

1 C was often offset by concurrent treatment with statins.⁶³³⁷ The safety and efficacy of using
2 prescription omega-3 in combination with a statin has been well-established.⁶³³⁸

3 Although an increase in LDL-C was generally observed when omega-3 fatty acids were
4 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a
5 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.

6 Therefore, the final LDL-C concentration may still be in the normal range.⁶³³⁹ Furthermore, it
7 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁶³⁴⁰

8 In two pivotal studies in very-high TG patients, both of which used prospective,
9 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
10 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).⁶³⁴¹ Correspondingly, prescription
11 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.⁶³⁴² Therefore,
12 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
13 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
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15 ⁶³³⁷ See Harris 2008 at 14, McKenney at 722.

16 ⁶³³⁸ McKenney at 722-23.

17 ⁶³³⁹ See Westphal at 918, Harris 1997 at 389.

18 ⁶³⁴⁰ See Pownall at 295 (stating that “[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals
with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester
transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he
19 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-
high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the
20 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
21 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
22 decreased non-HDL-C levels (TC minus HDL-C”).

23 ⁶³⁴¹ McKenney 2007 at 721 (citing Harris 1997 and Pownall).

24 ⁶³⁴² McKenney 2007 at 722 (see Fig. 1).

1 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
2 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
3 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the
4 number of small, dense LDL particles to larger LDL particles.⁶³⁴³ Lovaza/Omacor “adversely
5 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
6 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”⁶³⁴⁴
7 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3
8 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not
9 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention
10 of [coronary heart disease].”⁶³⁴⁵

11 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
12 the time of the claimed inventions would have been motivated to find a therapy that would
13 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting
14 LDL-C levels,”⁶³⁴⁶ one of ordinary skill in the art at the time of the invention understood that the
15 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with
16 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to
17 increase in very-high TG patients, and in some instances the rise was not concerning because
18 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final
19 concentration would still be in the normal range. When LDL-C levels increased beyond what
20 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

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22 ⁶³⁴³ McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

23 ⁶³⁴⁴ Stalenhoef at 134.

24 ⁶³⁴⁵ Harris 1997 at 389.

⁶³⁴⁶ Defendants’ Joint Invalidation Contentions at 795.

1 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of
2 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to
3 identify any other basis upon which a person of ordinary skill would have been motivated to find
4 a therapy that would reduce TG levels in patients with very-high TG levels without negatively
5 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood
6 that EPA therapy would *not* reduce Apo-B⁶³⁴⁷ (which is a reflection of total atherogenic
7 lipoproteins)⁶³⁴⁸ in very high TG patients, and accordingly would not have been motivated to
8 administer the claimed EPA composition to the very high TG patient population.

9 Defendants make the conclusory allegation that “routine optimization” by a person of
10 ordinary skill would yield the claimed invention.⁶³⁴⁹ Defendants, however, have offered no
11 explanation to support that allegation and they further fail to establish any of the required criteria
12 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
13 factual detail to support their allegation and they fail to link the allegation to any particular claim
14 or claim element. Defendants mere allegation constitute an improper placeholder to later
15 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
16 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the
17 combinations alleged by Defendants and, for the same reasons, it would not be routine to
18 combine such references. Where, for example, defendants argue that it would be routine to go
19 from the high TG patient population to the very high TG patient population,⁶³⁵⁰ they provide no
20 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill

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22 ⁶³⁴⁷ see Section V.O.

23 ⁶³⁴⁸ see Section III.

24 ⁶³⁴⁹ See, e.g., Defendants’ Joint Invalidation Contentions at 822, 790, 804, .

⁶³⁵⁰ Defendants’ Joint Invalidation Contentions at 816-17

1 would have understood these patient populations to be distinct with different impacts of lipid
2 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
3 not have considered the dosage modification suggested by defendants to be routine; Defendants'
4 argument to the contrary represents hindsight bias.

5 In addition, a person of ordinary skill would have no motivation to combine these
6 references because EPA would have been expected to have same result as the mixture of EPA
7 and DHA used in Lovaza/Omacor.

8 (v) A Person of Ordinary Skill Would Not Have
9 Had a Reasonable Expectation of Success
10 with the Combinations Defendants
11 Hypothesize

12 Defendants provide no evidence that a person of ordinary skill would have had a
13 reasonable expectation of successfully obtaining the claimed invention—a method of reducing
14 triglycerides in a subject having very-high triglyceride levels by administering EPA of the
15 recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by
16 combining the references cited by defendants. For a particular combination of references, there
17 must be a reasonable expectation that the combination will produce the claimed invention. In
18 this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with
19 very-high TG levels.⁶³⁵¹ A person of ordinary skill would have expected EPA, like
20 Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG
21 patient population. As discussed in Section III and above, it was well known that TG-lowering

22 ⁶³⁵¹ As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to
23 have the same TG lowering mechanism and would have further understood that the increase in LDL-C
24 accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar
fashion to Lovaza or DHA alone.

1 agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for
 2 normal to high TG patients, but caused significant increases in LDL-C levels for patients with
 3 very-high triglycerides. The art cited by Defendants provides no basis for a person of ordinary
 4 skill to expect anything to the contrary. A person of ordinary skill would have understood that
 5 omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among
 6 very high TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁶³⁵²	-20%	+45%
Lovaza/Omacor ⁶³⁵³	-6%	+45%

11 Accordingly, a person of ordinary skill would *not* have a reasonable expectation of
 12 success in achieving a reduction in TG levels without substantially increasing LDL-C in patients
 13 with very-high TG levels.⁶³⁵⁴

14 Defendants’ position that a person of ordinary skill would have had a reasonable
 15 expectation of success in administering purified EPA to patients with very high triglyceride
 16 levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that
 17 Defendants’ provide no evidence that anyone thought to administer Epadel.⁶³⁵⁵ Epadel was
 18 available for many years prior to the invention of the ’594 patent, to patients with very-high TGs
 19 as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,

21 ⁶³⁵² Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

22 ⁶³⁵³ Chan 2002 I at 2381 (Table 3).

23 ⁶³⁵⁴ Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall
 effect on lipid parameters, teaching away from this combination.

24 ⁶³⁵⁵ Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not
 examined in any study directed to the very-high TG patient population supports Amarin’s position.

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