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Comparison of Systemic Exposure of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) Following Multiple Doses of Epanova® and Vascepa® in Healthy Normal Subjects after a Low-Fat Meal

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Conclusions

- **This randomized, open-label study compared the bioavailability of EPA and a combination of EPA and DHA (total omega-3 fatty acids) after dosing with omega-3 carboxylic acids (OM3-CA; Epanova®) 2 g or 4 g once daily, or icosapent ethyl (IPE; Vascepa®) 2 g twice daily.**
- **Despite the concentration of EPA in each 1 g capsule of IPE being almost double that in each 1 g capsule of OM3-CA (not less than 96% vs approximately 55%), overall baseline-adjusted EPA exposures over a 24-hour period (area under the concentration–time curve [$AUC_{0\text{-}24}$]) following multiple doses were comparable for the two drugs (geometric mean ratio [GMR] 93.9% for OM3-CA 4 g once daily relative to IPE 2 g twice daily).**
- **The maximum observed concentration at steady state ($C_{max,ss}$) of EPA was 39.3% higher after dosing with OM3-CA 4 g once daily than after dosing with IPE 2 g twice daily.**
- **The $AUC_{0\text{-}24}$ and $C_{max,ss}$ values for total omega-3 fatty acids were 30.6% and 91.8% greater, respectively, after dosing with OM3-CA 4 g once daily than after dosing with IPE 2 g twice daily.**
- **These results are consistent with superior absorption under low-fat dietary conditions of the free fatty acid forms of EPA and DHA found in OM3-CA, relative to the ethyl ester form of EPA found in IPE.**

Purpose

- Individuals with elevated triglyceride (TG) levels have an increased risk of cardiovascular events relative to those with normal TG levels.[1–3]
- Omega-3 fatty acid preparations are a treatment option for lowering TG levels in patients with severe hypertriglyceridemia (≥ 500 mg/dL), when used as an adjunct to dietary modification.[4]
- OM3-CA is a complex mixture of fatty acids, of which EPA and DHA are the most prevalent (approximately 55% and approximately 20%, respectively).
- In contrast to other available omega-3 fatty acid preparations, OM3-CA contains the free fatty acid forms of EPA and DHA, rather than ethyl esters.[5]
- IPE is an omega-3 fatty acid preparation containing the ethyl ester form of EPA only (not less than 96%).
- The use of the free fatty acid forms of EPA and DHA, rather than the ethyl ester forms, results in increased bioavailability after dosing under low-fat dietary conditions, because the ethyl esters require hydrolysis by intestinal lipases before absorption. Patients with hypertriglyceridemia are advised to restrict dietary fat intake, thereby lowering intestinal lipase secretion.[6,7]
- One of the aims of the ECLIPSE III study was to compare the bioavailability of EPA and total omega-3 fatty acids after dosing with OM3-CA or IPE.

Methods

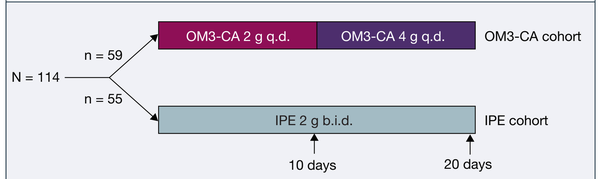
Study design

- ECLIPSE III was a randomized, open-label, two-cohort, multiple-dose bioavailability study of healthy adults consuming a low-fat diet, funded by Omthera Pharmaceuticals.
- Included volunteers were healthy, non-smoking adults, 18–55 years of age, with a body mass index (BMI) between 18.5 and 32.0 kg/m^2. Women were required not to be of childbearing potential.
- A total of 114 individuals were randomized to two cohorts (Figure 1).
  - Cohort 1 (OM3-CA cohort, n = 59) received OM3-CA 2 g once daily for 10 days, followed by OM3-CA 4 g once daily for a further 10 days.
  - Cohort 2 (IPE cohort, n = 55) received IPE 2 g twice daily for a total of 20 days.
- A minimum 10-day dosing regimen was chosen to ensure that steady-state levels of OM3-CA and IPE, respectively, were reached.
- Participants followed the Therapeutic Lifestyle Change diet throughout the study, consuming 25–30% of total calories as fat.
- After a 3-day dietary standardization period and before the first dose of either OM3-CA or IPE, seven blood samples were taken over 24 hours for assessment of mean baseline EPA, DHA and total omega-3 fatty acid levels. Further blood samples were taken at specified times over a 24-hour period (hourly for 12 hours, then again at 24 hours) on day 10 and day 20 in both cohorts.
- Safety and tolerability were monitored throughout the study.

EPA and total omega-3 fatty acids assessment

- Plasma EPA and DHA concentrations were measured using validated methods, with a lower limit of quantification of 1.0 µg/mL.

Figure 1. Study design.



b.i.d., twice daily; IPE, icosapent ethyl; OM3-CA, omega-3 carboxylic acids; q.d., once daily.

- For baseline-adjusted results, the mean pre-dose EPA and DHA levels for each individual were subtracted from their measured, unadjusted post-dose EPA or DHA concentrations, respectively, before the calculation of pharmacokinetic parameters.
- EPA and DHA concentrations were expressed as µg/mL, whereas total omega-3 fatty acid concentrations were calculated as nmol/mL by adding the molar concentrations of EPA and DHA at each time point.
- Pharmacokinetic parameters were calculated for EPA and total omega-3 fatty acids, including the following.
  - $AUC_{0\text{–}t}$: AUC from 0 hours to the end of the dosing period (24 hours for the OM3-CA cohort [once-daily dosing] and 12 hours for the IPE cohort [twice-daily dosing]).
  - $AUC_{0\text{–}24}$ (calculated as $AUC_{0\text{–}t} \times 2$ for the IPE cohort).
  - $C_{max,ss}$: the maximum observed concentration at steady state.
  - C_{avg}: the mean concentration for the dosing period ($AUC_{0\text{–}t}$/24 for the OM-3 CA cohort; $AUC_{0\text{–}t}$/12 for the IPE cohort).
- GMRs and 90% confidence intervals (CIs) were calculated using ln-transformed parameters, after baseline adjustment for baseline-adjusted analysis.
- Pharmacokinetic analysis was performed using Phoenix® WinNonlin® version 6.3 (Pharsight, St Louis, MO, USA) and statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and baseline characteristics

- The demographic and baseline characteristics of both cohorts were similar.
- A total of 93.9% of participants were men, and 61.4% were black or African–American, 31.6% were white and 7.0% were of mixed race.
- The mean age was 37 years (range 18–55 years) and the mean BMI was 27.0 kg/m^2 (range 18.6–31.9 kg/m^2).

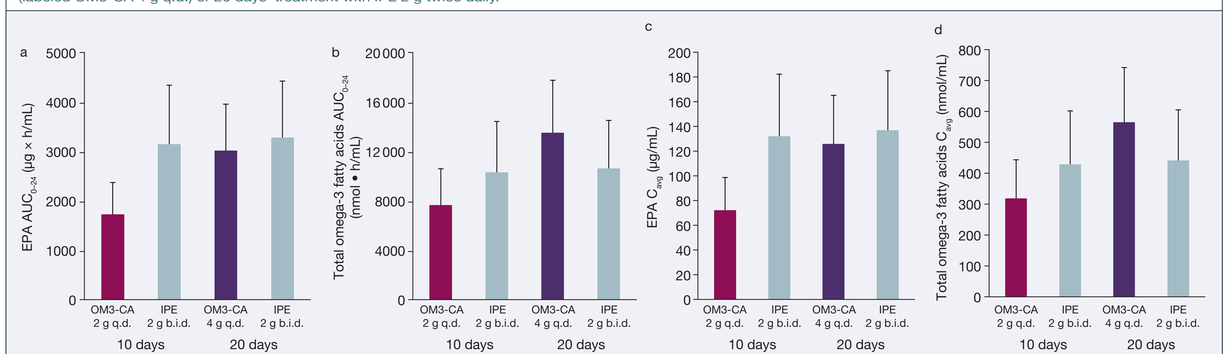
Baseline-adjusted EPA and total omega-3 fatty acid pharmacokinetic parameters

- The baseline-adjusted $AUC_{0\text{–}24}$ values for EPA at the end of the treatment period were comparable with OM3-CA 4 g once daily and IPE 2 g twice daily (GMR 93.9%, 90% CI within 80–125% limits) (Table 1, Figure 2a).
- In comparison, $AUC_{0\text{–}24}$ values for total omega-3 fatty acids were 30.6% greater after OM3-CA 4 g once daily than after IPE 2 g twice daily at day 20 (IPE does not contain DHA) (Table 1, Figure 2b).
- $C_{max,ss}$ values for both EPA and total omega-3 fatty acids were higher in the OM3-CA cohort than in the IPE cohort at day 20 (GMR 139.3% for EPA and 191.8% for total omega-3 fatty acids), while C_{avg} values for EPA were comparable, and for total omega-3 fatty acids were higher in the OM3-CA cohort than in the IPE cohort (Table 1, Figure 2c and d).
- $AUC_{0\text{–}t}$ values for EPA were similar after dosing with either OM3-CA 2 g once daily or IPE 2 g twice daily for 10 days (GMR 111.0%, 90% CI within 80–125% limits), but $AUC_{0\text{–}t}$ for total omega-3 fatty acids was higher with OM3-CA than with IPE (GMR 149.9%) (Table 2).

Safety

- Both OM3-CA and IPE appeared to be well tolerated throughout the study.

Figure 2. Arithmetic mean $AUC_{0\text{–}24}$[a] for (a) EPA and (b) total omega-3 fatty acids, and C_{avg} for (c) EPA and (d) total omega-3 fatty acids after 10 days' treatment with OM3-CA 2 g once daily, 10 days' treatment with IPE 2 g twice daily, treatment with OM3-CA 2 g once daily for 10 days followed by OM3-CA 4 g once daily for 10 days (labeled OM3-CA 4 g q.d.) or 20 days' treatment with IPE 2 g twice daily.



Error bars show standard deviation.
[a]$AUC_{0\text{–}t} \times 2$ for the IPE cohort.
AUC, area under the curve; b.i.d., twice daily; C_{avg}, average concentration; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IPE, icosapent ethyl; OM3-CA, omega-3 carboxylic acids; q.d., once daily.

Table 1. Baseline-adjusted geometric mean pharmacokinetic parameters of EPA and total omega-3 fatty acids after 20 days' dosing with OM3-CA or IPE (per protocol assessment).

		OM3-CA cohort 20 days' dosing[a] n = 56[b]	IPE cohort 20 days' dosing[c] n = 53[d]	Percentage GMR[e] (90% CI)
EPA	$C_{max,ss}$, µg/mL	202.3	145.2	139.3 (126.6–153.3)
	C_{avg}, µg/mL	121.8	129.7	93.9 (85.6–103.0)
	$AUC_{0\text{–}24}$, µg · h/mL[f]	2923.3	3112.6	93.9 (85.6–103.0)
Total omega-3 fatty acids	$C_{max,ss}$, nmol/mL	911.1	475.1	191.8 (173.2–212.4)
	C_{avg}, nmol/mL	541.8	414.8	130.6 (118.0–144.5)
	$AUC_{0\text{–}24}$, nmol · h/mL[f]	13 002.9	9955.2	130.6 (118.0–144.5)

Data for the OM3-CA and IPE cohorts are geometric least-squares means.
[a]2 g once daily for 10 days then 4 g once daily for 10 days. [b]Three patients in cohort 1 were excluded from the day 20 analysis. [c]2 g twice daily. [d]Two patients in cohort 2 were excluded from the day 20 analysis. [e]GMR expressed as OM3-CA/IPE. [f]$AUC_{0\text{–}t} \times 2$ for the IPE cohort.
AUC, area under the curve; CI, confidence interval; C_{avg}, mean concentration; $C_{max,ss}$, maximum concentration; EPA, eicosapentaenoic acid; GMR, geometric mean ratio; IPE, icosapent ethyl; OM3-CA, omega-3 caroxylic acids.

Table 2. Baseline-adjusted geometric mean pharmacokinetic parameters of EPA and total omega-3 fatty acids after 10 days' dosing with OM3-CA or IPE (per protocol assessment).

		OM3-CA cohort 10 days' dosing[a] n = 56[b]	IPE cohort 10 days' dosing[c] n = 54[d]	Percentage GMR[e] (90% CI)
EPA	$C_{max,ss}$, µg/mL	122.7	141.8	86.6 (78.1–95.9)
	C_{avg}, µg/mL	68.4	123.3	55.5 (50.1–61.5)
	$AUC_{0\text{–}t}$, µg · h/mL	1642.5	1480.1	111.0 (100.2–123.0)
	$AUC_{0\text{–}24}$, µg · h/mL[f]	1642.5	2960.2	55.5 (50.1–61.5)
Total omega-3 fatty acids	$C_{max,ss}$, nmol/mL	559.0	470.0	119.0 (106.7–132.6)
	C_{avg}, nmol/mL	300.5	401.0	74.9 (67.1–83.7)
	$AUC_{0\text{–}t}$, nmol · h/mL	7211.5	4811.5	149.9 (134.1–167.5)
	$AUC_{0\text{–}24}$, nmol · h/mL[f]	7211.5	9623.9	74.9 (67.1–83.7)

Data for the OM3-CA and IPE cohorts are geometric least-squares means.
[a]2 g once daily. [b]Three patients in cohort 1 were excluded from the day 10 analysis. [c]2 g twice daily. [d]One patient in cohort 2 was excluded from the day 10 analysis. [e]GMR expressed as OM3-CA/IPE. [f]$AUC_{0\text{–}t} \times 2$ for the IPE cohort.
AUC, area under the curve; CI, confidence interval; C_{avg}, mean concentration; $C_{max,ss}$, maximum concentration; EPA, eicosapentaenoic acid; GMR, geometric mean ratio; IPE, icosapent ethyl; OM3-CA, omega-3 caroxylic acids.

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Disclosures

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