COLT, Multicenter CaPre® Open Label Randomized Dose-Ranging Phase II Trial to Assess Efficacy/Safety in Patients with Mild-to-High Hypertriglyceridemia

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Abstract

Background: Long-chain polyunsaturated omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to reduce hepatic secretion of TG rich lipoproteins and plasma TG levels. CaPre® is a novel highly purified omega-3 krill oil extract with a high content of EPA and DHA phospholipid conjugates.

Objective/Purpose: To evaluate the efficacy of CaPre® to reduce fasting plasma TG ranging between 200-877 mg/dL after 4 and 8 weeks vs. Standard Of Care (SOC). Additional endpoints were changes in TC, LDL-C, HDL-C, non-HDL-C, and HbA1c.

Methods: Total of 288 patients from 34 centers aged 18-75 were randomized to Standard of Care (SOC), or CaPre® given daily with dose doubling at week 4 for 0.5g, 1g, and 2g groups while the 4g group was dosed for 8 weeks. Standard safety assessments were performed during the trial. Statistical analysis was performed using ANOVA followed by post-hoc contrast analysis assessing % change between baseline, week 4 and 8 with CaPre® compared to SOC.

Results: CaPre® SOC-compared 4-week TG % difference was -8% (p=NS), -16% (p=0.007), -13% (p=0.025) and -18% (p=0.002), for 0.5g, 1g, 2g, and 4g, respectively, while the SOC-compared 8-week TG % difference was 2% (p=NS), 16% (p=0.021), -6% (p=NS) and -14% (p=0.038), for 0.5g, 1g, 2g, and 4g, respectively. CaPre® 4g SOC-compared 8-week TC % difference was -7% (p=0.06) and while the non-HDL-C was -10% (p=0.036). Similarly to beneficial lipid effects, HbA1c was significantly lowered with CaPre® 2g (-18%, p=0.013) and 4g (-15%, p=0.039). CaPre® was safe, well-tolerated, with incidence of AEs similar to SOC.

Conclusions: CaPre® at daily doses of 1g-4g was effective and safe in reducing serum triglycerides and increasing HDL-C without deleterious effects on increasing LDL-C in patients with mild-to-high hypertriglyceridemia (NCT01516151).

Introduction

Many health organizations, such as American Heart Association (AHA), American College of Cardiology, US National Cholesterol Education Program (NCEP) Third Adult Treatment Panel (ATP III), and the European Society of Cardiology have issued recommendations to increase the intake of omega-3 fatty acids above the typical level of consumption in the diets of most developed countries [Harris 2008]. For secondary prevention in patients with established CHD, the AHA recommends increasing intake of EPA + DHA to 1 g/day in the form of oily fish or fish oil capsules; and for individuals with hypertriglyceridemia, the recommendation is 2–4 g/day under the supervision of a physician. There are currently at least four prescription-grade omega-3 products available or in development, Lovaza® (capsules contain DHA, EPA, and other fish oils in the form of the ethyl ester), Vascepa® (contains only synthetic derivative of EPA), Epanova® (capsules contain EPA and DHA in their free fatty acid form) and CaPre®, which is the prescription drug candidate of Acasti Pharma composed of a highly purified EPA- and DHA-phospholipid concentrate derived from krill oil.

Serum triglycerides had continued to rise until about 2005, when decreases began to be observed [National Center for Health Statistics 2013; Cohen 2010]. The increase in prevalence of hypertriglyceridemia in the United States and globally, correlates to the increasing incidence of obesity and diabetes. It is estimated that one-third of the population in the United States has elevated levels of triglycerides, including over 40 million people diagnosed with mild to moderate hypertriglyceridemia and over 4 million people diagnosed with severe hypertriglyceridemia. According to the AHA Scientific Statement on Triglycerides and Cardiovascular Disease [Miller 2011], triglyceride levels provide important information as a marker associated with the risk for heart disease and stroke, especially when an individual also has low HDL-C and elevated levels of LDL-C. Lowering triglyceride levels is one of the primary goals to reduce a patient's risk of atherosclerotic cardiovascular disease. Hypertriglyceridemia is due to both genetic and environmental factors, including obesity, sedentary lifestyle and high-calorie diets and is also associated with comorbid conditions such as diabetes, chronic renal failure, pancreatitis and nephrotic syndrome. A meta-analysis including 29 prospective studies showed a 72% higher risk (adjusted odds ratio of 1.72) of coronary heart disease for the patients with triglyceride levels greater than or equal to 200 mg/dL compared to those with normal triglyceride levels [Sawar 2007]. The conclusion of the study was that there are moderately strong associations between triglyceride levels and cardiovascular disease risk.

The first-line drug therapy in patients with severe hypertriglyceridemia is often a prescription omega-3 fatty acid, niacin or fibrates as adjunct to therapeutic life style changes. However, niacin is not well tolerated and safety may be an issue with fibrates especially when used in combination with a statin [Oh 2007, Bradberry 2013]. Lovaza® and Vascepa® are two omega-3 fatty acids derived from fish oil that are currently approved for treatment of severe hypertriglyceridemia in the United States, while Epanova® is under FDA review.

CaPre®, a new investigational new drug is a highly purified EPA- and DHA-phospholipid concentrate derived from krill oil that is being developed as a prescription drug for the treatment of hypertriglyceridemia. The drug substance, NKPL66, is an omega-3 phospholipid concentrate composed of approximately 66% in total phospholipids and at least 30% in omega-3 (total EPA/DHA). The active constituents consist of EPA and DHA, including the omega-3 phospholipid conjugates as well as EPA and DHA as fatty acids. EPA and DHA in krill oil are mainly carried by phospholipids, while EPA and DHA derived from fish oil are mainly carried by triglycerides which may lead to better bioavailability and distribution with CaPre® compared to other omega-3 sources [Schuchardt 2011].

Objectives

The primary outcome measure of the study was the percent change in serum triglycerides after 4 weeks of treatment in patients with mild-to-high hypertriglyceridemia (200-877 mg/dL) as compared to the standard of care (SOC) alone.

Secondary outcomes included:

- To evaluate the efficacy of 4.0g/ day of CaPre® in reducing fasting plasma serum TGs over an 8-week period in patients with mild-to-high hypertriglyceridemia as compared to the SOC alone;
- To assess and compare the effect of dose doubling from 0.5 to 1.0g / day, 1.0 to 2.0g / day, 2.0 to 4.0g / day over two consecutive 4 week periods and SOC on fasting plasma serum TG;
- To evaluate and compare the effect of four weeks of treatment with 0.5, 1.0, 2.0 and 4.0g per day and eight weeks of treatment with 4.0 g/ day of CaPre® to SOC on the changes in fasting plasma serum LDL-C (direct measurement), HDL-C, hs-CRP and glucose tolerance;
- To assess and compare the effect of dose doubling from 0.5 to 1.0g / day, 1.0 to 2.0g / day and 2.0 to 4.0g / day and standard of care over two consecutive 4 week periods on fasting plasma serum LDL-C (direct measurement), HDL-C, hs-CRP and glucose tolerance;
- To assess the tolerability and safety of a 4-week treatment with 0.5, 1.0, 2.0 and 4.0g/day and 8 week treatment with 4.0g/day of CaPre®;
- To assess the safety and tolerability of dose doubling from 0.5 to 1.0g / day, 1.0 to 2.0 / day and 2.0 to 4.0g / day of CaPre® over two consecutive 4-week periods.

Methods

The COLT study was a phase 2, prospective, randomized, open-label, dose-ranging, multi-center, 8-week clinical trial conducted at in 259 with mild-to-high hypertriglyceridemia (TG between 200-877 mg/dL) patients from 34 Canadian sites from December 2011 through June 2013. The protocol was approved by institutional review boards and all patients underwent the informed consent process before enrollment, as evidenced by their written informed consent. The clinical trial registration number was NCT01516151 (available at: http://clinicaltrials.gov/show/NCT01516151).

Subjects were randomized in a 1:1:1:1:0.3 ratio to the CaPre® 0.5g, CaPre® 1g, CaPre® 2g, CaPre® 4g or SOC groups, respectively and as follow:

- CaPre® 0.5 g per day for 4 weeks followed by CaPre® 1.0 g daily for the next 4 weeks (0.5 – 1.0g),
- CaPre® 1.0 g per day for 4 weeks followed by CaPre® 2.0 g daily for the next 4 weeks (1.0 – 2.0g),
- CaPre® 2.0 g per day for 4 weeks followed by CaPre® 4.0 g daily for the next 4 weeks (2.0 – 4.0g), and
- CaPre® 4.0 g per day for 8 weeks (4.0 – 4.0g).
- Standard of Care (SOC) as defined by weight reduction, dietary modification and exercise, as well as pharmacological treatment (statins or ezetimibe only) following current Canadian Guidelines for the treatment of hypertriglyceridemia [Yuan 2011]. Treating physicians had the option of changing SOC treatment options at week 4 of the study if deemed warranted.

The dosing regimens consisted of 2-week lead-in on the NCEP Step 1 Diet, on which subjects remained until the end of the study. Standard safety measurements were conducted through blood sampling (hematology, biochemistry and coagulation) as well as medical examinations including extensive physical examination, blood pressure assessment and ECG.

Statistical analysis was performed using ANOVA followed by post-hoc contrast analysis assessing % change between baseline, weeks 4 and 8 with CaPre® compared to SOC. To further analyze the data, multiple linear regression and general linear models using terms for the treatment group, baseline TG and potential confounders identified by the comparison of baseline characteristics among groups will be used to produce adjusted estimates of between group differences with respect to primary efficacy measure. Sample size considerations were based on the assumption that the percent change in TGs for the SOC, 0.5g, 1.0g, 2.0g and 4.0g CaPre® doses were -5%, -15%, -20% and -25%. A total of 230 evaluable patients were required for 80% power and 5% significance assuming a ratio of SOC to CaPre® patients of 1.7. Specifically there were 30 patients in the SOC group and 50 patients each in the four CaPre® groups.

Table 1: Patient Demographics of All Subjects Enrolled in the Study

			Groups				
			SOC	0.5 - 1.0 g	1.0 - 2.0 g	2.0 - 4.0 g	4.0 - 4.0 g
Age (Years)	Total N		29	52	56	57	62
	Mean ± SD		53.9 ± 11.8	53.4 ± 10.1	52.7 ± 11.0	55.4 ±12.0	54.5 ± 10.7
Gender	Female	N	13	20	29	24	31
		%	44.8%	38.5%	51.8%	42.1%	50.0%
	Male	N	16	32	27	33	31
		%	55.2%	61.5%	48.2%	57.9%	50.0%
Race	Caucasian	N	26	47	52	50	55
		%	89.7%	90.4%	92.9%	87.7%	88.7%
	Others	N	3	5	4	7	7
		%	10.3%	9.6%	7.1%	12.3%	11.3%
Diabetes	Yes	N	2	5	5	15	11
		%	6.9%	9.6%	8.9%	26.3%	17.7%
Statin use	Yes	N	15	13	16	22	22
		%	51%	25%	29%	39%	36%

Table 2: Serum Triglycerides Mean Percent Change over 4 Weeks versus Baseline

Parameter	SOC[a]			0.5g			1.0g			2.0g			4.0g		
	N=29			N=52			N=56			N=57			N=62		
	BL	W4	Mean % Change	BL	W4	Mean % Change	BL	W4	Mean % Change	BL	W4	Mean % Change	BL	EOT	Mean % Change
Triglycerides[b] (mg/dL)	364.0	346.0	+2.5	388.8	358.4	-5.2[c]	395.0	336.2	**-13.7[d]**	339.2	293.8	**-10.1[e]**	341.0	278.8	**-15.4[f]**

Values are presented as Means. BL = Baseline, W4 = week 4, Mean % change = Unadjusted mean percent change from BL; [a]Standard of Care (SOC), CaPre® 0.5 g per day for 4 weeks, CaPre® 1.0 g for 4 weeks, CaPre® 2.0 g for 4 weeks, and CaPre® 4.0 g for 4 weeks; [b]TG mean % difference between all CaPre® groups and SOC (-13.6 %, p-value= 0.009); [c]TG mean SOC-compared % difference (-7.7 %, p-value= 0.210); [d]TG mean SOC-compared % difference (-16.2 %, p-value= 0.007); [e]TG mean SOC-compared % difference (-12.7%, p-value=0.025); [f]TG mean SOC-compared % difference (-18.0%, p-value= 0.002).

Table 3: Lipid and Glycemic Parameters Mean Percent Change Over 8 Weeks versus Baseline

Parameter	SOC[a]			0.5-1.0g			1.0- 2.0g			2.0-4.0g			4.0g		
	N=29			N=52			N=56			N=57			N=62		
	BL	EOT	Mean % Change	BL	EOT	Mean % Change	BL	EOT	Mean % Change	BL	EOT	Mean % Change	BL	EOT	Mean % Change
Triglycerides[b] (mg/dL)	364.0	330.4	-7.1	388.8	347.2	-8.8[c]	395.0	300.3	**-23.3[d]**	339.2	279.9	-13.6[e]	341.0	257.8	**-21.6[f]**
Total Cholesterol (mg/dL)	211.5	207.7	-1.5	223.1	209.6	-4.1	212.7	203.0	-3.1	204.6	198.8	0.4	215.0	195.3	**-8.4[g]**
LDL-C (mg/dL)	112.9	114.1	3.3	126.1	115.2	-6.6	106.3	106.3	8.8	113.0	109.8	6.5	125.7	116.0	-7.2
HDL-C[h] (mg/dL)	42.2	43.3	2.6	45.2	41.8	4.1	38.3	42.2	10.0	44.5	46.4	5.4	40.6	44.1	**10.4[i]**
Non-HDL-C (Calculated) (mg/dL)	169.4	164.4	-2.3	177.9	167.8	-5.6	174.4	160.9	-5.7	160.1	152.4	-0.3	174.4	151.2	**-12.0[j]**
HbA1c (%)	4.14	4.19	11.5	4.7	4.8	4.9	4.6	4.8	7.9	5.21	4.81	**-6.8[k]**	4.9	4.6	**-3.5[l]**
Glucose (mg/dL)	98.8	99.0	0.0	97.2	96.5	3.9	94.9	92.2	-1.4	104.8	105.3	1.2	102.4	105.1	2.6

Values are presented as Means. BL= Baseline, EOT= End of treatment, Mean % change = Unadjusted mean percent change from BL; [a]Standard of Care (SOC), CaPre® 0.5 g per day for 4 weeks followed by CaPre® 1.0 g for the next 4 weeks (0.5 – 1.0g), CaPre® 1.0 g for 4 weeks followed by CaPre® 2.0 g for the next 4 weeks (1.0 – 2.0g), CaPre® 2.0 g for 4 weeks followed by CaPre® 4.0 g for the next 4 weeks (2.0 – 4.0g), and CaPre® 4.0 g for 8 weeks (4.0 – 4.0g); [b]TG mean % difference between all CaPre® groups and SOC (-15.2 %, p-value = 0.015); [c]TG mean SOC-compared % difference (-1.7%, p-value=0.81); [d]TG mean SOC-compared % difference (-16.2 %, p-value= 0.021); [e]TG mean SOC-compared % difference (-6.5%, p-value=0.35); [f]TG mean SOC-compared % difference (-14.4%, p-value=0.038); [g]TC mean SOC-compared % difference (-7.0%, p-value= 0.06); [h]HDL-C mean % difference between all CaPre® groups and SOC (7.5 %, p-value= 0.04); [i]HDL-C mean SOC-compared % difference (7.7%, p-value = 0.07); [j]Non-HDL-C mean SOC-compared % difference (-9.8%, p-value =0.036); [k]HbA1c mean SOC-compared % difference (-18.2%, p-value=0.013); [l]HbA1c mean SOC-compared % difference (-15.0%, p-value=0.039).

Table 4: Overall Incidence of Adverse Events

	Groups									
	SOC N=29		0.5 - 1.0 g N=52		1.0 - 2.0 g N=56		2.0 - 4.0 g N=57		4.0 - 4.0 g N=62	
	N	%	N	%	N	%	N	%	N	%
Total Number of Patients with an AE (%)	10	34.5%	7	13.5%	16	28.6%	25	43.9%	24	38.7%
Total Number of AEs (Events per patient)	22	0.76	11	0.21	26	0.46	44	0.77	46	0.74

AE = Adverse Events.

Table 5: Most Common Reported (> 2% of patients in all CaPre® groups)

	Groups			
	SOC (N=29)		All CaPre® (N=259)	
	N	%	N	%
Gastro-oesphageal reflux disease	1	3.4	9	3.9
Blood creatine phosphokinase increased	2	6.9	8	3.1
Diarrhea	0	0	7	2.7
C-reactive protein increase	1	3.4	7	2.7
Myalgia	0	0	7	2.7

Table 6: Safety Blood Parameters at Baseline and After 8 weeks of Treatment

		Groups				
Parameter	**Visit**	**SOC (N=18-29)**	**0.5 - 1.0 g (N=25-52)**	**1.0 - 2.0 g (N=33-55)**	**2.0 - 4.0 g (N=44-57)**	**4.0 - 4.0 g (N=50-62)**
aPTT (seconds)	Baseline	30.5 ± 6.2	28.5 ± 5.4	27.1 ± 5.4	30.8 ± 7.6	31.7 ± 8.5
	EOT	29.4 ± 7.8	28.1 ± 4.4	28.3 ± 4.2	31.2 ± 10.3	30.2 ± 8.3
PT (seconds)	Baseline	11.2 ± 6.7	8.6 ± 6.6	7.8 ± 7.1	10.2 ± 7.4	9.7 ± 5.9
	EOT	10.4 ± 6.2	8.7 ± 6.0	7.4 ± 6.6	10.2 ± 8.0	10.0 ± 7.0
Potassium (mEq/L)	Baseline	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5
	EOT	3.9 ± 0.4	3.9 ± 0.5	4.0 ± 0.5	4.1 ± 0.4	4.1 ± 0.5
Urea (BUN) (mg/dL)	Baseline	15.8 ± 5.2	13.9 ± 3.3	14.4 ± 4.0	15.2 ± 4.2	15.1 ± 4.0
	EOT	15.0 ± 6.5	13.2 ± 3.4	14.7 ± 4.7	15.7 ± 4.2	14.6 ± 4.3
Creatinine	Baseline	6.1 ± 1.3	5.9 ± 1.0	5.9 ± 1.0	5.9 ± 1.1	5.8 ± 1.3
	EOT	5.8 ± 1.2	5.1 ± 1.3	6.0 ± 1.3	6.0 ± 1.3	5.8 ± 1.2
ALT (SGPT) (U/L)	Baseline	31.7 ± 11.8	37.1 ± 23.5	35.2 ± 24.2	28.6 ± 13.7	33.1 ± 16.4
	EOT	34.8 ± 17.1	37.1 ± 31.4	33.9 ± 23.2	30.1 ± 15.1	32.1 ± 14.7
AST (SGOT) (U/L)	Baseline	24.3 ± 6.0	31.3 ± 15.2	30.4 ± 15.1	27.8 ± 14.0	28.8 ± 11.4
	EOT	26.4 ± 9.2	33.7 ± 18.9	30.5 ± 12.9	27.0 ± 11.5	30.8 ± 19.5
ALP (U/L)	Baseline	68.4 ± 14.5	73.1 ± 16.8	76.1 ± 20.0	71.0 ± 18.4	73.1 ± 31.4
	EOT	72.2 ± 24.0	72.8 ± 19.1	77.9 ± 18.6	71.9 ± 20.0	71.3 ± 16.3
Amylase (U/L)	Baseline	59.7 ± 19.0	65.1 ± 27.0	66.4 ± 22.4	66.8 ± 23.8	65.1 ± 22.3
	EOT	57.0 ± 25.3	63.5 ± 27.9	67.1 ± 25.6	72.1 ± 28.9	66.4 ± 28.3
Lipase (U/L)	Baseline	52.8 ± 33.6	67.6 ± 51.5	54.3 ± 37.5	60.3 ± 41.1	68.7 ± 49.8
	EOT	58.0 ± 39.2	77.8 ± 64.2	60.9 ± 46.9	71.5 ± 56.1	82.4 ± 70.4

Values are presented as Means ± SD. EOT = End of treatment.

Discussion

The results of this randomized, open-label trial evaluating the effect of CaPre® on patients with mild to high hypertriglyceridemia, showed that 4 weeks treatment with CaPre® achieved a significantly higher reduction of serum TG as compared to SOC by 13.6% ($P = 0.009$) when taken collectively, and by 16.3% ($P = 0.007$), 12.7% ($P = 0.025$) and 18.0% ($P = 0.002$) for CaPre® 1g, 2g and 4g CaPre®, respectively. CaPre® (all groups) continued to achieve a statistically significant TG reduction after 8 weeks of treatment as compared to SOC (-15%, $P = 0.015$). The TG differences at week 8 between SOC and CaPre® 1g – 2g and 4g – 4g were 16.2% ($P = 0.021$) and 14.4% ($P = 0.038$) respectively.

In addition to the significant reduction in fasting serum TG, patients treated with CaPre® 4g for 8 weeks achieved a reduction of total cholesterol by 7% (SOC- compared, $P = 0.06$) an increase of HDL-C by 7.7% (SOC-compared, $P = 0.07$) and a significant reduction of non-HDL-C by 9.8% (SOC-compared, $P = 0.036$).

CaPre® at any dose level had no deleterious effects on LDL-C. In this primarily non-diabetic population, it is noteworthy to mention that 8-week treatment with CaPre® 2.0 – 4.0 and CaPre® 4.0 – 4.0 significantly reduced mean SOC-compared HbA1c by 18% ($P = 0.013$) and 15% ($P = 0.039$), respectively. In addition, a significant increase in HDL-C concentrations by 7.5% ($P = 0.048$) was noted among all CaPre® treatment groups as compared to SOC.

In the COLT study, significant triglyceride lowering effects of CaPre® with both 2g and 4g doses after 4 and 8 weeks were observed in a patient population where the majority of them (88%) had baseline fasting TG between 200 – 500 mg/dL. The COLT population is comparable to that of ANCHOR (Vascepa®, Ballentyne, 2012) and ESPRIT (Epanova®, Maki, 2013) in which the TG lowering effects were lower or similar to that of CaPre®. We found that 4-week treatment with 2g CaPre® significantly lowered triglycerides by 12.7% (SOC-compared), while 12-week treatment with 2g Vascepa® lowered triglycerides by 10% (Placebo-adjusted) and 2g Epanova® achieved the same triglyceride lowering (8.7%, Placebo-compared) after 6 weeks [Maki 2013, Ballantyne 2012]. Similar triglyceride lowering effects was found with the 4g doses of all three compounds. Since lipid management is complex and involves many parameters including but not limited to LDL-C, HDL-C, total cholesterol, and non-HDL, it is important for products not to have deleterious effects on these parameters. In COLT study, a significant lowering of non-HDL-C (SOC-compared, -9.8%), and a reduction in total cholesterol (SOC-compared,-7%) with CaPre® 4g daily was reported along with an increase in HDL-C (SOC-compared +7.7%). In addition, a significant reduction in HbA1c values after 8 weeks of treatment at daily doses of 2g (SOC-compared, -18.2%) and 4g (SOC-compared, -15.0%) was reported. CaPre® treatment significantly increased HDL-C by 7.5% compared to SOC while increases in HDL-C were not significant with Vascepa® or Epanova®. We also found that CaPre® significantly lowered HbA1c values after 8 weeks of treatment at daily doses of 2g and 4g.

CaPre® was safe and well-tolerated with a low incidence of adverse events, and those present were mostly mild and no serious adverse events were reported.

Conclusions

In summary, results from the COLT study demonstrated:

- CaPre® had a positive impact on lowering triglycerides that is dose-dependent, providing physicians with titrable dosing flexibility;
- CaPre® significantly reduced triglycerides by 18.0% at 4 weeks and by 14.4% at 8 weeks with a 4.0g dose, (SOC-compared);
- In addition to lowering triglycerides, CaPre® had a positive impact on multiple lipoproteins, including HDL-C and non-HDL-C, without any significant deleterious effects on LDL-C.

This study demonstrates that CaPre® has significant triglyceride lowering properties as well as beneficial overall lipid management effects in patients with mild to high hypertriglyceridemia.

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