8, 47.1)	0.522
	LCQ908 40 mg	8	414.5	-1.0	vs. Placebo	3.8	(-22.0, 38.0)	0.829
	Fenofibrate	9	492.0	-47.8	vs. Placebo	-45.4	(-58.8, -27.5)	<0.001
	Lovaza	10	361.5	-16.1	vs. Placebo	-12.1	(-32.8, 15.1)	0.427
	Placebo	9	399.0	-4.5				

-Baseline median shown only for subjects with baseline and post-baseline measurements.
- Week 6 endpoint is the last non-missing post-baseline value collected on or prior to Week 6
- p-values not adjusted for multiple comparisons. CI= confidence intervals
* For ApoB48, CM-TG and VLDL-TG the mean % change from baseline was calculated by back-transforming the adjusted mean from the analysis of the log-transformed ratio to baseline values All statistical models contained treatment and region as factors and baseline as a covariate (log-transformed as appropriate).

The effects of fenofibrate and Lovaza® on the PK of pradigastat were inconclusive given the small sample size and high variability observed in the trough concentrations.

Summary of Safety

Safety Results

Number (%) of patients with AEs by primary system organ class over Weeks 0-12 (Safety set)

Primary system organ class	LCQ908 5 mg N=11 n (%)	LCQ908 20 mg N=9 n (%)	LCQ908 40 mg N=9 n (%)	Fenofibrate N=10 n (%)	Lovaza N=10 n (%)	Placebo N=9 n (%)	Total N=58 n (%)

Primary system organ class	LCQ908 5 mg N=11 n (%)	LCQ908 20 mg N=9 n (%)	LCQ908 40 mg N=9 n (%)	Fenofibrate N=10 n (%)	Lovaza N=10 n (%)	Placebo N=9 n (%)	Total N=58 n (%)
Any primary system organ class	7 (63.6)	6 (66.7)	9 (100)	2 (20.0)	3 (30.0)	4 (44.4)	31 (53.4)
Blood and lymphatic system disorders	1 (9.1)	0	0	0	0	1 (11.1)	2 (3.4)
Eye disorders	0	1 (11.1)	0	0	0	0	1 (1.7)
Gastrointestinal disorders	4 (36.4)	5 (55.6)	9 (100)	2 (20.0)	3 (30.0)	4 (44.4)	27 (46.6)
General disorders and administration site conditions	1 (9.1)	1 (11.1)	0	0	0	0	2 (3.4)
Hepatobiliary disorders	0	0	0	0	0	1 (11.1)	1 (1.7)
Infections and infestations	2 (18.2)	2 (22.2)	2 (22.2)	0	0	0	6 (10.3)
Injury, poisoning and procedural complications	0	0	0	0	0	1 (11.1)	1 (1.7)
Investigations	2 (18.2)	0	0	0	0	0	2 (3.4)
Metabolism and nutrition disorders	0	1 (11.1)	0	0	0	0	1 (1.7)
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (10.0)	1 (11.1)	2 (3.4)
Nervous system disorders	1 (9.1)	1 (11.1)	0	0	0	2 (22.2)	4 (6.9)
Psychiatric disorders	0	1 (11.1)	1 (11.1)	0	0	1 (11.1)	3 (5.2)
Reproductive system and breast disorders	0	0	1 (11.1)	0	0	0	1 (1.7)
Respiratory, thoracic and mediastinal disorders	0	1 (11.1)	0	0	0	0	1 (1.7)
Skin and subcutaneous tissue disorders	0	1 (11.1)	0	0	0	1 (11.1)	2 (3.4)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE category for that treatment group.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
MedDRA version 16.0 has been used for the reporting of adverse events.

Number (%) of patients reporting common AEs (greater than or equal to 15% in any group) by preferred term over Week 0-12 (Safety set)

Preferred term	LCQ908 5 mg N=11 n (%)	LCQ908 20 mg N=9 n (%)	LCQ908 40 mg N=9 n (%)	Fenofibrate (from Week 6 + LCQ908 20 mg) N=10 n (%)	Lovaza (from Week 6 + LCQ908 20 mg) N=10 n (%)	Placebo N=9 n (%)	Total N=58 n (%)
Number of patients with at least one AE	9 (81.8)	9 (100)	9 (100)	7 (70.0)	8 (80.0)	6 (66.7)	48 (82.8)
Diarrhoea	7 (63.6)	7 (77.8)	9 (100)	6 (60.0)	6 (60.0)	2 (22.2)	37 (63.8)
Abdominal pain	1 (9.1)	1 (11.1)	3 (33.3)	0	1 (10.0)	0	6 (10.3)
Nausea	1 (9.1)	1 (11.1)	3 (33.3)	2 (20.0)	5 (50.0)	3 (33.3)	15 (25.9)

Preferred term	LCQ908 5 mg N=11 n (%)	LCQ908 20 mg N=9 n (%)	LCQ908 40 mg N=9 n (%)	Fenofibrate (from Week 6 + LCQ908 20 mg) N=10 n (%)	Lovaza (from Week 6 + LCQ908 20 mg) N=10 n (%)	Placebo N=9 n (%)	Total N=58 n (%)
Eructation	1 (9.1)	0	2 (22.2)	0	2 (20.0)	0	5 (8.6)
Abdominal pain upper	2 (18.2)	0	1 (11.1)	1 (10.0)	3 (30.0)	1 (11.1)	8 (13.8)
Constipation	0	1 (11.1)	1 (11.1)	1 (10.0)	2 (20.0)	0	5 (8.6)
Flatulence	2 (18.2)	0	1 (11.1)	1 (10.0)	2 (20.0)	0	6 (10.3)
Nasopharyngitis	1 (9.1)	2 (22.2)	1 (11.1)	0	1 (10.0)	0	5 (8.6)
Abdominal discomfort	1 (9.1)	0	0	0	2 (20.0)	0	3 (5.2)
Abdominal distension	2 (18.2)	0	0	0	3 (30.0)	1 (11.1)	6 (10.3)
Dehydration	0	0	0	0	2 (20.0)	0	2 (3.4)
Dyspepsia	2 (18.2)	0	0	1 (10.0)	1 (10.0)	0	4 (6.9)
Gastroesophageal reflux disease	0	0	0	0	2 (20.0)	1 (11.1)	3 (5.2)

A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE category.
Preferred terms are sorted by descending order of incidence in the LCQ908 40 mg group.
MedDRA version 16.0 has been used for the reporting of adverse events.

Deaths, serious or non-serious adverse events or related discontinuations — n (%) of patients (Safety set)

	LCQ908 5 mg N=11 n (%)	LCQ908 20 mg N=9 n (%)	LCQ908 40 mg N=9 n (%)	Fenofibrate (from Week 6 + LCQ908 20 mg) N=10 n (%)	Lovaza (from Week 6 + LCQ908 20 mg) N=10 n (%)	Placebo N=9 n (%)	Total N=58 n (%)
Patients with AE(s)	9 (81.8)	9 (100)	9 (100)	7 (70.0)	8 (80.0)	6 (66.7)	48 (82.8)
Serious or other significant events							
Death	0	0	0	0	0	0	0
At least one SAE	0	0	1 (11.1)	0	1 (10.0)	1 (11.1)	3 (5.2)
Discontinued due to SAE(s)	0	0	1 (11.1)	0	0	1 (11.1)	2 (3.4)
Discontinued due to non-serious AE(s)	0	2 (22.2)	4 (44.4)	0	3 (30.0)	2 (22.2)	11 (19.0)

Other Relevant Findings

Not applicable

Conclusion:

- The primary efficacy objective for this study was not met. A dose response signal in fasting TG reduction could not be demonstrated with 3 doses of pradigastat (5 mg, 20 mg, and 40 mg) in patients with multifactorial chylomicronemia.
- The placebo-adjusted reduction in fasting TG at Week 6 ranged from 2.8% to 14.8% for the three pradigastat doses. None of these reductions was statistically significant.
- Fenofibrate 145 mg and Lovaza® 4 gm were associated with placebo-adjusted reductions in fasting TG by 64.2% ($p<0.001$) and 27.6% ($p=0.056$), respectively, at Week 6.
- Additional non-significant fasting TG reductions by 26.6% and 18.3% were observed after adding pradigastat 20 mg to background therapy of fenofibrate 145 mg or Lovaza® 4 gm, respectively, from Week 6 to Week 12.
- Safety and tolerability data confirmed that the most common AEs for pradigastat are GI related, with a dose related increase in the frequency and severity of diarrhea.
- Pradigastat failed to demonstrate a dose proportional increase in exposure from 5 mg to 40 mg in this study. The exposure at 40 mg was lower than 20 mg over the 12 week treatment period.

Date of Clinical Trial Report

27 FEBRUARY 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

26 JUNE 2014

Date of Latest Update

16 JUNE 2014

Reason for Update

Not applicable