

# BIOAVAILABILITY OF A SINGLE 4G DOSE EPANOVA® (OMEGA-3 FREE FATTY ACIDS) VERSUS LOVAZA® (OMEGA-3-ACID ETHYL ESTERS) WHEN CONSUMED WITH LOW-FAT AND HIGH-FAT MEALS IN HEALTHY ADULTS

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## BACKGROUND AND RATIONALE

- In patients with severe hypertriglyceridemia (TG ≥ 500 mg/dL), the National Cholesterol Education Program (NCEP) Adult Treatment Panel III recognized that statins are not powerful TG-lowering drugs, and therefore recommended the use of specific therapies such as n-3 (omega) fatty acids as an adjunct to diet to lower TG levels.<sup>1</sup>
- Once absorbed, the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) lower serum TGs by reducing hepatic secretion of triglyceride-rich lipoproteins.<sup>1</sup>
- Ethyl esters (EE) of omega-3 fatty acids require pancreatic lipase (PL) hydrolysis to be converted into a free fatty acid (FFA) for intestinal absorption, and consequently ingestion of omega-3-acid EE with high or low fat meals is known to significantly affect PL activity and absorption.<sup>2-5</sup>
- In contrast to prodrug EE forms, FFA forms of omega-3's are not dependent on PL activity and therefore have improved bioavailability which is especially independent of meal fat content as demonstrated in previous human trials.<sup>2-5</sup>
- The additional EE moieties in Lovaza result in a larger molecular weight than Epanova. Therefore, a greater mass weight of the prodrug (Lovaza) is required to yield, upon hydrolysis, the same amount of EPA+DHA FFA contained in Epanova.
- Epanova (4 g) has a greater mass ratio of EPA to DHA than Lovaza and provides 2.20 g EPA and 0.80 g DHA as FFA. Lovaza (4 g) has 1.86 g of EPA-EE which yields 1.70 g EPA FFA, and 1.5 g of DHA-EE which yields 1.38 g DHA FFA.
- The NCEP ATP III has recommended that patients with hypertriglyceridemia consume very low-fat meals (<15% of total calories as fat).<sup>1</sup>
- We hypothesized that Epanova®, as a FFA prescription formulation of omega-3 would demonstrate a superior and more predictable (less dependent upon fat content of the meal) bioavailability profile vs. Lovaza, a EE prescription formulation of omega-3.

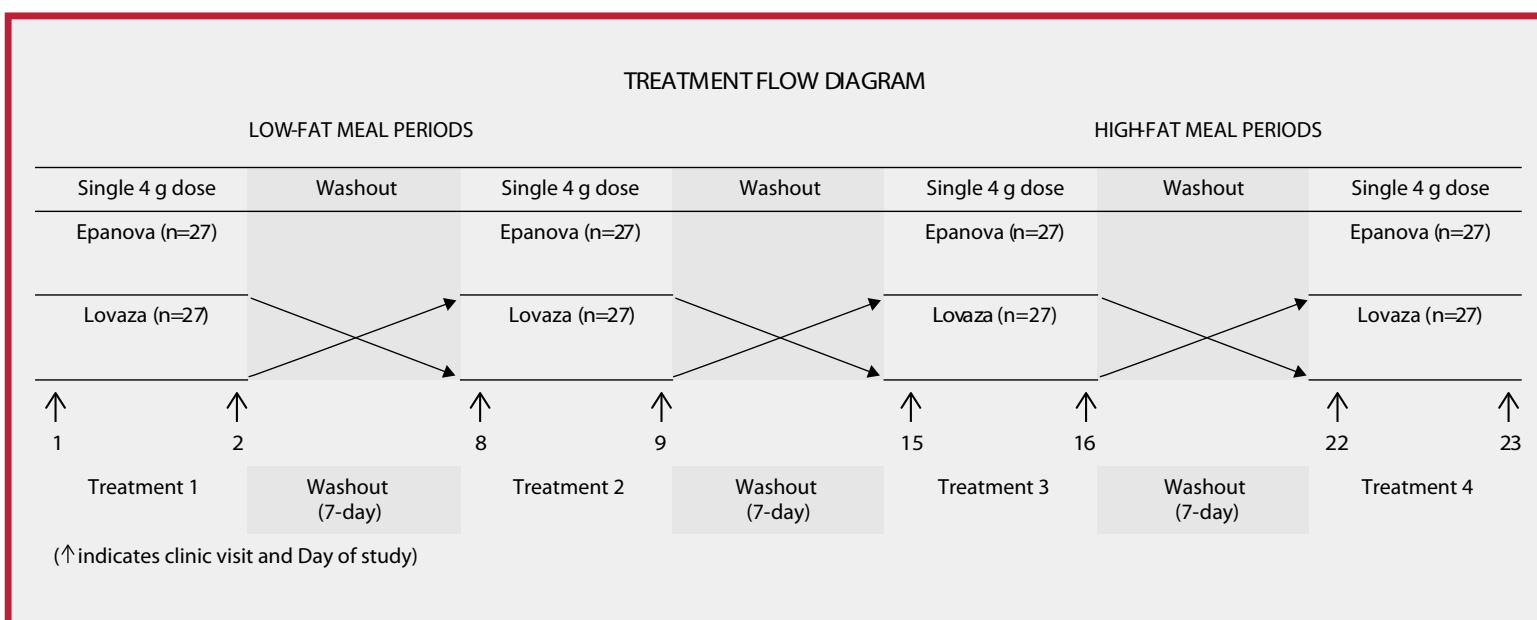
## OBJECTIVE

To compare the relative bioavailability of total and free EPA and DHA from a single 4 g dose of Epanova® and Lovaza® after consumption of low-fat and high-fat meals.

## METHODS

- This was a single dose, randomized, open-label, 4-way crossover, bioavailability study with 2 treatments: 4 g of Epanova or 4 g of Lovaza, each administered with a low-fat and a high-fat meal to 54 healthy adults.
- After a washout period, subjects randomized to one of the 2 sequences (see Flow Diagram):
  - Epanova (low-fat) – Lovaza (low-fat) – Epanova (high-fat) – Lovaza (high-fat)
  - Lovaza (low-fat) – Epanova (low-fat) – Lovaza (high-fat) – Epanova (high-fat)

### TREATMENT FLOW DIAGRAM



- Screening washout requirements:
  - 60 days for fish oil, EPA or DHA supplements or fortified foods.
  - 7 days for fish, flaxseed, perilla seed, hemp, spirulina, or black currant oils; statins, bile acid sequestrants, cholesterol absorption inhibitors or fibrates.
- Evening before in-clinic visit: subjects consume a low-fat dinner 12 hours before Time 0 of each treatment period (9 g fat; 900 kcal).
- Investigational product (Epanova or Lovaza) administered in the morning after the pre-dose blood draws (time 0).
- Pharmacokinetic blood sampling for each 2-day treatment period at -1.0, -0.5 and 0 hours (pre-dosing) and post-dosing at 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours (±5 min) for the 1st day and at 24 hours (±15 min) for the 2nd day.
- Crossover washout period of at least 7 days.
- Low-Fat Period Meals (Periods 1 and 2): no breakfast, no-fat lunch (0 g fat; 600 kcal) after the 4-hour blood draw, a low-fat dinner (9 g fat; 900kcal) after the 12-hour blood draw.
- High-Fat Period Meals (Periods 3 and 4): high-fat breakfast (20 g fat; 600 kcal) immediately after the 0.5 hr blood draw, high-fat lunch (30 g fat; 900 kcal) after the 4-hour blood draw, and high-fat dinner (30 g fat; 900 kcal) after the 12-hour blood draw.

### PHARMACOKINETIC AND STATISTICAL ANALYSES

- Pharmacokinetic parameters for EPA and DHA plasma concentrations calculated for the baseline-adjusted change in total and individual EPA and DHA concentrations by standard noncompartmental methods:  $AUC_{0-24}$ ,  $AUC_{0-12}$ ,  $C_{max}$  and  $T_{max}$ .
- Primary determinants of bioavailability: In-transformed area under the plasma concentration versus time curve ( $AUC_i$ ) and maximum measured plasma concentration ( $C_{max}$ ) over a 24-hour interval for the baseline-adjusted change in total and individual EPA and DHA concentrations.
- Plasma concentrations were baseline-adjusted prior to the calculation of pharmacokinetic parameters. Figures are plotted for the baseline-adjusted change in geometric means (ln-transformed).
- Analysis of variance (ANOVA) was used to evaluate the ln-transformed pharmacokinetic parameters for differences due to treatments, period, dosing sequence, and subjects within sequence.
- Ratios of means calculated using the least square means for ln-transformed  $AUC_{0-24}$ ,  $AUC_{0-12}$  and  $C_{max}$ .
- The ratios of means and their 90% confidence intervals are to lie above the upper limit of 125.00% for  $AUC_{0-24}$ ,  $AUC_{0-12}$  and  $C_{max}$  in order to show Epanova® has superior relative bioavailability compared to Lovaza® with regards to diet.

## RESULTS

### STUDY POPULATION

The study enrolled 54 healthy adults, 41 males (75.9%) and 13 females (24.1%), aged 21 to 77. All of treatment periods were completed by 51 (94.4%) subjects, with 53 (98.1%) subjects completing the low fat portion of the study. The population was predominantly Black or African-American (66.7%) with 31.5% White and 1.8% Asian.

### BIOAVAILABILITY

With low-fat period meals, Epanova resulted in significantly greater bioavailability of total and individual EPA and DHA compared to Lovaza:

- Figure 1 – The baseline-adjusted change in total plasma EPA + DHA levels show a 4.6-fold greater  $AUC_i$  for Epanova than Lovaza during low-fat meal periods: 3077.8 vs 668.9 nmol-h/mL, respectively;  $p < 0.0001$  (LS mean data in Table 1).  $C_{max}$  of Epanova is 3.2-fold greater than Lovaza ( $p < 0.0001$ ) and  $T_{max}$  is 20% shorter than Lovaza (8 vs 10 hrs, respectively;  $p = 0.0138$ ).
- Figure 2 – The baseline-adjusted change in total plasma EPA levels show a 13.5-fold greater  $AUC_i$  for Epanova than Lovaza during low-fat meal periods: 578.2 vs 42.7  $\mu$ g-h/mL, respectively;  $p < 0.0001$  (LS mean data in Table 2).  $C_{max}$  of Epanova is 5.6-fold greater than Lovaza ( $p < 0.0001$ ) and  $T_{max}$  is 12% shorter than Lovaza (8 vs 9 hrs, respectively;  $p = 0.2605$ ).
- Figure 3 – The baseline-adjusted change in total plasma DHA levels show a 2.2-fold greater  $AUC_i$  for Epanova than Lovaza during low-fat meal periods: 383.1 vs 173.4  $\mu$ g-h/mL, respectively;  $p < 0.0001$  (LS mean data in Table 3).  $C_{max}$  of Epanova is 1.9-fold greater than Lovaza ( $p < 0.0001$ ) and  $T_{max}$  is 21% shorter than Lovaza (8 vs 11 hrs, respectively;  $p = 0.0148$ ). The 2.2-fold greater DHA bioavailability in Epanova vs Lovaza occurred despite having 42% less DHA in the Epanova formulation.
- Figure 4 – The baseline-adjusted change in total plasma EPA + DHA levels show that the  $AUC_i$  for Lovaza in the low-fat meal period is decreased by 83.3% compared to Lovaza in the high-fat meal period: 661.6 vs 3959.5 nmol-h/mL, respectively;  $p < 0.0001$  (LS mean data in Table 4).  $C_{max}$  of Lovaza in the low-fat period decreased by 80.6% compared to the high-fat period ( $p < 0.0001$ ) and the  $T_{max}$  increased 62% in the low-fat period compared to the high-fat period (10.2 vs 6.3 hrs, respectively;  $p = 0.0001$ ).

### SAFETY

A total of 51 adverse events were reported by 29 subjects. The most common adverse events were headaches (10 subjects) and loose stools or diarrhea (9 subjects). All adverse events were mild in severity, and none were serious. There were no clinically significant changes in laboratory, vital sign or physical assessments.

Figure 1. Bioavailability of Total EPA + DHA (Baseline-adjusted Change) Following a Single Dose (4 g) of Epanova vs Lovaza During the Low-fat Diet Period

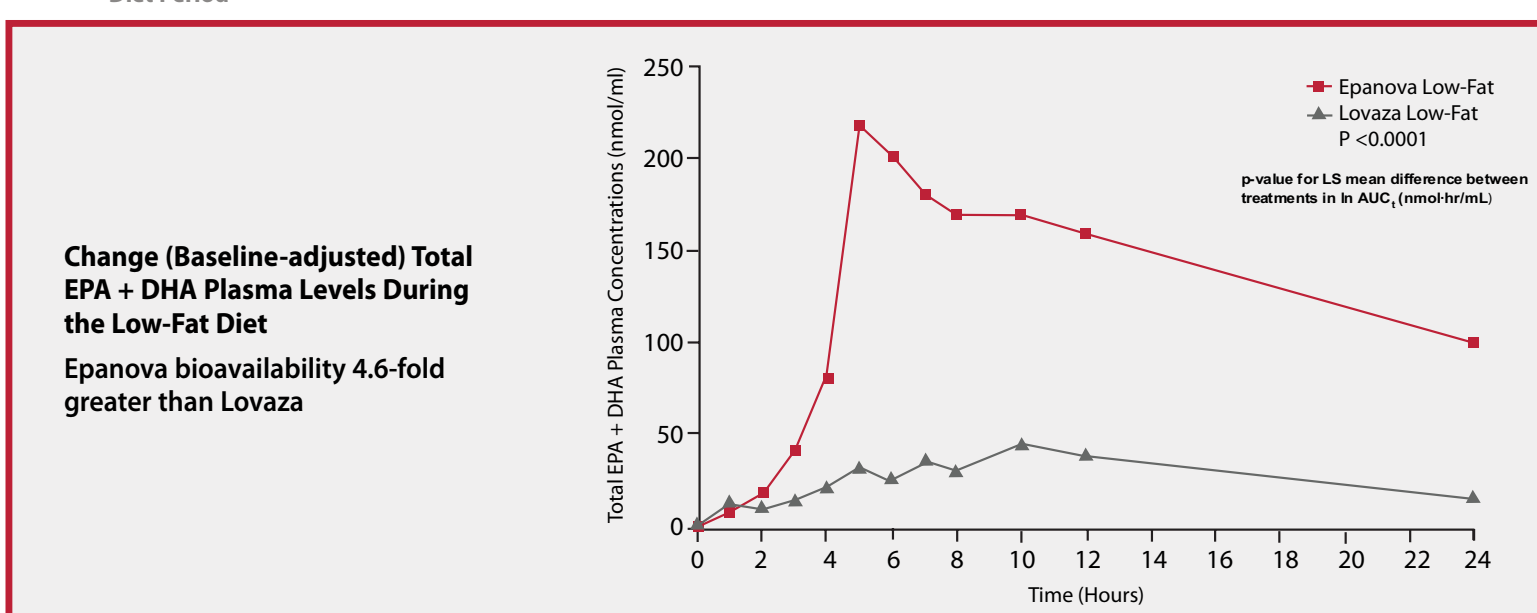


Table 1. Pharmacokinetic Analysis of Total EPA + DHA Following a Single Dose (4 g) of Epanova vs Lovaza During the Low-fat Diet Period

Bioavailability Parameter	Least Square Mean		Ratio of Means (%)	P-value <sup>a</sup>	Intra Subject C.V. % <sup>b</sup>	Inter Subject C.V. % <sup>b</sup>	90% Confidence Interval Limits (%)	
	Epanova	Lovaza					Lower	Upper
Baseline-Adjusted Change								
$AUC_i$ (nmol-hr/mL)	3077.83	668.95	460.10	<0.0001	62.9	25.3	402.77	517.42
$C_{max}$ (nmol/mL)	277.58	86.35	321.46	<0.0001	71.6	48.9	272.36	370.56
$T_{max}$ (hr)	8.08	10.21	79.23	0.0138	45.8	24.6	65.60	92.86
Baseline-Adjusted Change (Ln-transformed) Data (Geometric Means)								
Ln $AUC_i$ (nmol-hr/mL)	2651.41	658.09	402.90	<0.0001	63.9	24.3	329.71	492.33
Ln $C_{max}$ (nmol/mL)	225.79	60.70	371.95	<0.0001	66.3	42.7	304.37	454.53

N = 53  
<sup>a</sup> P-value is for the Least Square (LS) Mean Difference between Epanova and Lovaza from the ANOVA model  
<sup>b</sup> Covariance %

Figure 2. Bioavailability of Total EPA (Baseline-adjusted Change) Following a Single Dose (4 g) of Epanova vs Lovaza During the Low-fat Diet Period

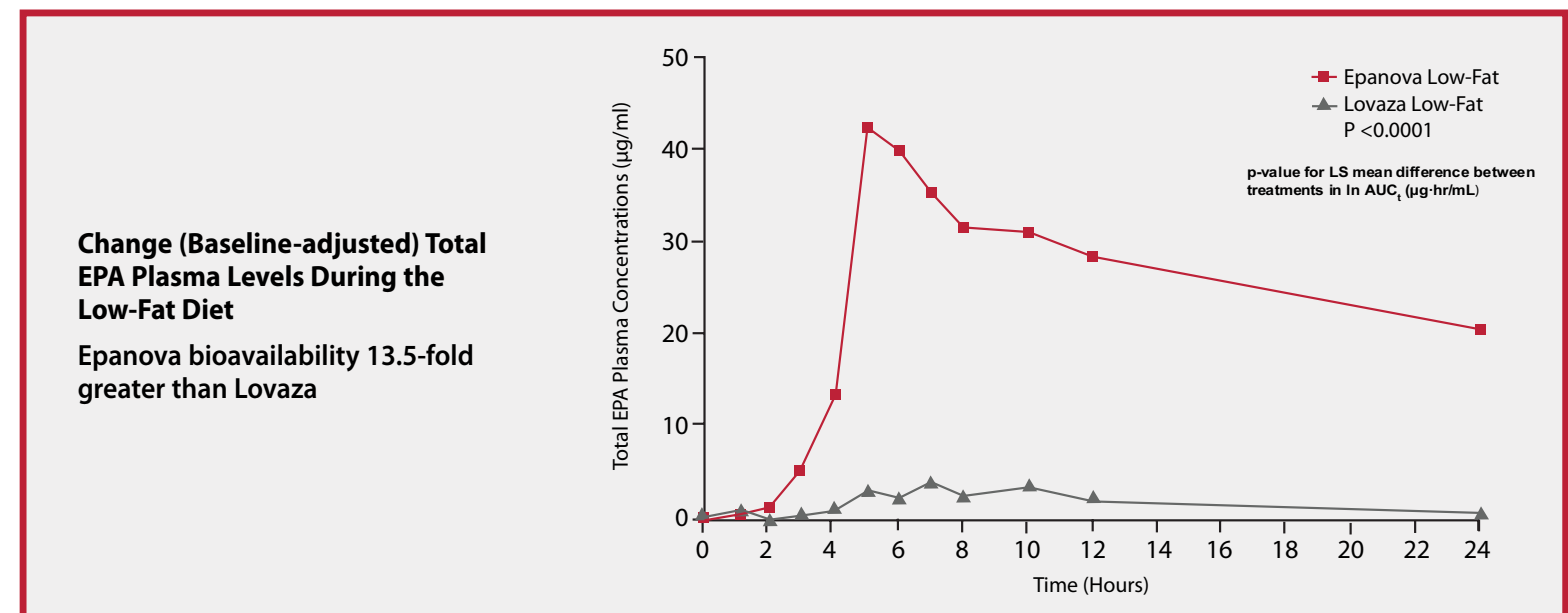


Table 2. Pharmacokinetic Analysis of Total EPA Following a Single Dose (4 g) of Epanova vs Lovaza During the Low-fat Diet Period

Bioavailability Parameter	Least Square Mean		Ratio of Means (%)	P-value <sup>a</sup>	Intra Subject C.V. % <sup>b</sup>	Inter Subject C.V. % <sup>b</sup>	90% Confidence Interval Limits (%)	
	Epanova	Lovaza					Lower	Upper
Baseline-Adjusted Change								
$AUC_i$ ( $\mu$ g-hr/mL)	578.22	42.67	1355.1	<0.0001	80.8	18.2	1163.8	1546.4
$C_{max}$ ( $\mu$ g/mL)	52.64	9.45	557.0	<0.0001	83.9	49.8	467.32	646.68
$T_{max}$ (hr)	8.06	9.13	88.28	0.2605	54.7	25.8	71.02	105.54
Baseline-Adjusted Change (Ln-transformed) Data (Geometric Means)								
Ln $AUC_i$ ( $\mu$ g-hr/mL)	495.66	48.65	957.09	<0.0001	93.0	23.5	713.46	1283.9
Ln $C_{max}$ ( $\mu$ g/mL)	39.02	4.66	837.53	<0.0001	102.1	52.3	630.85	1111.9

N = 53  
<sup>a</sup> P-value is for the Least Square (LS) Mean Difference between Epanova and Lovaza from the ANOVA model  
<sup>b</sup> Covariance %

Figure 3. Bioavailability of Total DHA (Baseline-adjusted Change) Following a Single Dose (4 g) of Epanova vs Lovaza During the Low-fat Diet Period

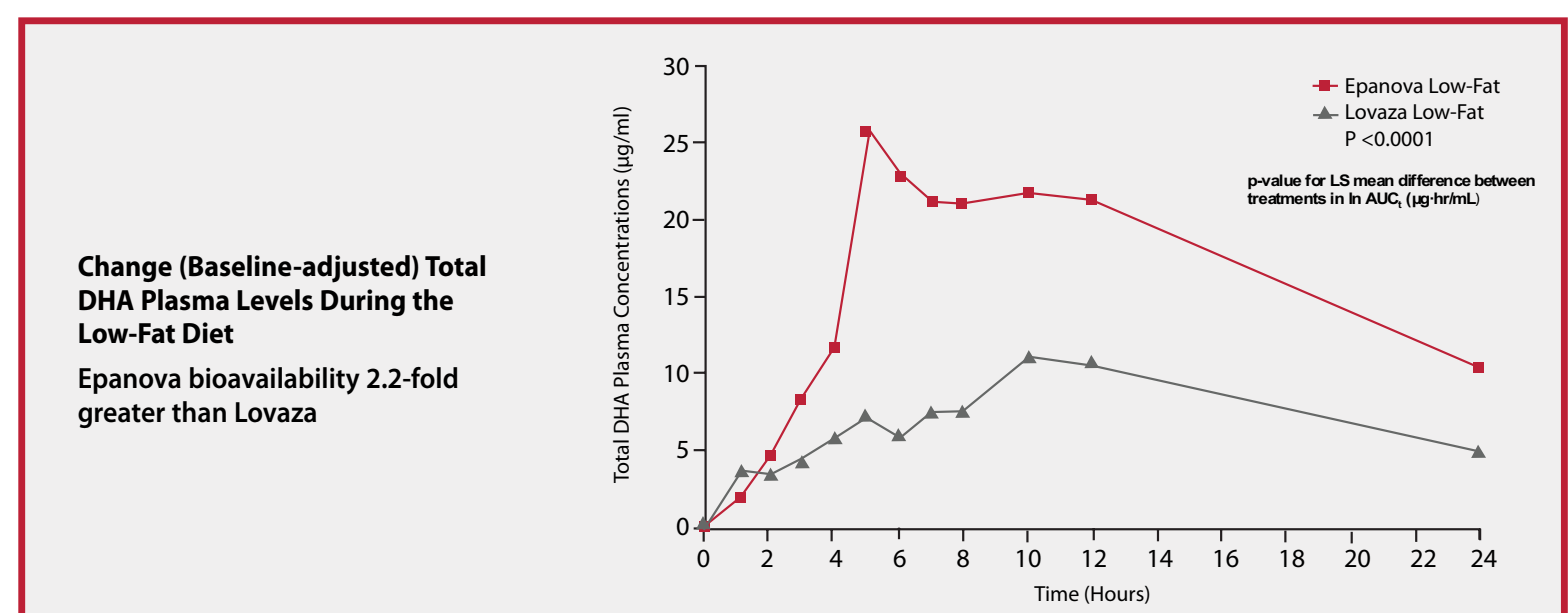


Table 3. Pharmacokinetic Analysis of Total DHA Following a Single Dose (4 g) of Epanova vs Lovaza During Low-fat Diet Period

Bioavailability Parameter	Least Square Mean		Ratio of Means (%)	P-value <sup>a</sup>	Intra Subject C.V. % <sup>b</sup>	Inter Subject C.V. % <sup>b</sup>	90% Confidence Interval Limits (%)	
	Epanova	Lovaza					Lower	Upper
Baseline-Adjusted Change								
$AUC_i$ ( $\mu$ g-hr/mL)	383.06	173.40	220.91	<0.0001	55.2	32.1	192.10	249.72
$C_{max}$ ( $\mu$ g/mL)	35.50	19.19	185.02	<0.0001	66.0	48.3	154.43	215.61
$T_{max}$ (hr)	8.45	10.72	78.84	0.0148	47.3	24.0	64.82	92.87
Baseline-Adjusted Change (Ln-transformed) Data (Geometric Means)								
Ln $AUC_i$ ( $\mu$ g-hr/mL)	337.09	162.19	207.84	<0.0001	61.3	21.4	171.98	251.17
Ln $C_{max}$ ( $\mu$ g/mL)	30.17	15.00	201.14	<0.0001	52.5	42.2	170.73	236.96

N = 53  
<sup>a</sup> P-value is for the Least Square (LS) Mean Difference between Epanova and Lovaza from the ANOVA model  
<sup>b</sup> Covariance %

Figure 4. Bioavailability of Total EPA + DHA (Baseline-adjusted Change) Following Single Dose (4 g) Lovaza During the Low-fat and High-fat Diet Periods

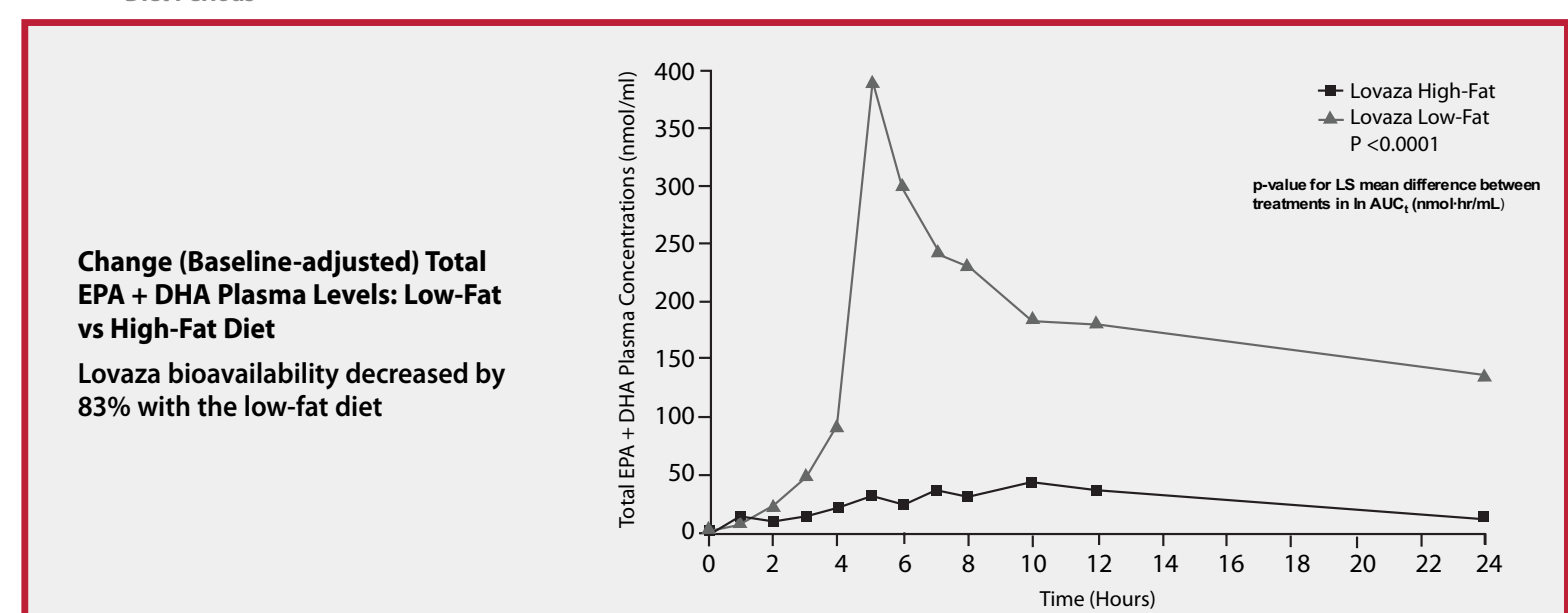


Table 4. Pharmacokinetic Analysis of Total EPA + DHA Following a Single Dose (4 g) of Lovaza During the Low-fat and High-fat Diet Periods

Bioavailability Parameter	Least Square Mean		Ratio of Means (%)	P-value <sup>a</sup>	Intra Subject C.V. % <sup>b</sup>	Inter Subject C.V. % <sup>b</sup>	90% Confidence Interval Limits (%)	
	Low-Fat	High-Fat					Lower	Upper
Baseline-Adjusted Change								
$AUC_i$ (nmol-hr/mL)	661.63	3959.52	16.7	<0.0001	69.1	3.47	3.47	29.95
$C_{max}$ (nmol/mL)	86.89	448.63	19.4	<0.0001	70.7	5.50	5.50	33.23
$T_{max}$ (hr)	10.19	6.28	162.3	0.0001	54.5	138.32	138.32	186.24
Baseline-Adjusted Change (Ln-transformed) Data (Geometric Means)								
Ln $AUC_i$ (nmol-hr/mL)	652.06	3468.17	18.8	<0.0001	55.3	15.72	15.72	22.49
Ln $C_{max}$ (nmol/mL)	60.61	398.07	15.2	<0.0001	69.2	12.35	12.35	18.78

N = 52  
<sup>a</sup> P-value is for the Least Square (LS) Mean Difference between low-fat and high Lovaza from the ANOVA model  
<sup>b</sup> Covariance %

## CONCLUSIONS

The baseline-adjusted change in total EPA + DHA and individual EPA and DHA absorption profiles ( $AUC_i$ ) with Epanova (omega-3 free fatty acids) were significantly greater than with Lovaza (omega-3-acid ethyl esters) during the high-fat diet period and dramatically better during the low-fat diet period. Furthermore, there was a very profound impact of fat content of the meals on the bioavailability of Lovaza, whereas the bioavailability of Epanova was much more predictable due to only a modest food effect. The superior fat-independent bioavailability of Epanova over Lovaza is expected to be clinically important as patients with severely elevated triglycerides require a very low-fat diet.

## REFERENCES

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