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

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[6339] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[6340]

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

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[6337] *See* Harris 2008 at 14, McKenney at 722.

[6338] McKenney at 722-23.

[6339] *See* Westphal at 918, Harris 1997 at 389.

[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 chancing LDL structure; lowering serum [cholesteryl ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C"); Harris 1997 at 389 (stating that "[t]he 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 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 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 decreased non-HDL-C levels (TC minus HDL-C)").

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

[6342] McKenney 2007 at 722 (*see* Fig. 1).

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

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

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

[6344] Stalenhoef at 134.

[6345] Harris 1997 at 389.

[6346] Defendants' Joint Invalidity Contentions at 795.

reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to identify any other basis upon which a person of ordinary skill would have been motivated to find a therapy that would reduce TG levels in patients with very-high TG levels without negatively impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[6347] (which is a reflection of total atherogenic lipoproteins) [6348] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

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

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[6347] *see* Section V.O.

[6348] *see* Section III.

[6349] *See, e.g.*, Defendants' Joint Invalidity Contentions at 822, 790, 804, .

[6350]Defendants' Joint Invalidity Contentions at 816-17

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

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

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

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

[6351] As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to have the same TG lowering mechanism and would have further understood that the increase in LDL-C 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.

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

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

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

[6352] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[6353] Chan 2002 I at 2381 (Table 3).

[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.

[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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