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National Lipid Association (NLA)

May 2017

A Phase 1, Single-Dose, Comparative Bioavailability Study of CaPre®, a Novel Omega-3 Derived from Krill Oil and Lovaza® under Fasting and Fed Conditions

Laurent Harvey[1], B.Pharm. M.Sc., Jean-François Lapointe[1], Ph.D., Pierre Lemieux[1], Ph.D., Radu Pop[2], Ph.D., Heather Jordan[2], MD., Robert A. Hegele[3], MD, FRCPC, FACP, FAHA, FCAHS
[1] Acasti Pharma Inc., [2] Pharma Medica Research Inc., [3] Blackburn Cardiovascular Genetics Lab and London Regional Genomics Centre.

CaPre® is a novel krill oil-derived mixture containing **EPA and DHA** present as a combination of phospholipid (PL) esters and free fatty acids (FFA). CaPre is being developed for the treatment of severe hypertriglyceridemia and has demonstrated efficacy in Phase 2 trials, with no safety concerns.

Objectives/Purpose: This study compared the relative bioavailability of EPA and DHA from 4-gram doses of CaPre to that of Lovaza containing ethyl ester forms (EE) of EPA and DHA, administered under fasting and fed conditions.

Methods: This was an open-label, randomized, 4-way, crossover bioavailability study. Fifty (56) subjects were randomized to receive single, 4-g doses (4 capsules) of CaPre and Lovaza administered under a fasted state maintained for 10 hours prior to and 4 hours following dose administration, and under fed conditions, 30 minutes after the start of a High Fat (HF) breakfast (919 kcal, 57.2% fat). Pharmacokinetic parameters (AUC_{0-72}, C_{max}) were estimated for baseline-adjusted concentrations of EPA+DHA in total plasma lipids (Total EPA+DHA) during a 72-hour post-dose sampling period.

Results: With fasting, CaPre showed 400% and 167% higher AUC_{0-72} and C_{max} respectively for Total EPA+DHA compared to Lovaza. Following a HF meal, the AUC_{0-72} and C_{max} for Total EPA+DHA were respectively 66% and 76% lower following CaPre compared to Lovaza, consistent with the EPA+DHA content in each product. Finally, administration of Lovaza with a HF meal increased the AUC_{0-72} and C_{max} of Total EPA+DHA by 2414% and 1031%, respectively as compared to administration in fasted state. In contrast, the AUC_{0-72} and C_{max} of Total EPA+DHA were only increased by 73% and 2%, respectively with CaPre administration.

Conclusion: Results demonstrated that the bioavailability of the PL and FFA forms of EPA and DHA in CaPre are far less affected when taken on an empty stomach as compared to the EE forms in Lovaza. The bioavailability of Lovaza is maximal following administration with a HF meal but is dramatically reduced under fasting conditions. Since patients with severe hypertriglyceridemia should adhere to a low fat diet, these findings suggest preserved exposure, and perhaps retained efficacy in patients taking CaPre in either the fasted state or with a low fat diet.

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❖ See how **CaPre differs** from other OM3 drug products

❖ See completed **clinical studies** with CaPre

The **bioavailability of EPA and DHA from CaPre** appears to be higher than Lovaza based on a cross-trial comparison between the completed Phase 1/pharmacokinetic study with CaPre (CAP13-101) and published PK data with Lovaza leading to similar (but not necessarily bioequivalent) systemic exposure to EPA and DHA active moieties between the two products.

❖ See **PK cross-trial comparison** between CaPre and Lovaza

It is believed that the **PL and FFA forms of EPA and DHA in CaPre are more bioavailable than EE**, and thus a lower daily dose of EPA and DHA from CaPre achieves a clinically significant TG-lowering activity.

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Design : Open-label, single-dose, randomized, four-period, four-treatment, four-sequence**,** crossover, comparative bioavailability study. Each period:
Washout between periods = 14 days

	PERIOD		
Check-in (-58h)	**Baseline (24h)**	**DOSE**	**Post-dose (72h)**
	PK sampling = 4 (-24,-16,-10, 0h)		**PK sampling = 20** (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 28, 32, 36, 48, 72h)

Sample Size:
Fifty (**56**) subjects to achieve 50 completers

Treatments:
Single, 4-g doses (4 capsules) of:
A: CaPre®/**Fast**; B: Lovaza/**Fast**; C: CaPre®/**Fed**; D: Lovaza/**Fed**

Fast = empty stomach
Fed = high-fat breakfast (~900 Kcal, 57% of energy from fat)

Analytes:
Measured and ***Baseline-corrected*, EPA and DHA in *total plasma lipids*** and as plasma free fatty acids

Key Pharmacokinetic Parameters:
Total exposure to EPA and DHA in blood (**$AUC_{0\text{-}72\ hrs}$**)
Peak concentration of EPA and DHA in blood (**C_{max}**)

Statistical analysis:
ANOVA(PROC GLM) performed on log-transformed measured and baseline-adjusted $AUC_{0\text{-}72}$ and C_{max}. Based on log-transformed data, the ratios of the geometric means (GMRs) for treatments and the corresponding 90% confidence intervals (CIs) were calculated.

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Baseline-Adjusted Analytes in Total Lipids Under Fasting Conditions

	Parameter	CaPre n	CaPre GM	Lovaza n	Lovaza GM	Ratio (%)	90% CI
EPA	AUC_{0-72}	50	218.8	36	32.1	681.2	552.0 – 840.7
	C_{max}	50	8.7	36	2.01	431.3	377.2 – 493.2
DHA	AUC_{0-72}	50	112.3	48	46.5	241.4	196.2 – 297.0
	C_{max}	50	9.0	48	5.0	179.2	155.6 – 206.4
EPA+DHA	AUC_{0-72}	50	954.8	45	191.1	**499.5**	410.6 – 607.7
	C_{max}	50	53.2	45	19.9	**267.2**	236.8 – 301.4

GM = Geometric mean from the least-squares means.
AUC results are given in µg•h/mL for EPA and DHA and µmol•h/L for EPA+DHA. C_{max} results are given in µg/mL for EPA and DHA and µmol/L for EPA+DHA.
Results based on the statistical analysis of the full dataset (all treatments included and all planned contrasts evaluated).
Ratio (%): CaPre/Lovaza

Under Fasting, CaPre showed 400% and 167% higher AUC_{0-72} and C_{max} respectively for Total EPA+DHA compared to Lovaza.

SEE GRAPH
SEE NORMALIZED DATA

Baseline-Adjusted Analytes in Total Lipids Under Fed (HF Meal) Conditions

	Parameter	CaPre n	CaPre GM	Lovaza n	Lovaza GM	Ratio (%)	90% CI
EPA	AUC_{0-72}	51	430.2	50	1059.1	40.6	33.7 – 49.0
	C_{max}	51	12.1	50	46.1	26.3	23.3 – 29.6
DHA	AUC_{0-72}	47	131.0	50	431.1	30.4	24.7 – 37.4
	C_{max}	47	6.3	50	25.5	24.7	21.4 – 28.5
EPA+DHA	AUC_{0-72}	51	1651.3	50	4805.2	**34.4**	28.5 – 41.5
	C_{max}	51	54.2	50	225.1	**24.1**	21.4 – 27.0

GM = Geometric mean from the least-squares means.
AUC results are given in µg•h/mL for EPA and DHA and µmol•h/L for EPA+DHA. C_{max} results are given in µg/mL for EPA and DHA and µmol/L for EPA+DHA.
Results based on the statistical analysis of the full dataset (all treatments included and all planned contrasts evaluated).
Ratio (%): CaPre/Lovaza

Under Fed (HF meal), the AUC_{0-72} and C_{max} for Total EPA+DHA were respectively 66% and 76% lower following CaPre compared to Lovaza, consistent with the EPA+DHA content in each product.

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Food Effect on Baseline-adjusted EPA + DHA in Total Lipids

	Parameter	Fed (HF meal)		Fast		Ratio Fed/Fast (%)	90% CI
		n	GM	n	GM		
CaPre	AUC_{0-72}	51	1651.3	50	954.8	173.0	143.2 – 209.0
	C_{max}	51	54.2	50	53.2	102.0	90.8 – 114.5
Lovaza	AUC_{0-72}	50	4805.2	45	191.1	**2514.0**	2064.0 – 3062.2
	C_{max}	50	226.0	45	19.9	**1131.2**	1002.0 – 1277.0

GM = Geometric mean from the least-squares means.
AUC results are given in µg•h/mL for EPA and DHA and µmol•h/L for EPA+DHA. C_{max} results are given in µg/mL for EPA and DHA and µmol/L for EPA+DHA.
Results based on the statistical analysis of the full dataset (all treatments included and all planned contrasts evaluated).
Ratio (%): CaPre/Lovaza

Food effect: administration of Lovaza with a HF meal increased the AUC_{0-72} and C_{max} of Total EPA+DHA by **2414%** and **1031%**, respectively as compared to administration in fasted state. In contrast, the AUC_{0-72} and C_{max} of Total EPA+DHA were only increased by 73% and 2%, respectively with CaPre administration.

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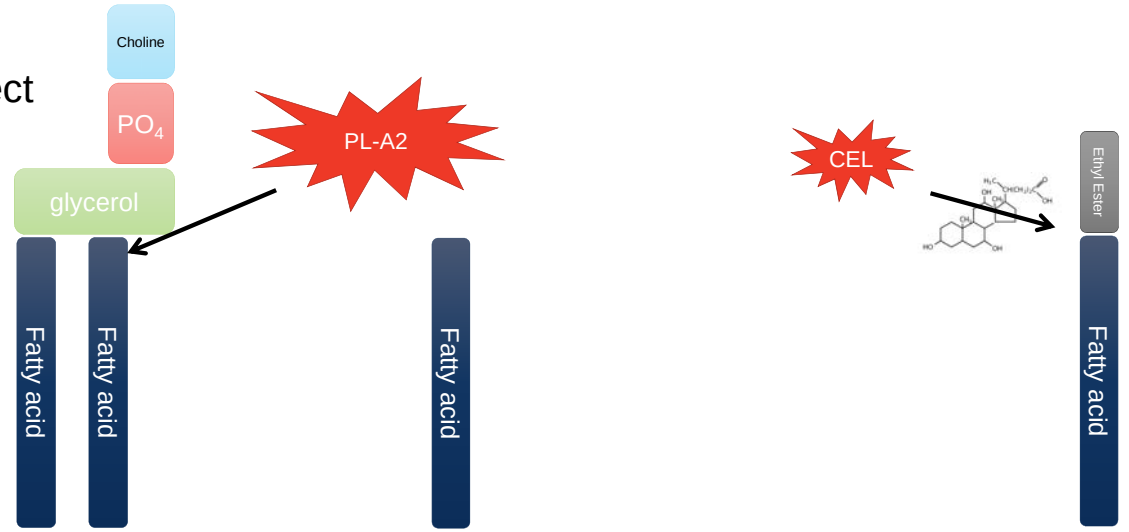
Why CaPre® Does Not Have a Significant Food Effect Compared to Ethyl Esters (EE)?

CaPre

No significant food effect

Ethyl Esters
(Lovaza, Vascepa)
Significant food effect



Phospholipid | **Free Fatty acid** | **Ethyl Ester**

- ❑ **Hydrolysis is primarily mediated by PL-A2, not a bile-salt dependent lipase such as CEL**
- ❑ **Readily accessible to lipases due to amphiphilic (interface) properties**

- ❑ **No digestion required**

- ❑ **Hydrolysis is mediated by carboxyl ester lipase (CEL), a bile-salt dependent lipase**
- ❑ **Dependent on the fat content of food for activity**
- ❑ **Results in lower efficiency of the hydrolysis of the EE bound**

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- Bioavailability of the PL and FFA forms of EPA and DHA in CaPre® are far less affected when taken on an empty stomach as compared to the EE forms in **Lovaza**
- Bioavailability of **Lovaza** is maximal following administration with a HF meal but is dramatically reduced under fasting conditions
- Since patients with severe hypertriglyceridemia should adhere to a low fat diet, these findings suggest preserved exposure, and perhaps retained efficacy in patients taking CaPre® in either the fasted state or with a low fat diet

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Clinical study reports:

- Study CAP13-101: Phase 1 / PK (USA): Evaluation of CaPre Pharmacokinetics following single and multiple oral doses in healthy volunteers (ClinicalStudy Report dated Jan 08, 2015).
- Study 2016-4010: Phase 1 / PK (USA): A Single-Dose, Comparative Bioavailability Study of CaPre® 1 g Capsules compared to Lovaza® 1 g Capsules under Fasting and Fed Conditions (ClinicalStudy Report dated Oct 21, 2016).

Published literature:

- Offman E, Marenco T, Ferber S, et al. Steady-state bioavailability of prescription omega-3 on a low-fat diet is significantly improved with a free fatty acid formulation compared with an ethyl ester formulation: the ECLIPSE II study. Vasc Health Risk Manag 2013;9:563-73.
- Yang LY, Kuksis A, Myher JJ. Lipolysis of menhaden oil triacylglycerols and the corresponding fatty acid alkyl esters by pancreatic lipase in vitro: a reexamination. J Lipid Res. Jan 1990;31(1):137-147.
- Schuchardt JP, Hahn A. Bioavailability of long-chain omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids.* Jul 2013;89(1):1-8.
- Hui DY, Howles PN. Carboxyl ester lipase: structure-function relationship and physiological role in lipoprotein metabolism and atherosclerosis. J Lipid Res. Dec 2002;43(12):2017-2030.
- Davidson MH, Johnson J, Rooney MW, Kyle ML, Kling DF. A novel omega-3 free fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: the ECLIPSE (Epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation) study. J Clin Lipidol. Nov-Dec 2012;6(6):573-584.

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Additional Slides

Combination of PL and FFA Forms of EPA and DHA Unique to CaPre®

	CaPre	Lovaza	Omtryg	Vascepa	Epanova
Sponsor	Acasti	GSK	Trygg Pharma	Amarin	AstraZeneca
Source material	Krill oil	Fish oil			
EPA/DHA (per g)	310 mg (EPA/DHA)	770 mg (EPA/DHA)	642 mg (EPA/DHA)	878 mg (EPA only)	750 mg (EPA/DHA)
Chemical form	PL esters and FFA	Ethyl esters			FFA
Approved Dose	under investigation (2 and 4g/day)	4g/day	4.6g/d	4g/day	2 and 4g/day

Additional information

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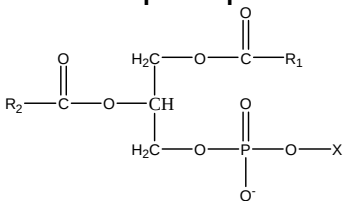
Composition of EPA and DHA in CaPre® vs Lovaza®

CaPre

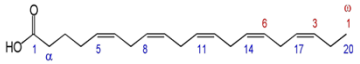
Phospholipids



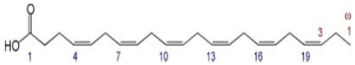
where R1 and/or R2 is EPA or DHA and X is mainly choline ($C_5H_{14}NO^+$)

Free Fatty acids

EPA-FFA



DHA-FFA

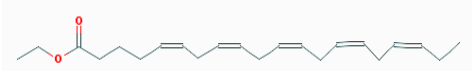


- In CaPre, EPA and DHA are found as a mixture of **Phospholipids esters** (50-60%) and **FFA** (40-50%), and account for approximately 45% of all fatty acids.
- The phospholipid backbone makes up a significant weight of the CaPre composition.
- During manufacturing, the natural distribution and composition of EPA and DHA onto phospholipids is maintained; most phospholipids that carry an EPA or DHA molecule in R1 or R2 also carry another fatty acid in the other position.

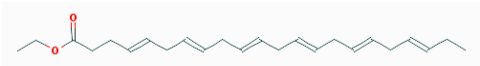
1240 mg EPA + DHA per 4 g dose
expressed as Free Fatty acid equivalent
(no chemical synthesis)

Lovaza

EPA-EE



DHA-EE



- In Lovaza, EPA and DHA are found as a **ethyl esters** only and account for approximately 85% of all fatty acids.
- The ethyl ester moiety does not makes up a significant weight of the Lovaza composition.
- During manufacturing, the ethyl ester derivatives of EPA and DHA are formed by the trans-esterification of fish oill.

3080 mg EPA + DHA per 4 g dose
expressed as Free Fatty acid equivalent
(chemical synthesis)

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Successful Phase 1 and Phase 2 Studies Completed Toward Initiation of Phase 3 Program in 2017

Clinical Studies Completed	# Patients Enrolled	2013	2014	2015	2016
Phase 1 (PK) Single & mutiple doses	42		→		
Phase 2 (COLT) Safety & efficacy HTG Open-label, 8-week	288	→			
Phase 2 (TRIFECTA) Safety & efficacy HTG Double-blind, 12-week	387	→	→	→	
Phase 1 (PK) CaPre vs Lovaza Bridging Single-dose Fed-Fast	56				→
TOTAL PATIENTS	773	*No safety concerns*			

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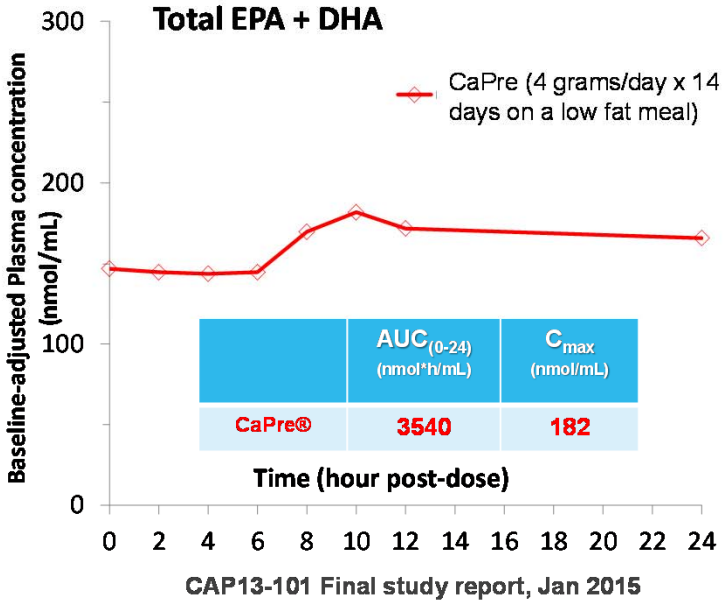
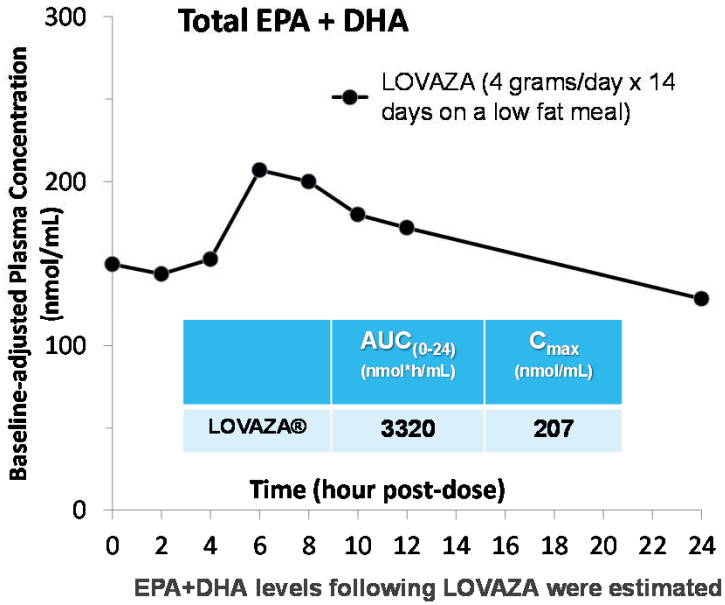
CaPre® Contains 2.5 Times Less EPA and DHA Compared to Lovaza®, and Yet Reaches Similar Blood and Therapeutic Levels



CAP13-101 Final study report, Jan 2015



EPA+DHA levels following LOVAZA were estimated from ECLIPSE II, Offman,VHRM 2013

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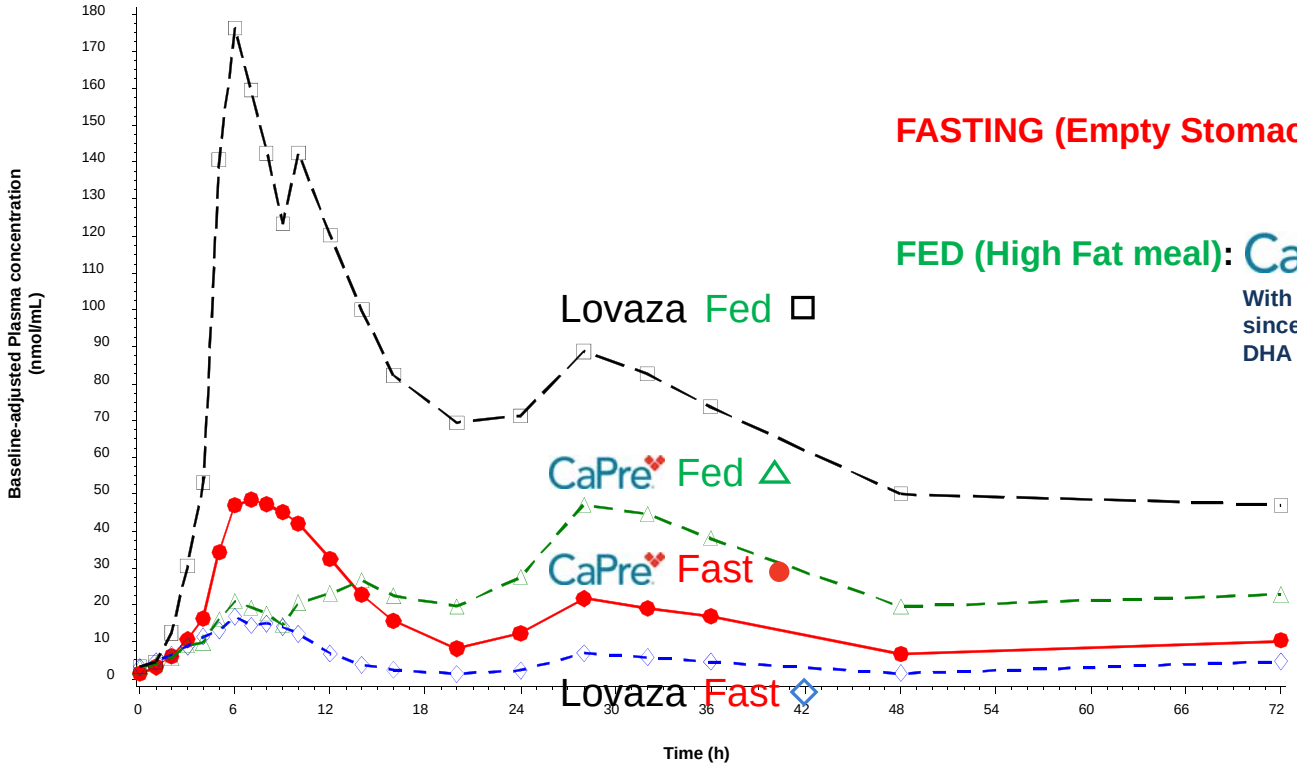
Mean Plasma Baseline-Adjusted EPA + DHA Total Lipids Concentration-Time Profile Over 72h Following 4g Single-Dose of Administration Under Fasting and Fed Conditions



FASTING (Empty Stomach): CaPre **> LOVAZA**

FED (High Fat meal): CaPre **< LOVAZA**

With a high fat meal, results were as expected since CaPre contains 2.5 times less EPA and DHA than Lovaza

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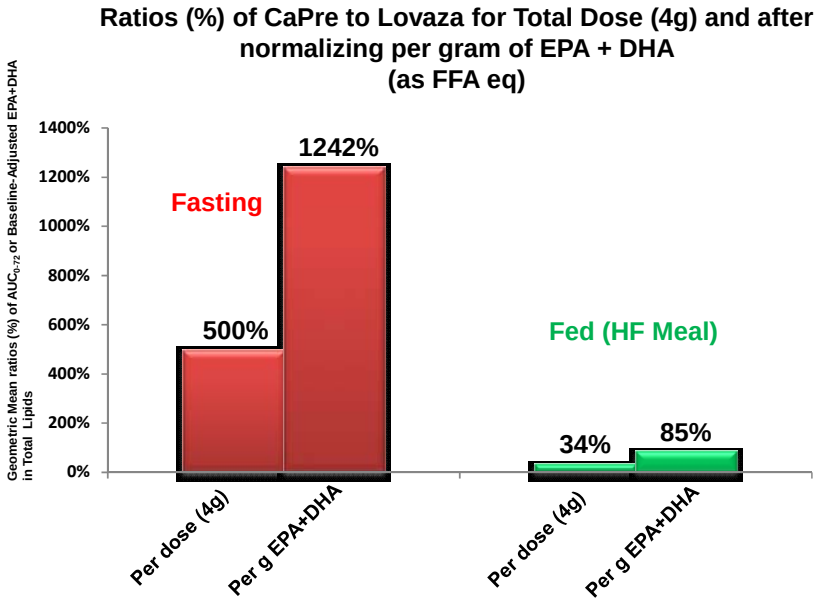
Better Bioavailability of CaPre® Under Fasting Condition is Evidenced After Normalizing Per Gram of EPA+DHA



	Dose (g)	EPA per dose (as FFA)	DHA per dose (as FFA)	EPA+DHA per dose (as FFA)
CaPre	4	760 mg	480 mg	1240 mg
Lovaza	4	1700 mg	1380 mg	3080 mg

FFA: free fatty acid equivalent. EE: ethyl ester
For Lovaza, 465 mg and 375 mg of EPA-EE and DHA-EE per g, respectively. EPA-E: The EPA moiety (FFA) corresponds to 91.5% of the total weight
DHA-E: The DHA moiety (FFA) corresponds to 92.1% of the total weight

Each gram of EPA+DHA taken from CaPre is more efficiently absorbed as compared to Lovaza

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