CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204977Orig1s000

MEDICAL REVIEW(S)

TO: NDA-204977: Trygg Pharmaceuticals 505(b)(2) application for AKR-963

FROM: Eric Colman

DATE: January 24, 2014

RE: Identity Standards and Naming Issues

I. LEGAL AND REGULATORY BACKGROUND

Section 502(e)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires the established names of a drug product and its active ingredient(s) be on the product label. Section 502(e)(3) of the FD&C Act in turn defines "established name," in relevant part as, if such article is "an article recognized in an official compendium, [] the official title thereof in such compendium." Section 201(j) of the FD&C Act defines as an "official compendium" the *United States Pharmacopeia-National Formulary* (*USP-NF),* the compendium published by the United States Pharmacopeial Convention. There also are statutory provisions that require, under specific circumstances, compliance with USP substantive compendial standards. Specifically, section 502(g) of the FD&C Act provides that a drug is misbranded if it "it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein." Section 501(b) of the FD&C Act provides that a drug is adulterated if it "purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from or its quality or purity falls below, the standards set forth in such compendium."

Food and Drug Administration (FDA or the Agency) regulations address compendial names, and provide that:

> The name by which a drug is designated shall be clearly distinguishing and differentiating from any name recognized in an official compendium unless such drug complies in identity with the identity prescribed in an official compendium under such recognized name.

21 CFR 299.5(a). Thus, under these statutory and regulatory provisions, a product's name cannot be the same as the relevant USP drug product monograph title unless the product complies with the identity prescribed in that monograph. Otherwise, the product risks being misbranded under section 502 of the FD&C Act.

Though neither the statute nor FDA's regulations expressly define "identity" for these purposes, FDA has provided guidance on this issue. In FDA's guidance for industry on *ANDAs: Pharmaceutical Solid Polymorphism Chemistry, Manufacturing, and Controls Information*, the Agency provided that: "[w]hen a United States Pharmacopeia (USP) monograph exists for a particular drug substance, standards for identity generally refer to the definition (e.g. chemical

name, empirical formula, molecular structure, description) at the beginning of the monograph."[1] The guidance also notes that FDA may prescribe additional standards that are material to the sameness of a drug substance.[2]

II. FACTUAL BACKGROUND

Trygg Pharmaceuticals (Trygg) submitted a new drug application (NDA) pursuant to section 505(b)(2) of the FD&C Act, for its fish oil product, AKR-963. Trygg's NDA references another, previously approved fish oil product, Lovaza (omega-3-acid ethyl esters) Capsules (NDA 21654). The Lovaza labeling describes that drug's content as follows: "Each 1-gram capsule of LOVAZA contains at least 900 mg. of the ethyl esters of omega-3 fatty acids sourced from fish oils."[3] According to its labeling, the predominant components of Lovaza are the ethyl esters of Eicosapentaenoic acid (EPAee) (approx. 465 mg.) and Docosahexaenoic acid (DHAee) (approx. 375 mg.). Lovaza also contains the ethyl esters of five other omega-3 fatty acids in lesser amounts. Together with EPAee and DHAee, these omega-3 fatty acid ethyl esters constitute at least 90% of Lovaza's active ingredient (the omega-3 component). The remainder of Lovaza's active ingredient includes various other components, not all of which have been characterized (the non-omega-3 component).

An official USP drug substance monograph exists for "Omega-3-Acid Ethyl Esters."[4] An official USP drug product monograph for "Omega-3-Acid Ethyl Esters Capsules" also exists, and incorporates the "Omega-3-Acid Ethyl Esters" drug substance monograph by reference.[5] The drug substance monograph provides, in its "definition" section, that omega-3-acid ethyl esters "contains [not less than] 90% (w/w) of the [the seven omega-3 fatty acid ethyl esters that comprise Lovaza's omega-3 component]."

Trygg describes AKR-963 as a 1.2 g. capsule that "contains at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils." The omega-3 component of AKR-963 also contains predominantly roughly the same amounts of EPAee and DHAee as in Lovaza. At the same time, since AKR-963 is a 1.2 g. capsule compared to Lovaza's 1g., it contains approximately 20% more fish oil than Lovaza, which means that it contains more of the non-omega-3 component than does Lovaza.[6]

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[1] Guidance for Industry on *ANDAs: Pharmaceutical Solid Polymorphism Chemistry, Manufacturing, and Controls Information*, at 5 (2007) (ANDA Polymorph Guidance). *See, e.g.*, Letter to P. Safif, Covington & Burling fr. D. Throckmorton, Dep. Dir. FDA CDER re. Docket No. FDA-2003-P-0273 (July 23, 2010) (addressing USP standards of identity for enoxaparin sodium injection).

[2] ANDA Polymorph Guidance, *supra* note 1, at 5. *See* FDA, *Abbreviated New Drug Application Regulations*, Final Rule, 57 Fed. Reg. 17950, 17959 (April 28, 1992).

[3] Lovaza Prescribing Information, at 5 (Sep. 2013 revision), *available at* http://www.accessdata fda.gov/drugsatfda_docs/label/2013/021654s039lbl.pdf.

[4] USP 36-NF 1, at 4571 (2013).

[5] *Id.* at 4574 ("Omega-3-Acid Ethyl Esters Capsules contain Omega-3-Acid Ethyl Esters . . . .").

[6] A separate memorandum describes FDA's reasoning as to why Lovaza and AKR-963 therefore have different

In its application, Trygg requested that FDA approve the product with the established name "[redacted]." FDA notified Trygg that the Agency had preliminarily determined that the proposed product did not meet the relevant USP standards for identity, and requested that Trygg provide proposed alternative established names consistent with 21 CFR 299.5.[7] In response, Trygg submitted proposed alternative names, but also asserted that AKR-963 meets the standards for identity under 21 CFR 299.5 because the product satisfies the tests provided in the "identification" section of the Omega-3-Acid Ethyl Esters monograph.[8] This memorandum addresses whether Trygg's proposed product meets the identity requirement in 21 CFR 299.5, and therefore, whether Trygg may use the name "[redacted]" as the product's established name.

III. DISCUSSION

As described above, in order for Trygg's product to be named "[redacted]," the product must comply with the standards for identity set forth in the USP drug product monograph for [redacted].[9] That monograph, in turn, incorporates by reference the USP drug substance monograph for Omega-3-Acid Ethyl Esters.[10] Therefore, AKR-963 must comply in identity with the standard of identity prescribed in the "definition" section of the drug substance monograph in order to be named "[redacted]."

Trygg's proposed drug substance does not meet the definition of omega-3-acid ethyl esters as set forth in the drug substance monograph. The "definition" section of the Omega-3-Acid Ethyl Esters monograph provides that the drug substance is "a substance derived from transesterification of the body oil obtained from fish that contains, among other things, "[not less than] 90% (w/w) of the sum of [seven different omega-3-acid ethyl ester components in Lovaza]." While Lovaza and proposed AKR-963 both contain at least 900 mg. of the omega-3 component, only Lovaza meets the compendial standard for "Omega-3-Acid Ethyl Esters" because Lovaza contains an omega-3 component that is consistent with the concentration range set forth in the drug substance monograph (i.e., not less than 90% (w/w)). In comparison, AKR-963's active ingredient does not contain an omega-3 component that complies with this

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active ingredients. See Eric Colman, Memo to File, Citizen Petition – Lovaza (Omega-3-Acid Ethyl Esters) Strength Listing (Docket No. FDA-2013-P-0148) (January 24, 2014).

[7] [redacted]

[8] [redacted]

[9] *Supra* note 5.

[10] Omega-3-Acid Ethyl Esters, *supra* note 4. *See* USP 35-NF 30, General Notices 3.10, Applicability of Standards ("Official products are prepared according to recognized principles of good manufacturing practice and from ingredients that meet USP or NF standards, where standards for such ingredients exist . . . .").

compendial requirement. Specifically, the sum of relevant omega-3-acid ethyl esters in a 1.2 g. capsule of AKR-963 is potentially as low as (b) (4)% (w/w). Thus, AKR-963 does not comply with the "definition" section of the Omega-3-Acid Ethyl Esters monograph because its omega-3 component is less than 90% (w/w).

Contrary to Trygg's assertion, data showing that a product satisfies the assays in the "identification" section of a relevant monograph is insufficient to demonstrate that the product "complies in identity with" the relevant monograph under 21 CFR 299.5(a). The assays set forth in the "identification" section of the "Omega-3-acid Ethyl Esters" monograph provide a mechanism to confirm that a drug product contains DHAee and EPAee, but not that it contains the omega-3-acid ethyl esters drug substance, which includes more than just those two components. The Omega-3-Acid Ethyl Esters monograph sets forth additional limits as to what the concentration of the omega-3 component should be in its "definition" section. Accordingly, consistent with FDA's prior guidance on this issue, the Agency has determined that Trygg's product must comply with both the "identification" section and the "definition" section of the Omega-3-Acid Ethyl Esters drug substance monograph in order to meet the identity requirement in 21 CFR 299.5(a).

The tests prescribed in the "identification" section only confirm the presence (but not the amount) of DHAee and EPAee in a drug product. Accordingly, these tests, without more, are overly broad and risk identifying as "Omega-3 Acid Ethyl Esters" drug substances that may have significant differences from the drug substance in Lovaza. Were FDA to permit Trygg's product to have the established name "(b) (4)" solely on the results of the assays in the "identification" section, this would result in two products, with different active ingredients, sharing the same established name. This is not consistent with FDA's interpretation how a drug would comply with the identity requirement in 21 CFR 299.5(a), i.e., what "standards of identity" in a USP monograph means within the context of that regulation.

In addition, FDA notes that, as reflected in the response to the citizen petition filed in FDA Docket No. 2013-P-0148 (which denies the Petitioner's request to revise Lovaza's strength listing), the Agency has determined that AKR-963 contains a different active ingredient than Lovaza. Thus, even if the definition in the Omega-3-Acid Ethyl Esters drug substance monograph were revised to include AKR-936, FDA would not approve AKR-936 as " (b) (4) ," because that would result in two products, with different active ingredients, sharing the same established name.

IV. CONCLUSION

Upon the foregoing, we conclude that under the relevant statutory provisions and regulations, AKR-963 cannot be named "(b) (4)." It is instead required to have a "clearly distinguishing and differentiating name."

[11] 21 CFR 299.5(a).

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/s/

ERIC C COLMAN
04/14/2014

MEMORANDUM

TO: NDA-204977: Trygg Pharmaceuticals 505(b)(2) application for AKR-963

FROM: Eric Colman

DATE: January 24, 2014

RE: Citizen Petition – Lovaza (Omega-3-Acid Ethyl Esters) Strength Listing (Docket No. FDA-2013-P-0148)

This memorandum discusses the citizen petition submitted by John H. Fuson of Crowell & Moring, LLPon February 6, 2013 (Petition),[1] which seeks a revision to the strength listing for Lovaza (omega-3-acid ethyl esters), and our approval decision regarding Trygg Pharma's 505(b)(2) new drug application (Trygg Application) for its fish oil product. The Trygg Application references another, previously approved fish oil product, Lovaza (omega-3 acid ethyl esters) Capsules (NDA 21654). As explained below, our response to the Petition has potential implications for the Trygg Application, and vice versa. In light of the action we intend to take with respect to the Trygg Application, we have reviewed certain issues raised by the Petition and have made the decisions described below.

Background:

The Food and Drug Administration (FDA or the Agency) approved Lovaza on November 10, 2004 as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. GlaxoSmithKline (GSK) is the current NDA holder for Lovaza.

Lovaza consists of partially purified fish oil which mainly contains a mixture of seven different omega-3 fatty acid ethyl esters (the omega-3 component).[2] The Lovaza labeling describes that drug's content as follows: "Each 1-gram capsule of LOVAZA contains at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils."[3] Eicosapentaenoic acid ethyl ester (EPAee) and docosahexaenoic acid ethyl ester (DHAee) are the principal ethyl esters of the omega-3 component. In addition to the omega-3 component, the fish oil mixture in Lovaza also contains [redacted] (b) (4), some of which have not been

[1] Although the citizen petition does not indicate as such, Mr. Fuson communicated to the Agency that the petition was filed on behalf of Trygg Pharma.

[2] These are: Eicosapentaenoic acid ethyl ester (EPAee), Docosahexaenoic acid ethyl ester (DHAee), Alpha-linolenic acid ethyl ester, Moroctic acid ethyl ester, Eicosatetraenoic acid ethyl ester, Heneicosapentaenoic acid ethyl ester, and Docosapentaenoic acid ethyl ester.

[3] Lovaza Prescribing Information, at 5 (Sep. 2013 revision), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021654s039lbl.pdf.

characterized (the non-omega-3 component). No additional excipients are added to a Lovaza capsule, aside from a small amount of alpha-tocopherol in soybean oil added as an antioxidant for aiding stability. As such, and as FDA appears to have acknowledged at the time it approved Lovaza, currently the entire fish oil mixture is considered to be Lovaza's active ingredient. The *Orange Book* lists the strength for Lovaza as "1 gm contains at least 900 mg of the ethyl esters of omega-3-fatty acids."

Existing USP monographs for Lovaza[4] also define the substance as being derived from transesterification [sic] of the body oil obtained from fish and containing, among other things, "[not less than] 90% (w/w) of the sum of [seven different omega-3 fatty acid ethyl ester components]."[5]

1. Citizen Petition

On February 6, 2013, John H. Fuson, Crowell & Moring, LLP submitted a citizen petition on behalf of Trygg Pharma, requesting that FDA:

(1) Amend the adopted strength for Lovaza to 900 mg., so that the strength appropriately identifies the amount of active ingredient per administration unit without reference to any other capsule properties, such as product weight/fill, excipients or other inactive ingredients.

(2) Or, alternatively, adopt a strength of 840 mg. for Lovaza based upon the fixed amount of major omega-3-acid ethyl esters [EPAee and DHAee] specified in the Lovaza new drug application (NDA) reviews and labeling.

On August 6, 2013, in a comment to the Petition docket, GSK, Lovaza's sponsor, maintained that the active ingredient of Lovaza is the entire mixture, not just the omega-3 component, pointing out, among other things, that the eight pivotal clinical studies that established Lovaza's effectiveness were based on the entire mixture.[6]

2. Trygg Pharma's 505(b)(2) Application

On January 31, 2013, Trygg Pharma submitted a 505(b)(2) application for its fish oil product (AKR-963), seeking to name it "(b) (4)" FDA subsequently notified Trygg that the Agency preliminarily had determined that the proposed product did not meet the relevant USP standards for identity, and requested that Trygg provide proposed alternative established names consistent with 21 CFR 299.5. In response, Trygg submitted

[4] *See* USP 36-NF 1 at 4571, 4574 (2013).

[5] USP 36-NF 1 at 4571.

[6] Covington & Burling, Comments to Docket No FDA-2013-P-0148, at 3 (August 6, 2013).

proposed alternative names, but also asserted that the company's proposed product meets the relevant USP standards for identity because the product satisfies the identification tests provided in the omega-3 acid ethyl esters monographs.[7]

(b) (4). In order for the two products to have the same strength, their active ingredients would need to be: (a) identical, and (b) present in the same amount per dosage form. The Trygg Application describes AKR-963 as a 1.2 g capsule that contains at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils. Accordingly, it appears that AKR-963 contains an omega-3 component that is (b) (4) and is present in roughly the same total amount as, Lovaza's. At the same time, however, AKR-963 has an overall different formulation. The major difference between Lovaza and Trygg's product appears to be the extent to which these products (b) (4) AKR-963 has a roughly 20% greater total volume (1.2 g. compared to Lovaza's 1 g.) and contains approximately 20% more of the non-omega-3 component than Lovaza.

Discussion:

The issue is whether Lovaza's active ingredient is the entire fish oil mixture as determined at the time of Lovaza's approval, or whether we should define Lovaza's active ingredient more narrowly to encompass only the omega-3 component, or even to encompass only the major omega-3 fatty acid ethyl esters, i.e., EPAee and DHAee. If we decide that the entire mixture is the active ingredient, Lovaza would have a different active ingredient than AKR-963 because it would contain a different fish oil mixture. Lovaza's strength would be unchanged at 1 g. and AKR-963 would have a strength of 1.2 g. On the other hand, if we decided to define the active ingredient narrowly to include only the omega-3 component, both products would have the same active ingredient, resulting in a strength listing of 900 mg. for both. Similarly, a determination that the active ingredient is only EPAee and DHAee would mean that both products would have a strength of 840 mg.

After substantial review and consideration of this issue, we have determined that we do not have enough information to change our initial determination that Lovaza's (and, by implication, AKR-963's) active ingredient is the entire fish oil mixture. This decision reflects the Agency's policy regarding products consisting of naturally-derived mixtures, such as Lovaza and AKR-963. In several previous cases where the components of a naturally-derived mixture were not completely

[7] A separate memorandum details our determination with respect to the identity standards and naming issue. See Eric Colman, Memo to File, NDA-204977: Trygg Pharmaceuticals 505(b)(2) application for AKR-963 (January 24, 2014).

characterized,[8] including Lovaza at the time of its approval, FDA has treated the entire mixture as the active ingredient.[9] This policy is reasonable because it is the entire mixture that was evaluated in the clinical trials and no factorial studies were performed to determine the contributions of the individual components or to rule out the possibility of synergistic effects between them. Because we are treating the entire mixture as the active ingredient, we will need to inform Trygg that AKR-963 should have its strength listed as 1.2 g when we approve the Trygg Application.

Though a substantial body of evidence indicates that EPAee and DHAee appear to contribute to the efficacy of Lovaza, evidence with respect to the rest of the components of the drug is lacking. We have been able to locate a significant body of evidence that supports the conclusion that the EPAee and DHAee significantly lower serum TG levels and thus meaningfully contribute to and at least in part are "responsible for physiological or pharmacological effect"[10] of the Lovaza mixture.[11] But, although there is data to show that EPAee and DHAee are at least partly responsible for the pharmacological effect of Lovaza, there is no data that directly demonstrates whether or to what extent the remaining or minor omega-3 fatty acid ethyl esters, (b) (4) of the mixture contribute to the drug's efficacy. We were able to locate publications which suggest that some of the minor omega-3 fatty acid ethyl esters may be converted to EPAee or DHA(ee).[12] But we have not been able to locate any study that

[8] *See, e.g.*, FDA, Conjugated Estrogens Tablets; Proposal to Refuse to Approve Two Abbreviated New Drug Applications, 62 Fed. Reg. 42562 (Aug. 7, 1997) [Conjugated Estrogens FR Notice] (describing the Agency's findings with respect to what constitutes the active ingredient of conjugated estrogens, a mixture derived from the urine of pregnant mares, and refusing to approve ANDAs for products that contained only some of the components of the mixture).

[9] This is not dispositive of whether individual components of such mixtures can be its active moieties, which would require a different analysis under a different set of considerations.

[10] 21 CFR § 314.108(a) (defining "drug substance").

[11] This field appears to be well studied. *See, e.g.*, Terry A. Jacobson, et al., *Effects of Eicosapentaenoic Acid and Docosahexaenoic Acid on Low-density Lipoprotein Cholesterol and Other Lipids: A review*, 6 J. of Clin. Lipidology (2012) (discussing 22 studies with EPA and/or DHA); Melissa Y. Wei & Terry A. Jacobson, *Effects of Eicosapentaenoic Acid versus Docosahexaenoic Acid on Serum Lipids: A Systematic Review and Meta-Analysis*, 13 Current Atherosclerosis Reports 474 (2011) (analyzing the results of 33 studies with EPA and/or DHA).

[12] Gerster H., *Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)?*, 68 Int. J. for Vitamin and Nutrition Research 159 (1998); M.E. Surette, et al., *Dietary echium oil increases plasma and neutrophil long-chain (n-3) fatty acids and lowers serum triacylglycerols in hypertriglyceridemic humans*, 134 J. Nutrition 1406 (2004); G.C. Burdge & P.C. Calder, *Conversion of alpha-linolenic acid to longer-chain polyunsaturated fatty acids in human adults*, 45 Reproduction Nutrition Development 581 (2005); W.S. Harris, et al., *Stearidonic Acid-Enriched Soybean oil increased the omega-3 index, an emerging cardiovascular risk marker*, 43 Lipids 805 (2008); N. Gotoh, et al., *Effects of three different highly purified n-3 series highly unsaturated fatty acids on lipid metabolism in C57BL/KsJ-db/db mice*, 57 J. Agricultural Food Chemistry 11047 (2009); G. Kaur, et al., *Short-term docosapentaenoic acid (22:5 n-3) supplementation increases tissue docosapentaenoic acid, DHA, and EPA concentrations in rats*, 103 *Br J Nutr.* 32 (2010); C.G. Walker, et al., *Stearidonic acid as a supplemental source of ω-3 polyunsaturated fatty acids to enhance status for improved human health*. 29 Nutrition 363 (2013).

provides direct evidence that supplementation with any of the individual minor omage-3 fatty acid ethyl esters can reduce TG levels. In addition, the role of (b) (4) – which are among the drug's non-omega-3 component – in reducing TG levels also has not been conclusively demonstrated.

Significantly, there has been no study comparing Lovaza to EPAee and DHAee or to just the omega-3 component, and we have not been able to locate sufficient evidence to rule out the potential contribution of its other components to Lovaza's efficacy. As the Agency has stated in several instances, the components of a naturally-derived mixture are frequently insufficiently characterized such that it is difficult to define the active ingredient in terms of the specific components of such a mixture.[13] Therefore, FDA believes that it is desirable from both a policy and scientific perspective to characterize the entire mixture as the active ingredient. (b) (4)

Trygg has not provided any information that would lead to the conclusion that the potential therapeutic contribution of either the non-omega-3 component of Lovaza, or the omega-3 fatty acid ethyl esters other than EPAee and DHAee can be discounted (b) (4) .

As GSK notes, Trygg appears to presume that the established name for Lovaza "omega-3 acid ethyl esters" provides sufficient proof that the active ingredient of Lovaza is its omega-3 component.[14] To the contrary, the Lovaza labeling and relevant files in the drug's NDA establish that FDA defined the drug's active ingredient as the entire mixture at the time of approval. For example, the approved labeling listed the drug's strength as 1 g.[15] The Clinical

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[13] *See* Conjugated Estrogens FR Notice, *supra* note 8, at 42566 ("At the time of marketing, products such as Premarin, that are derived from natural source material, frequently are not characterized as completely as synthetic products would be. The term 'adequate characterization' is intended to mean an amount of scientific information on a product that is sufficient to determine what constituents in the product are responsible for making clinically meaningful contributions to its therapeutic effects.").

[14] Covington & Burling, Comments to Docket No FDA-2013-P-0148, at 4 (August 6, 2013).

[15] Omacor label, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21654lbl.pdf (2004) (stating that "Each capsule contains 1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.") (The label is on page 8 of the pdf document). *See* Omacor Prescribing Information at 8, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_Prntlbl.pdf (2004) ("The daily dose of Omacor® is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).").

Pharmacology review characterized the drug substance as "one gram of omega-3-acid ethyl ester drug substance consisting of at least 900 mg. of omega-3-ethyl esters."[16] Moreover, at the time of approval, FDA rejected the suggestion that Lovaza's established name should consist of the names for (b) (4). Instead the Agency determined that the name "omega-3 acid ethyl esters" would be suitable because it "was designed to correspond to *the mixture* (natural product containing EPA and DHA ethyl esters, among other compounds)."[17]

We therefore conclude that the mixture for Lovaza has not been sufficiently characterized such that our initial determination that the mixture in its entirety constitutes the active ingredient of Lovaza would need to be changed. Trygg has not provided any new information or data to support a decision to characterize the active ingredient more narrowly such that it consists only of the omega-3 component (a strength of 900 mg.) (b) (4) Accordingly, AKR-963's active ingredient is also the entire fish oil mixture present in that product. As such, it is a different active ingredient than the one in Lovaza, and AKR-963's strength should be listed as 1.2 g or 1.2 g contains at least 900 mg of the ethyl esters of omega-3 fatty acids upon approval.

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[16] FDA, *Clinical Pharmacology and Biopharmaceutics Review*, Application Number 21-654 at 16 (Oct. 20, 2004) available at http://www.accessdata fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_BioPharmr.pdf.

[17] CDER, Approval Package for NDA 21-654, Administrative/Correspondence, Omacor Action Letters (Nov. 1, 2004) (emphasis added).

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/s/

ERIC C COLMAN
04/14/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204977
Priority or Standard	Standard
Submit Date(s)	1/31/2013
Received Date(s)	1/31/2013
PDUFA Goal Date	11/30/2013
Division / Office	Division of Metabolism and Endocrine Products/Office of New Drugs
Reviewer Name(s)	Iffat Nasrin Chowdhury, MD
Review Completion Date	November 26, 2013
Established Name	Omega-3-acid ethyl esters
(Proposed) Trade Name	Omtryg
Therapeutic Class	Lipid-lowering Agent
Applicant	Trygg Pharma, Inc.
Formulation(s)	Capsules
Dosing Regimen	Oral
Indication(s)	Severe hypertriglyceridemia
Intended Population(s)	Patients with TG $\geq$ 500 mg/dL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

AKR-963 is a fish oil product proposed for the treatment of severe hypertriglyceridemia (TG ≥500 mg/dL). This NDA was submitted as a 505(b)(2) application with the listed drug as Lovaza. (b) (4)

Additional issues related to the approval of this 505(b)(2) application include designation of an established name for AKR-963 as well as determination of the active ingredient and strength. A drug product cannot be marketed in the US without an established name; established names are usually names designated by the USP or USAN. To date, this product does not have an established name. The determination of the active ingredient and strength are the subject of a citizen's petition and a decision is pending with the Office of Regulatory Policy. These other issues, although mentioned in this clinical review, are discussed in documents by other disciplines.

(b) (4)

In this 505(b)(2) application, the applicant conducted a 28-day bridging toxicity study, four bioequivalence trials and an efficacy/safety trial (TRGG-963-002). The usual approach for 505(b)(2) applications is to establish bioequivalence with the listed drug, via bioequivalence trials. However, according to the applicant, the efficacy/safety trial was conducted to establish that the differences between its product and the listed drug do not result in a meaningful therapeutic difference between the two products.

The recommendation from the Office of Clinical Pharmacology is that this NDA be approved. The clinical pharmacology team found that bioequivalence was appropriately demonstrated between AKR-963 and Lovaza under fed and fasted conditions for C_{max} and $AUC_{0\text{-}72hr}$ for total plasma EPA and DHA (the major omega-3-acid ethyl esters).

Although the bioequivalence trials showed that AKR-963 was bioequivalent to Lovaza, a number of statistical issues with study TRGG-963-002 (see details in the following

section) rendered the results of this trial difficult to interpret. AKR-963 was marginally superior to placebo, but because of significant problems with the establishment of a non-inferiority (NI) margin, AKR-963's non-inferior status could not be determined.

In conclusion, the totality of the NDA data supports the bioequivalence of AKR-963 to Lovaza, but a claim for non-inferiority cannot be supported. However, since usually bioequivalence results support a 505(b)(2) application, and bioequivalence was demonstrated, this 505(b)(2) application for AKR-963 can be recommended for approval.

Summary of Important Efficacy Findings

Study TRGG-963-002, the Phase 3 efficacy/safety trial was a 76 week, double-blind trial of patients with TG ≥500 mg/dL but <1500 mg/dL randomized to either AKR-963 (N=106), Lovaza (N=105), or placebo (N=43) for the first 12 weeks (Period A). Subsequently, those on placebo were re-randomized to either AKR-963 or Lovaza for an additional 40 weeks (Period B) and an additional 24 weeks (Period C) as a safety extension.

The primary objective was to demonstrate superiority of AKR-963 to placebo as well as demonstrate the superiority of Lovaza to placebo for lowering TG in patients with severe hypertriglyceridemia. The secondary objective was to demonstrate non-inferiority of AKR-963 to Lovaza with a pre-specified NI margin of 15%. The following table summarizes the median percent change in TG from Baseline to Period A Endpoint for the modified intent to treat (mITT) population.

Table 1: Median Percent Difference in TG from Baseline to Period A Endpoint

	Median% Difference and 95% Confidence Interval	P value
AKR-963 vs. Placebo	-12.2 (-23.9, -0.4)	p=0.041*
Lovaza vs. Placebo	-14.0 (-26.9, -1.1)	p=0.023*
AKR-963 vs.Lovaza	+2.3 (-6%, +10.5%)	p=0.577*

*Wilcoxon test

Although AKR-963 did meet the primary objective of the trial to demonstrate superiority to placebo, the p-value was of borderline statistical significance. The median percent difference in TG of AKR-963 vs. placebo was -12.2 (-23.9, -0.4). p=0.041. Multiple sensitivity analyses confirmed borderline statistical significance.

One hypothesis for the borderline statistical significance is that the placebo treatment arm did better than expected; placebo decreased TG by -17%. This is in comparison with historical Lovaza trials (NDA 021654) in which placebo increased TG by +7%. Placebo was composed of vegetable oil in the applicant's trial and of corn oil in the historical Lovaza trials.

In study TRGG-963-002, the effect of Lovaza, as compared to placebo, was smaller than in the historical Lovaza studies. The median percent difference in TG of Lovaza vs. placebo was -14.0 (-26.9, -1.1), p=0.023. In fact, the -14% TG reduction with Lovaza was smaller than the pre-specified non-inferiority margin of 15% and represents an internal inconsistency that does not allow determination of non-inferiority.

An assumption critical to the interpretation of any non-inferiority trial is the so called constancy assumption. The constancy assumption assumes that the effect of the active control in any NI trial is larger than the margin which is calculated from historical data and represents a conservative estimate of previous differences between Lovaza and placebo. The absolute value of the median difference between Lovaza and placebo was 14% which is smaller, not larger than, the margin. Therefore, these data violate the constancy assumption and the margin of 15% could not be used to evaluate non-inferiority in this trial. Any other calculation of a new NI margin was considered post-hoc analysis.

A hypothesis of why the effect of Lovaza (and AKR-963) was smaller than expected is that patients may have had lower exposure to the active drugs than in historical Lovaza trials. A significant food effect on the bioavailability of Total EPA and Total DHA in plasma was observed for both AKR-963 and Lovaza. This effect has not been submitted to the Agency previously for any approved omega-3 fatty acid based fish-oil product and may be the basis for appropriate changes to the listed drug labeling.

According to the clinical pharmacology review, when AKR-963 was administered under fasted conditions, on average the Cmax and AUC0-72 hrs exposures were lower by up to 20 to 80-fold, respectively, for total plasma EPA and by up to 2 to 4-fold, respectively for total plasma DHA in comparison to those observed under fed conditions. In study TRGG-963-002, patients were not instructed to take their study drugs with food, and this may have accounted for the lower than expected TG results. On the other hand, the in the Lovaza historical trials, patients were instructed to take study drugs with food.

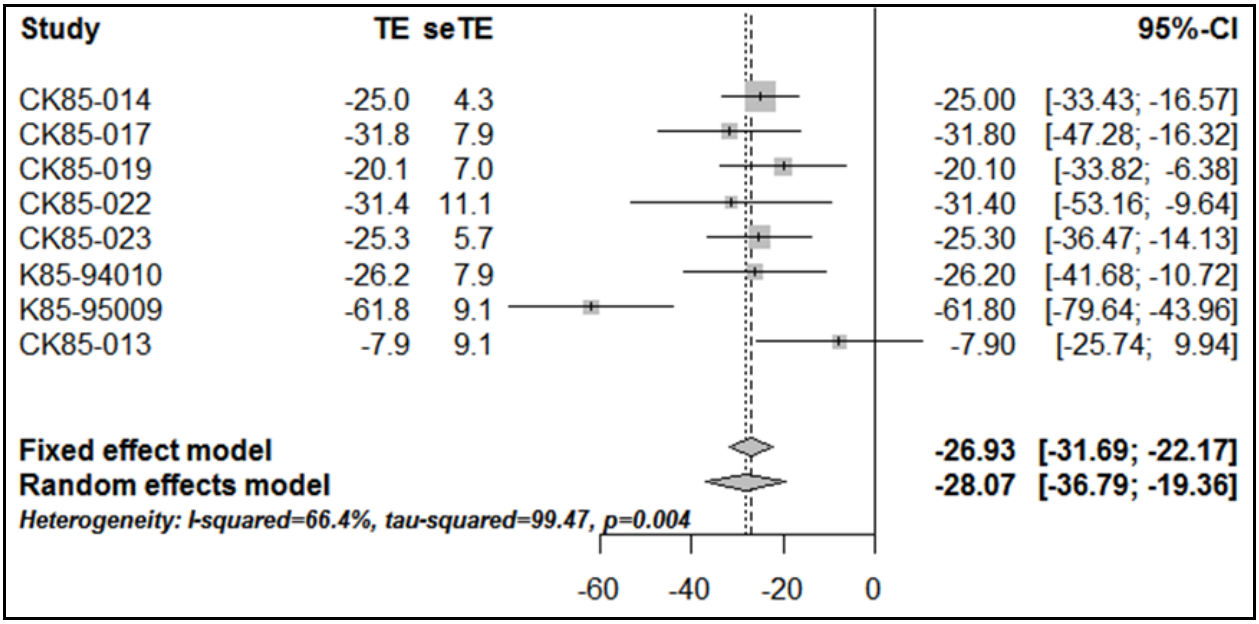
During the course of the review cycle, the Division asked the applicant to explain why the treatment effects of AKR-963 and Lovaza were far less than expected when compared with placebo and noted the fact that the constancy assumption did not hold for study TRGG-963-002.

The applicant responded that the heterogeneity of the placebo response reported in the literature is a confounding factor in interpretation of fish oil trials. Among thirteen placebo-controlled trials (eleven with Lovaza, two with Vascepa), the median percent change from baseline in TG for placebo was 2.6% and with minimum and maximum reported values of -13% and +16%, respectively.

With regard to the constancy assumption, the applicant listed 14 clinical trials with Lovaza 4g dose, but included populations beyond the severe hypertriglyceridemia

population. The applicant stated that the constancy assumption is fulfilled if data beyond the two historical Lovaza trials is considered. However, the clinical review team determined that because the indication was for the population with severe hypertriglyceridemia (TG ≥500 mg/dL), this was the relevant population to consider when establishing a NI margin.

In response to the applicant's submission, the statistical reviewer performed a meta-analysis of seven trials conducted with Lovaza from NDA 021654 using a random effects model; the previous NI margin was calculated using two of the Lovaza trials. The least squared mean (LSM) treatment differences and 95% CI intervals in TG percent change were estimated from the ANCOVA model.



Source: Dr. Lee Ping Pian, Statistical Reviewer

Figure 1: Meta-Analysis of All Eight Lovaza Trials in NDA 021654

Using these seven trials and the random effects model, the median percent difference in TG was -28.07 (-36.79, -19.36). Based on half of the -19.36% upper limit of the 95% confidence interval, the non-inferiority margin was +9.7%. In TRGG-963-002, the treatment difference between AKR-963 and Lovaza was +2.3% (-6%, +10.5%). Therefore, even using the new NI margin of +9.7%, AKR-963 slightly exceeded (+10.5%) this post-hoc calculation of the NI margin.

The applicant also submitted a re-analysis of the primary endpoint. The applicant identified three main problems with the statistical methods used in TRGG-963-002. The problems identified were

- Use of a multiplicity adjustment (when there was no need to adjust)
- Use of Wilcoxon test (that did not account for the randomization strata)
- No incorporation of lipid data at Weeks 2 and 6 to estimate variance

The reanalysis showed a more distinct separation between active product and placebo than the original analysis. The difference is due to the use of intermediate data, the incorporation of the randomization strata, and to the use of a randomization test which does not rely on any distributional assumptions. The results were as follows:

- The estimated placebo-adjusted difference for AKR-963 is -16.8%; one-sided p=0.005, 95% confidence interval = (-30.5%,-3.4%).
- The estimated placebo-adjusted difference for Lovaza is -16.9%; one-sided p=0.002, 95% confidence interval = (-31.8%, -5.0%).
- The lower bound of the 95% CI comparing AKR-963 to Lovaza is 8.7%
- The p-value for the NI test of AKR-963 to Lovaza under a hypothesized margin of 10 is 0.013.

The statistical team reviewed the applicant's re-analyses. They concluded that the applicant's approach to deal with the issues with the departure from normality of residuals was reasonable. The re-analyses supported the primary efficacy analysis of active treatment vs. placebo (superiority claim). However, the applicant's analysis was considered post-hoc.

Furthermore, the applicant's response to include the general population of patients with the severe hypertriglyceridemia patients in order to uphold the constancy assumption is rejected. The literature shows that baseline TG levels affect the degree of efficacy of TG lowering therapy. Therefore, it is important to consider only the severe hypertriglyceridemia population for which this drug is indicated.

For these reasons, it is concluded that in the evaluation of non-inferiority, the constancy assumption did not hold, and further determination of this status could not be made. All other analyses are post-hoc analyses and therefore are not compelling enough to support the non-inferiority claim.

1.2 Risk Benefit Assessment

Very high TG (>500 mg/dL) has a strong genetic component and is associated with an increasing risk for acute pancreatitis. The most frequently reported genetic defects for persons with very high TG are in the enzyme lipoprotein lipase (LPL) or in Apo C-II, a protein that activates LPL. These genetic defects result in the inability to breakdown triglycerides. Impaired catabolism of triglyceride-rich lipoproteins (TGRLP) also is induced by overproduction of Apo C-III, an inhibitor of LPL activity. Because of the danger of acute pancreatitis, persons with severely elevated TG > 2000 mg/dL should be treated as a medical urgency.[1]

1 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation 2002;106;3336.

According to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III), the first priority for persons with very high TG is to prevent acute pancreatitis. Prevention of CHD is a secondary priority in this population. Furthermore, efficacy of drug therapy to prevent CHD in persons with very high TG has not been demonstrated by clinical cardiovascular outcomes trials.

In addition to very low-fat diets and increased physical activity, TG lowering drugs are usually required in persons with very high TG to prevent acute pancreatitis. Currently fibrates, nicotinic acid and an omega-3 fatty acid product are available to lower TG to <500 mg/dL.

This application is for a fish oil product, AKR-963 to lower TG in adjunct to diet in patients with severe hypertriglyceridemia TG $\geq$500 mg/dL. The safety review elicited no clinically significant risk that would outweigh the benefit of decreasing TG patients with severe hypertriglyceridemia. Compared to placebo, AKR-963 did statistically significantly lower TG levels. Therefore, the risk/benefit ratio is favorable for approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No safety signals were noted in the marketing application which would require specific post-marketing safety evaluation other than outlined under 21 CFR 314.80.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

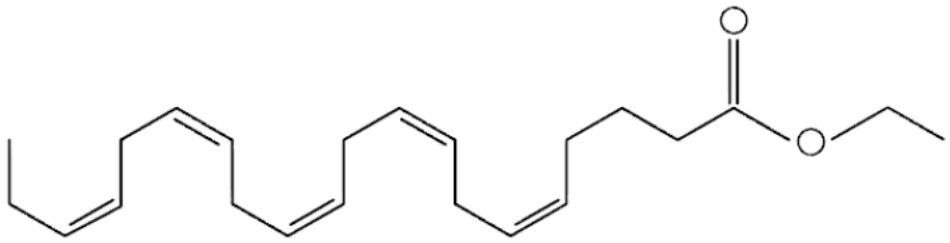
2 Introduction and Regulatory Background

2.1 Product Information

AKR-963 (proposed name Omtryg) is a formulation of omega-3-acid ethyl esters. The applicant expresses the strength of AKR-963 as 0.9 g to reflect that each capsule contains at least 900 mg of total omega-3-scid ethyl esters. The actual drug product is a soft gelatin capsule, weighing approximately 1.16 gram.

The main components in AKR-963 are ethyl EPA and ethyl DHA:

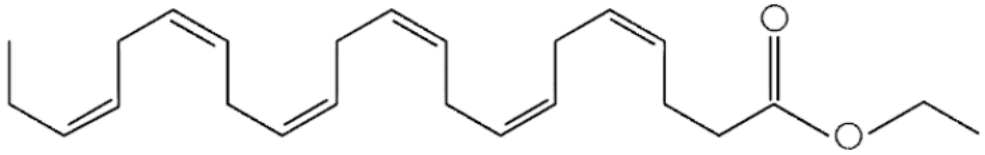
EPAee



Molecular Formula: $C_{22}H_{34}O_2$

Molecular Weight: 330.51

DHAee



Molecular Formula: $C_{24}H_{36}O_2$

Molecular Weight: 356.55

According to the applicant, AKR-963 is obtained by esterification (b) (4)

The applicant lists the active ingredient as total omega-3-acid ethyl esters, which is defined as the ethyl esters (b) (4) The determination of the active ingredient and strength of AKR-963 are the subject of a citizen's petition and a decision is pending with the Office of Regulatory Policy.

AKR-963 contains about (b) (4) mg per capsule of eicosapentaenoic acid ethyl ester (EPAee or EPA), about (b) (4) mg per capsule of docosahexaenoic acid ethyl ester (DHAee or DHA), about (b) (4) mg per capsule of EPAee + DHAee, and not less than (b) (4) mg per capsule of total omega-3-acid ethyl esters. AKR-963 is stabilized with 4 mg capsule of dα-tocopherol.

In comparison, Lovaza contains approximately 465 mg per capsule of EPA and 375 mg per capsule of DHA.

Table 2: Release Specification for AKR-963

Test	Acceptance Criteria		Analytical Procedure
Appearance	Clear, colorless to faint yellow liquid		Visual inspection
EPA ethyl ester identification	Retention time in conformance with reference standard		*Ph Eur 2.4.29*
DHA ethyl ester identification	Retention time in conformance with reference standard		
Composition (mg/g):	Minimum	Maximum	*Ph Eur 2.4.29*
EPA ethyl ester	365	435	
DHA ethyl ester	290	360	
(b) (4)			GC, (b) (4)
			USP <401>, *Ph Eur 2.5.1*
			USP <401>, *Ph Eur 2.5.5, Method A*
			USP <401>, *Ph Eur 2.5.36*
			HPLC, (b) (4)
			AAS (*Section 3.2.S.4.2*)
			GC, Refer to *DMF* (b) (4)
(b) (4)			

AAS = Atomic absorption spectroscopy.
GC = Gas chromatography.
HPLC = High performance liquid chromatography.

Source: NDA 204977, Drug Substance, Table 2.3S-17.

According to the applicant, the AKR-963 manufacturing process is a multistep process starting with (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Other products currently available for the indication of severe hypertriglyceridemia are niacin, fibrates, and omega-3-acid ethyl esters.

Table 3: List of Products for Proposed Indication: Severe Hypertriglyceridemia

Trade Name	NDA (date of approval)	Class of Drugs
Lopid	NDA 18,422 (21 December 1981)	Gemfibrozil
Tricor (micronized)	NDA 19,304 (31 Dec 1993)	Fenofibrate
Tricor	NDA 21,656 (5 Nov 2004)	Fenofibrate
Antara	NDA 21,695 (30 Nov 2004)	Fenofibrate
Triglide	NDA 21,350 (7 May 2005)	Fenofibrate
Lipofen	NDA 21, 612 (11 January 2006)	Fenofibrate
Fenoglide	NDA 22,118 (10 Aug 2007)	Fenofibrate
Trilipix	NDA 22,224 (15 Dec 2008)	Choline fenofibrate
Fibricor	NDA 22,418 (14 August 2009)	Fenofibric acid
Niaspan	NDA 20,381 (28 July 1997)	Niacin
Simcor	NDA 22,078 (15 February 2008)	Niacin; Simvastatin
Advicor	NDA 21,249 (17 Dec 2001)	Niacin; Lovastatin
Lovaza	NDA 21,654 (10 November 2004)	Omega-3-acid Ethyl esters
Vascepa	NDA 202057 (26 July 2012)	Icosapent ethyl

Ethyl EPA has been marketed under the name Epadel Capsules (sponsor: Mochida) in Japan since 1991.

2.3 Availability of Proposed Active Ingredient in the United States

In the US, there are two fish oil products available for the treatment of severe hypertriglyceridemia, Lovaza and Vascepa. Lovaza (omega-3-acid ethyl esters) is a mixture of ethyl esters of omega-3 fatty acids, principally EPA and DHA. Vascepa (icosapent ethyl) contains only EPA as its active ingredient.

2.4 Important Safety Issues With Consideration to Related Drugs

With regard to the only other FDA approved omega-3 fatty acid product (Lovaza), there have been four areas of potential safety concern: increases in LDL-C, liver enzymes, blood glucose, and a possible increase in bleeding risk.

The increase in LDL-C is thought to be due to the increased activity of lipoprotein lipase (LPL) activity.[2] This increased activity enhances the conversion of very low density lipoprotein (VLDL) and intermediate –density lipoproteins (IDL) to LDL-C.

The current Lovaza label states that patients with hepatic impairment should have ALT and AST monitored periodically during therapy. This stems from a greater number of patients with upward shifts in ALT levels, without a concurrent increase in AST shifts in the Integrated Summary of Safety (ISS) of Lovaza monotherapy trials.

Historically, some studies have raised concern that omega-3 ethyl ester consumption could increase fasting plasma glucose (FPG) without corresponding increase in HbA1C.[3] However, a recent Cochrane meta-analysis suggested that neither the FPG nor the HbA1c increased with omega-3 ethyl ester therapy.[4] Pooled data from the Lovaza NDA datasets (post-hoc) showed a slight increase in median FPG in the Lovaza treatment group (median change +6.5mg/dL) as compared to the placebo group (+2 mg/dL).

Metabolism of omega-3 fatty acids, specifically EPA, produces eicosanoids of the thromboxane A3 and leukotriene 5 series, which are associated with reduced platelet aggregation, increased vasodilation, and inhibited leukocyte chemotaxis.[5] Omega-3 acid ethyl esters have been shown in vitro to significantly reduce platelet aggregation by reducing production of thromboxane A2 and increasing production of thromboxane A3. The relationship of these in vitro findings to bleeding risk is much less clear. Currently the labeling for Lovaza includes cautionary statements with regard to bleeding risk.

In addition to safety issues related to Lovaza, ethyl EPA has been investigated in a large study in Japan. In the effects of eicosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): a randomized open-label, blinded endpoint analysis, 18,645 Japanese patients were randomly assigned to 1800 mg of EPA plus a statin or statin alone. Safety concerns in this study included changes in creatine phosphokinase (CPK) and liver enzymes. Adverse effects (AEs) that were more common in the treatment group than in the control group included gastrointestinal disturbances, skin abnormality, and hemorrhage (cerebral, fundus, epitaxis, subcutaneous). No further information on bleeding events is available from the published JELIS report.

2 Harris WS and Bulchandani D. Why do omega-3 fatty acids lower serum triglyceride? Curr Opion Lipidol.2006; 17:387-393.
3 Balk EM, Lichtenstein AH, Chung M, et al. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis 2006; 189:19-30.
4 Hartweg J, Perera R, Montori VM, Dinneen SF, et al. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Cochrane Database of Systematic Review. 2008, Issue 1. Art. No.: CD003205.DOI: 10.1002/14651858.CD003205.pub2.
5 Schmidt EB, Dyerberg J. Omega-3 fatty acids. Current status in cardiovascular medicine. Drugs.1994; 47:405-24.

The Agency issued a review of the safety of EPA and DHA administered or consumed together in the Federal Register of June 5, 1997 (US FDA Substances Affirmed as Generally Recognized as Safe, 1997). This review focused on potentially adverse effects of these omega-3 fatty acids on bleeding time, control of blood sugar in type 2 diabetics, and LDL-C concentrations. The review was undertaken as part of the Agency's assessment of the safety of menhaden oil as a direct human food ingredient. Menhaden are the primary source of fishmeal, used as food for poultry and pen-raised fish, such as salmon. Menhaden oil is known to have the highest concentrations of EPA (13.1%) and DHA (6.7%).

With respect to effects on bleeding time, the FDA concluded that although EPA and DHA appeared to cause small, dose-related increases in bleeding time of unclear clinical relevance, bleeding time increases associated with the use of 3g/day or less of EPA plus DHA either do not occur or are of no adverse significance.

With respect to the effects on glycemic control in type 2 diabetics, the FDA concluded that a dose-related effect is likely, and may be clinically relevant at high daily intake levels, but a daily intake if 3g/day or less of EPA and DHA causes no clinically significant effects on glycemic control.

With respect to effects of EPA and DHA on LDL-C, the FDA concluded that there appeared to be a trend toward increased LDL-C with increased fish oil consumption in all population subgroups, with a magnitude of the increase appearing greater in populations with abnormal blood lipid levels, hypertension, diabetes, and cardiovascular disease.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On November 20, 2009, the applicant submitted a Pre-IND meeting request, which was denied.

On December 18, 2009, the applicant submitted a Pre-IND background package for written responses from the Agency in lieu of a Pre-IND meeting. In this document, the applicant described the brief outlines of two clinical trials: a bioequivalence assessment of AKR-963 to Lovaza and a confirmatory clinical efficacy evaluation of AKR-963 vs. placebo.

On March 25, 2010, the Agency provided responses to the background package submitted on December 18, 2009.

On June 29, 2010, the applicant submitted the initial clinical trial under IND 107259 which described a therapeutic equivalence trial of AKR-963 vs. placebo vs. Lovaza.

On August 17, 2010, DMEP provided comments and requested additional information for protocols TRGG-963-001 and TRGG-963-002.

On August 26, 2010, the applicant submitted responses to address the clinical, statistical, and clinical pharmacology aspects of their development plan.

On September 02, 2010, DMEP communicated that the primary endpoints for study TRGG-963-001 be Cmax and AUC of EPA, DHA, and their ethyl esters.

On December 14, 2010, DMEP provided statistical responses in reference to protocol TRGG-963-002.

On August 16, 2011, DMEP concurred on the proposal to include labeling comments in lieu of conducting drug interaction studies with Coumadin. On September 13, 2012, ONDQA and the applicant discussed CMC considerations for the forthcoming NDA. On December 10, 2012, DMEP and the applicant met for a Pre-NDA discussion. At this meeting, the applicant highlighted that Lovaza's strength is described in three different ways and requested Agency guidance on which description to use in their forthcoming NDA. The Agency responded that the applicant should decide on which strength description to use and justify that choice of strength description.

2.6 Other Relevant Background Information

Generic Name Issue
On August 5, 2013, the applicant responded to the Agency's request to explain how their proposed omega-3-acid ethyl esters product (AKR-963) (b) (4)

The applicant responded that they developed an omega-3-acid ethyl esters product (AKR-963) that has a different overall formulation than Lovaza, but that still delivers the same amount of the same active ingredient in the same dosage form and route of administration as Lovaza.

According to the applicant, the concentration of the drug substance in AKR-963 differs from Lovaza and therefore AKR-963 has a different fill weight ((b) (4)). The applicant argued that they have the clinical, non-clinical, bio-equivalence, and CMC data to establish that the (b) (4) formulation difference does not alter the nonclinical, clinical, or pharmacokinetic profile of AKR-963 relative to Lovaza as evidenced in their NDA for AKR-963.

(b) (4)

(b) (4)

(b) (4)

However, according to Section 502(e)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), the labeling of the drug must bear its established name. Therefore an established/generic name must be determined prior to the approval of this NDA.

Strength Issue

On February 6, 2013, the Agency received a citizen's petition requesting that the Agency take the following actions on Lovaza

1. Amend FDA's adopted strength for Lovaza capsules, including the strength listing in the Orange Book, to "0.9 gm (or 900 mg)", so that the strength appropriately identifies the amount of active ingredient per administration unit without reference to any other capsule properties such as product weight/fill weight, excipients or other inactive ingredients;
2. Or alternatively, adopt a strength of 840 mg for Lovaza based upon the fixed amount of major omega-3-acid ethyl esters specified in the Lovaza new drug application (NDA) reviews and labeling.

To date, a response to this citizen's petition is pending.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the NDA submission quality and integrity were satisfactory. The submission was well organized and information was relatively easy to find.

3.2 Compliance with Good Clinical Practices

All nonclinical studies submitted in this NDA were conducted under GLP conditions. All clinical studies submitted in this NDA were conducted under Good Clinical Practices (GCP) conditions. Statements to this effect were included in each of the study reports. As certified in the submission, no debarred investigators participated in the clinical trials.

3.3 Financial Disclosures

A signed FDA form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was included in the submission declaring the absence of financial interests and arrangements between the applicant and clinical investigators. The form

was appended with a list of investigators who participated in all the Phase 2 and Phase 3 studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Dr. Martin Haber's review for a complete report. The following is from the applicant's report.

The drug substance or active ingredient is omega-3-acid ethyl esters derived from fish oil of which the main components are EPA and DHA. AKR-963 contains about (b) (4) mg of EPA per capsule and (b) (4) mg of DHA per capsule.

Manufacturing of omega-3-acid ethyl esters is a multistep process starting with (b) (4)

For comparison, the USP monograph for Lovaza specifies the following for the two most abundant components of Lovaza:

Eicosapentaenoic acid ethyl ester (EPAee; C20:5 n-3)	430 - 495 mg/g
Docosahexaenoic acid ethyl ester (DHAee; C22:6 n-3)	347 - 403 mg/g
Sum of EPAee and DHAee	800 - 880 mg/g
Total omega-3 acid ethyl esters	NLT 90% (w/w)

The following table shows the comparison of AKR-963 and Lovaza concentrations of fish oil fatty acid ethyl esters:

Table 4: Comparison of AKR-963 and USP Omega-3-acid ethyl esters (Lovaza) Monograph

Concentrations of Fish Oil Fatty Acid Ethyl Esters (mg per g of oil)				
	EPAee	DHAee	EPAee+DHAee	Total omega-3-acid ee
USP Monograph for Omega-3-acid ethyl esters (Lovaza)	430-495	347-403	800-880	> 900
AKR-963	365-435	290-360	700-749	(b) (4)

The lower concentration of AKR-963 is compensated for by using a greater fill weight for the Trygg NDA product capsules (1.16 g for this product vs. 1.0 g for Lovaza). This results in equivalent total amounts of omega-3 acid ethyl esters per capsule.

4.2 Clinical Microbiology

According to the applicant, the drug product was tested for microbiological properties for non-aqueous preparations for oral use. No growth was observed in release or stability testing out to 24 months.
According to the review by Dr. Bryan Riley, microbiology reviewer, the microbial limits specification for AKR-963 is acceptable from a product quality microbiology perspective. The following is an excerpt from his review.

The drug product was tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria were consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for Microbial Limits annually as part of the post-approval stability protocol.

4.3 Preclinical Pharmacology/Toxicology

The following is an excerpt from the pharmacology/toxicology report by Dr. Indra Antonipillai.

This NDA is a 505(b)(2), based on the prior approval of the drug Lovaza (NDA 21654) and the published literature on fish oils to describe the toxicology of AKR-963. In terms of nonclinical studies, the applicant submitted a comparative bridging 28-day toxicity study in rats with AKR-963 and Lovaza and two geno-toxicity studies.

According to the pharmacology/toxicology reviewer, in the 28-day toxicity study, AUC exposures of DHA and EPA were generally comparable with both drugs, and exposures were higher on Day 28 than on Day 1 in both AKR-963 and Lovaza. Male rats had a higher exposure of DHA than female rats. It was noted that the drug accumulates over time.

One male rat dosed with AKR-963 at 4000/mg/kg/day was found dead on Day 14 which was not seen with Lovaza. Applicant stated that the pale appearance of the heart and pulmonary congestion without any other obvious signs of toxicity was highly suggestive of acute cardiac failure in this animal. There were no other signs of toxicity in this rat. The applicant submitted literature which also showed a single death in another 28-day rat study, evidence of shortened ventricular action potential in pigs, and *in vitro* hERG channel effects all suggesting an occasional pro-arrhythmic effect of fish oil. This is despite a weight of evidence of anti-arrhythmogenic effect of fish oil in the literature.

According to the pharmacology/toxicology reviewer, overall, similar histopathology findings were noted with both drug products. Target organs of toxicity with both drugs were liver (inflammation in 3/20 rats vs. 3/20 rats with Lovaza), kidney (inflammation in 3/20 rats vs. 3/20 with Lovaza) and eyes (focal retinal degeneration of mild severity in 1/10 female rats with both AKR-963 and Lovaza respectively, but at the end of drug free recovery period it was only noted with AKR-963 in 1/5 males vs. 0/5 with Lovaza). Findings in the urinary bladder were noted with AKR-963, not noted with Lovaza (in females subchronic and diffuse mucosal inflammation in 2/10 vs. 0/10 with Lovaza). Additionally skin findings (hypotrichosis, of moderate severity) were noted in 1/5 female rats at the end of drug free recovery period with AKR-963, but not with Lovaza.

The NOAEL or tolerated doses of AKR-963 in a 4-week oral toxicity study in rats is considered 200 mg/kg/day (1200 mg/m2/day) which provides the safety margin of approximately 0.5X in humans at a recommended dose of 3600 mg/day (60 mg/kg/day or 2220 mg/m2/day, assuming 60 kg subject), based on body surface area.

However the HD, that produced mortality (1/6 TK animal died) and histopathology findings in the liver, kidney and eyes (in both sexes), and in the urinary bladder (in females), provides safety margin of approximately 10X in humans at a recommended dose of 3600 mg/day (60 mg/kg/day or 2220 mg/m2/day, assuming 60 kg subject), based on body surface area. Thus, nonclinical data support approval of NDA 204977.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of omega-3 ethyl esters is not completely understood. Potential mechanisms of action include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Omega-3 ethyl esters may reduce the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids

4.4.2 Pharmacodynamics

The applicant is relying on the Agency's previous finding of safety and effectiveness for the listed drug, Lovaza, for the pharmacodynamics profile of AKR-963.

4.4.3 Pharmacokinetics

The applicant conducted a series of four studies under a variety of fed and fasted conditions to evaluate the comparative bioavailability of AKR-963 versus Lovaza.

Study designs evolved from testing total EPA and DHA lipid plasma concentrations after a moderate-fat (34% of total kcal) meal over a relatively short postdose time interval (24 hours) to a replicate study design after either a high fat (50% of total kcal) meal or in the fasting state over a 72-hour postdose sampling period for total EPA and DHA lipids, as well as EPA and DHA fatty acids and in the case of the postdose with high-fat meal, the EPA and DHA ethyl esters. These studies indicated bioequivalence of AKR-963 capsules to Lovaza capsules on the following parameters following a high-fat breakfast or in the fasting state:

- Unadjusted and baseline-adjusted EPA and DHA from total lipids (AUC0-72 and Cmax)
- Unadjusted and baseline-adjusted EPA and DHA from free fatty acids (AUC0-72 and Cmax)

Please refer to the clinical pharmacology review for complete details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5: Summary of Clinical Trials

Study / Objectives of Study	Study Design and Type of Control	Dosage Regimen Duration, Test Products	Healthy Subjects or Diagnosis of Patients Number of Patients
TRGG-963-002 Primary: to evaluate the efficacy of AKR-963 as adjunctive therapy to diet for the treatment of severe hypertriglyceridemia	Randomized, double-blind, placebo controlled, parallel-group non-inferiority of AKR-963 vs. Lovaza design Up to 76 weeks of treatment consisting of: ☐ Diet Lead In Period: 6-week diet-only ☐ Period A: a 12-week double-blind, AKR-963 vs. Lovaza, placebo controlled treatment period ☐ Period B: a 40-week double-blind AKR-963 vs. Lovaza treatment period ☐ Period C: an up to 24-week double-blind safety extension treatment period	AKR-963 (3600 mg of omega-3 ethyl esters [4 capsules] once daily in the morning) for up to 76 weeks Lovaza (3600 mg of omega-3 ethyl esters [4 capsules] once daily in the morning) for up to 76 weeks Placebo capsules (4 capsules once daily in the morning) for up to 12 weeks (Period A only)	Patients with severe hypertriglyceridemia (fasting TG $\geq$ 500 mg/dL and < 1500 mg/dL) Planned enrollment/actual enrollment (Period A): Placebo: 40/43 Lovaza: 100/105 AKR-963: 100/106
TRGG-963-003 To evaluate the BE of AKR-963 relative to Lovaza by assessing plasma EPA + DHA concentrations following a single dose of 4 capsules	Randomized, double-blind, two-period, two-treatment, two-sequence crossover design of single doses of AKR-963 and Lovaza immediately following a standardized low fat (≤ 15% of kcal) meal	AKR-963 (3600 mg of omega-3 ethyl esters [4 capsules] single dose) Lovaza (3600 mg of omega-3 ethyl esters [4 capsules] single dose)	Healthy subjects 72 subjects randomized 65 subjects included in PK population
TRGG-963-004 Primary: To evaluate the comparative BA of AKR-963 and Lovaza after a single dose in healthy subjects under fasting and fed conditions	Open-label, single-dose, randomized, 4-period, 4-sequence, 4-treatment, crossover, comparative BA study under fasting and fed (FDA high fat [50% of kcal], high-caloric breakfast) conditions	AKR-963 (3600 mg of omega-3 ethyl esters [4 capsules] single dose) Lovaza (3600 mg of omega-3 ethyl esters [4 capsules] single dose)	Healthy subjects 16 subjects randomized 16 subjects included in PK population, 14 subjects in statistical analysis population
TRGG-963-005 To evaluate the comparative BA of AKR-963 and Lovaza after a single dose in healthy subjects under fed conditions	Open-label, single-dose, randomized, 4-period, 2-sequence, 2-treatment, replicate, crossover, comparative BA study under fed (FDA high fat [50% of kcal], high-caloric breakfast) conditions	AKR-963 (3600 mg of omega-3 ethyl esters [4 capsules] single dose) Lovaza (3600 mg of omega-3 ethyl esters [4 capsules] single dose)	Healthy subjects 44 subjects randomized 39 subjects included in PK and statistical analysis populations
TRGG-963-006 To evaluate the comparative BA of AKR-963 and Lovaza after a single dose in healthy subjects under fasted conditions	Open-label, single-dose, randomized, 4-period, 2-sequence, 2-treatment, replicate, crossover, comparative BA study under fasted conditions	AKR-963 (3600 mg of omega-3 ethyl esters [4 capsules] single dose) Lovaza (3600 mg of omega-3 ethyl esters [4 capsules] single dose)	Healthy subjects 50 subjects randomized 49 subjects included in PK and statistical data set

Study / Objectives of Study	Study Design and Type of Control	Dosage Regimen Duration, Test Products	Healthy Subjects or Diagnosis of Patients Number of Patients
		oral	

Source: NDA 204977,Table 5.2-1.

5.2 Review Strategy

Study TRGG-963-002 was the only safety and efficacy study conducted by the applicant in support of the current NDA. The purpose of this study was to demonstrate non-inferiority of AKR-963 to the RLD (Lovaza) with a placebo-treatment group included to demonstrate assay sensitivity of the trial.

5.3 Discussion of Individual Studies/Clinical Trials

See Dr. Manoj Khurana's clinical pharmacology review for detailed analysis of the following four bioequivalence trials. I reviewed the trials' safety results in this section.

Study: TRGG-963-003
A Randomized, Double-Blind, Two Period Crossover, Bioequivalence Trial of Two Omega-3-Acid Ethyl Ester Products in Healthy Adult Volunteers

Primary Objective: The primary objective was to evaluate the bioequivalence of AKR-963 relative to Lovaza by assessing plasma EPA + DHA concentrations following a single dose of 4 capsules.

Methods: Patients were administered a single dose of the first assigned treatment (consisting of 4 capsules of either AKR-963 or Lovaza) with a standardized EPA/DHA-free breakfast. The breakfast had 21 g of fat, equating to 34% of energy.

Blood samples for pharmacokinetic (PK) assessments were obtained via venipuncture pre-dose (t = - 0.5 and -0.25 hours) and at t = 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours, where t = 0 hours was the start of the breakfast meal and study drug consumption.

On day 14 [i.e., 14 days (washout period) after receiving the first assigned treatment in period 1, patients received the alternate treatment, and the above-described procedures and PK evaluations were repeated (period 2).

Number of Patients: A total of 72 subjects were enrolled and randomized.

Inclusion Criteria: Healthy non-smoking men and women 18 to 45 years of age, inclusive, each with a body mass index (BMI) between 18.00 and 29.99 kg/m2 (inclusive) and fasting TG concentration < 150 mg/dL were eligible for this study after giving written informed consent.

Safety Measurements: Safety was assessed through the evaluation of treatment-emergent AEs. Pre-dose chemistry, hematology, and urinalysis assessments were completed to ensure that no laboratory abnormalities occurred between treatment I (measured at visit 2, day -1) and treatment II (measured at visit 3, day 13).

Safety Results:
Five of 72 patients had at least 1 treatment-emergent AE (3 (4.2%) AKR-963, and 3 (4.2%) Lovaza. One patient (#249) had an AE during both periods. No SAEs were reported and no deaths occurred during the study. The incidence of AEs was similar between the AKR-963 and Lovaza treatment groups.

Four different treatment-emergent AEs were reported during this study: hematuria (1 in each of the AKR-963 and Lovaza treatment groups), hepatitis (1 in the AKR-963 group), microcytic anemia (1 in each of the AKR-963 and Lovaza groups), and rash (1in the Lovaza group).

Study: TRGG-963-004
A Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters Capsules under Fasting and Fed Conditions

Primary Objective: The primary objective of this study was to evaluate the comparative bioavailability between AKR-963 and Lovaza capsules after a single-dose in healthy patients under fasting and fed conditions.

All pharmacokinetic parameters were determined from plasma concentration data.

- Total EPA and Total DHA: AUC_{72}, C_{max}, T_{max} (measured & baseline-adjusted data)
- EPA Ethyl-ester and DHA Ethyl-ester: AUC_t, AUC_{inf}, C_{max}, T_{max}, Kel, T_{half} (measured data)

The secondary objective of this study was to evaluate the effect of food on the study medications.

Methods:

- This was an open-label, single-dose, randomized, 4-period, 4-sequence, 4-treatment, crossover study, designed to evaluate the comparative bioavailability of AKR-963 and Lovaza, administered to healthy patients under fasting and fed conditions.
- Patients were randomly assigned to one of the four dosing sequences DCAB, ADBC, BACD or CBDA under fasting and fed conditions.
- Concentrations of Total EPA and Total DHA were measured from samples collected over a 72-hour interval after dosing in each period.
- Concentrations of EPA Ethyl-ester and DHA Ethyl-ester were measured from the samples collected over a 10-hour interval after dosing in each period.

Number of Subjects: Sixteen patients were dosed and are included in the safety dataset.

Inclusion Criteria: The study population included non-smoking, male and female volunteers 18 years of age or older, with a BMI from 19.0 to 30.0 kg/m2, who were judged to be healthy based on a medical history, ECG, laboratory evaluation and physical examination and vital signs measurements.

Safety Measurements: Adverse events and vital signs were monitored throughout study. There was no formal safety analysis planned.

Safety Results: There were no deaths, Serious Adverse Events (SAEs), or other significant adverse events in the study. A total of 19 AEs were reported by 9 of the 16 patients who were dosed in the study. The most frequently reported adverse events were constipation (2 patients) and pruritus (1 patient) all with mild intensity. One patient withdrew from the study due to an AE of fever.

Study: TRGG-963-005
A Replicate, Single-Dose, Comparative Bioavailability Study if Two Formulations of Omega-3- Acid Ethyl Esters Capsules Under Fed Conditions

Primary Objective: The objective of this study was to evaluate the comparative bioavailability between AKR-963 capsules and Lovaza capsules after a single-dose in healthy subjects under fed conditions.

Methods: This was an open-label, single-dose, randomized, 4-period, 2-sequence, 2-treatment, replicate, crossover study, designed to evaluate the comparative bioavailability ofAKr-963 and Lovaza, administered to healthy male and female subjects under fed conditions.

- Subjects were randomly assigned to one of the two dosing sequences ABAB or BABA under fed conditions.
- Concentrations of EPA and DHA from Total Lipids (Total EPA and DHA), EPA Ethyl-ester, and DHA Ethyl-ester, and EPA and DHA from Free Fatty Acids (Free EPA and DHA) were measured from samples collected over a 72-hour interval after dosing in each period.

Number of Patients: Forty-four (44) subjects were dosed and included in the safety dataset.

Inclusion Criteria: The study population included non-smoking, male and female volunteers 18 years of age or older with a BMI from 19.0 to 30.0 kg/m2, who were judged to be healthy based on a medical, history, physical examination a ECG, laboratory evaluation and vital signs measurements.

Safety Measurements: Adverse events and vital signs were monitored throughout study. There was no formal safety analysis planned.

Safety Results: There were no deaths, Serious Adverse Events (SAEs), or other significant adverse events in the study. A total of 78 AEs were reported by 30 of the 44 subjects who were dosed in the study. The most frequently reported adverse events were catheter site hematoma (5 patients) and catheter site swelling (4 patients) all with mild intensity. One patient discontinued due to an AE of insomnia and nightmares; this patient was on Lovaza.

Study: TRGG-963-006
A Replicate, Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters Capsules under Fasting Conditions

Primary objective: The objective of this study was to evaluate the comparative bioavailability between AKR-963 capsules and Lovaza capsules after a single-dose in healthy subjects under fasting conditions.

Methods: This is an open-label, single-dose, randomized, 4-period, 2-sequence, 2-treatment, replicate, crossover study, designed to evaluate the comparative bioavailability of AKR-963 and Lovaza, administered to healthy male and female patients under fasting conditions.

- Patients were randomly assigned to one of the two dosing sequences ABAB or BABA under fasting conditions.
- Concentrations of EPA and DHA from Total Lipids (Total EPA and DHA) and EPA and DHA from Free

Fatty Acids (Free EPA and DHA) were measured from samples collected over a 72-hour interval after dosing in each period.

Number of Patients: Fifty (50) subjects were dosed and included in the safety dataset.

Inclusion Criteria: The study population included non-smoking, male and female volunteers 18 years of age or older with a BMI from 19.0 to 30.0 kg/m2, who were judged to be healthy based on a medical history, ECG, laboratory evaluation and physical examination and vital signs measurements.

Safety Measurements: Adverse event and vital signs information were documented. There was no formal safety analysis planned for this study.

Safety Results: There was one death (cause still under investigation, see below) but no other SAEs in this study. A total of 59 AEs were reported by 27 of the 50 subjects who were dosed in the study.

Narrative of Patient Death

Screening
Subject 34 was screened for study 2013-3105 on October 23, 2012. The subject reported that he had an appendectomy due to appendicitis in 1973 (no complications) and a fractured left hand in 1975 due to a punching accident (casted, no restrictions). Subject 34 reported consuming 3 bottles of beer per year for 10 years with his last alcohol consumption on December 31, 2011. The subject did not smoke and the urine drugs of abuse and cotinine tests were negative at screening.

Vital signs measurements during medical screening on October 23, 2012 were: blood pressure: 125/69 mmHg, pulse: 61 bpm, temperature: 36.2ºC, and respiration: 14 breaths/minute. Screening ECG was deemed within normal limits by the Sub-Investigator, (b) (4). Screening laboratory tests conducted on October 23, 2012 had calcium oxalate crystals (occasional) and sperm seen in urine which were both considered not clinically significant by (b) (4). All other clinical laboratory results (hematology and biochemistry) were within their respective reference ranges.

Period 1
At Period 1 check-in on November 04, 2012, the urine drugs of abuse test, cotinine test, and alcohol breath test were all negative. The pre-study physical examination was deemed normal by the PI and temperature measurements throughout Period 1 were within normal range. The subject was dosed at 08:39 on November 07, 2012 with Lovaza and did not report any adverse events throughout the study period.

Period 2
At Period 2 check-in on November 18, 2012, the urine drugs of abuse test, cotinine test, and alcohol breath test were all negative. Temperature measurements throughout Period 2 were within normal range. The subject was dosed at 08:39 on November 21, 2012 with AKR-963. From Period 2 drug administration to the end of Period 2 confinement, Subject 34 did not report any adverse events. On December 01, 2012, the subject reported sneezing (mild in severity) over the telephone. The onset was at 09:00 on November 30, 2012, and resolved at 10:00 on December 01, 2012 with no action taken.

Period 3
At Period 3 check-in on December 02, 2012, the urine drugs of abuse test, cotinine test, and alcohol breath test were all negative. Temperature measurements throughout Period 3 were within normal range. The subject was dosed at 08:39 on December 05, 2012 Lovaza and did not report any adverse events throughout the study period.

Period 4
Subject 34 was not present for Period 4 check-in on December 16, 2012. Staff attempted to contact the subject by telephone at 19:40 and 20:41 but was unsuccessful. On December 17, 2012, staff attempted to contact the subject by telephone at

09:25 but was unsuccessful. An e-mail was sent to the subject on the same day at 10:40 but no response was received. Staff attempted to contact the Subject 34 again by telephone on (b) (6) but was unsuccessful. At (b) (6), staff received a call from the (b) (6) requesting emergency contact information for Subject 34. During the same phone call, the police stated that Subject 34 was found deceased by his roommate.

In response to a question posed by the Division on September 9, 2013 regarding an update as to the cause of death, the applicant, in conjunction with PMRI, diligently took all possible actions to secure additional details. PMRI immediately began contacting the (b) (6) at Trygg's request and sought further details. Following several interactions with the (b) (6), PMRI reached the detective responsible for the case, and the detective indicated that he would check the case file and follow-up with PMRI. PMRI received a call back from the detective on the evening of September 17th. The (b) (6) detective informed PMRI that he cannot disclose the cause of death. The detective indicated that the (b) (6) police have closed the case.

Based upon these interactions, there is not an update as to the cause of death, and it appears that the (b) (6) police do not intend to release the information.

6 Review of Efficacy

Efficacy Summary

Conclusions on AKR-963's TG-lowering efficacy are based on study TRGG-963-002. This trial is both a superiority trial (versus placebo) and an inferiority trial (versus Lovaza).

The primary objective in study TRGG-963-002 was to demonstrate superiority of AKR-963 to placebo as well as demonstrate the superiority of Lovaza to placebo for lowering TG in patients with severe hypertriglyceridemia. The secondary objective was to demonstrate non-inferiority of AKR-963 to Lovaza with a pre-specified margin of 15%.

AKR-963 did meet the primary objective of the trial to demonstrate superiority to placebo; the median differences in TG percent change from Baseline are summarized in the following table:

Table 6: Median Percent Difference in TG from Baseline to Period A Endpoint, mITT Population

	Median% Difference and 95% Confidence Interval	P value
AKR-963 vs Placebo	-12.2 (-23.9, -0.4)	p=0.041
Lovaza vs Placebo	-14.0 (-26.9, -1.1)	p=0.023
AKR-963 vs.Lovaza	+2.3 (-6%, +10.5%)	p=0.577

At issue is the p-value of 0.041 for AKR-963 vs. placebo. Although this value is statistically significant, it is not robust. Multiple sensitivity analyses conducted by the statistical review team showed results that were not significantly different from placebo:

- log-transformed analysis yielded p=0.046
- Kruskal-Wallis analysis yielded p=0.049
- analysis with the completers population yielded p=0.051

The difference between placebo and AKR-963 was of borderline statistical significance in part because placebo had a more favorable TG reduction than expected. Placebo (vegetable oil) *decreased* TG by 17%. By contrast, in the MARINE trial (Vascepa NDA) placebo (mineral oil) increased TG by 9.7%. In the original Lovaza trials, placebo (corn oil) increased TG by 6.7%.

In addition to placebo having a more favorable effect than expectation, in trial TRGG-963-002, AKR-963 and Lovaza did not decrease TG to levels seen in Lovaza NDA 021654. Historically, Lovaza decreased TG by 45% whereas in TRGG-963-002, Lovaza decreased TG by 27% and AKR-963 decreased TG by 25%.

A hypothesis of why the effect of Lovaza and AKR-963 was smaller than expected is that patients in study TRGG-963-002 were not given specific instructions to take their study drug with food while patients in the historical Lovaza trials were told to take their study drug with food. Food exposure relationships in PK trials show that both Lovaza and AKR-963 exposure significantly increased in the presence of food. Therefore, if patients were not taking their study drug with food, the TG-lowering effect of Lovaza and AKR-963 would be smaller than expected.

Even if the superiority of AKR-963 to placebo were accepted, the non-inferiority comparison of AKR-963 to Lovaza raises concern. The constancy assumption states that the effect of the active control in a non-inferiority trial is similar to the historical effect of the active control established through placebo-controlled data. The constancy assumption is not upheld in TRGG-963-002 because the absolute value of the median difference between Lovaza and placebo was 14%, which is smaller than the non-inferiority margin of 15%.Furthermore, the 95% CI of the median % difference in TG between Lovaza and placebo does not overlap with the historical 95% CI of the comparison that was used to calculate the margin. Thus the constancy assumption does not hold in study TRGG-963-002. Because the constancy assumption is not upheld, non-inferiority between AKR-963 and Lovaza cannot be determined.

The figure below shows the historical treatment difference in TG percent change for Lovaza (red) compared to results in TRGG-963-002 for AKR-963 (square) and Lovaza (circle). For the treatment difference between Lovaza and placebo, the current confidence interval does not overlap with the historical confidence interval margins.

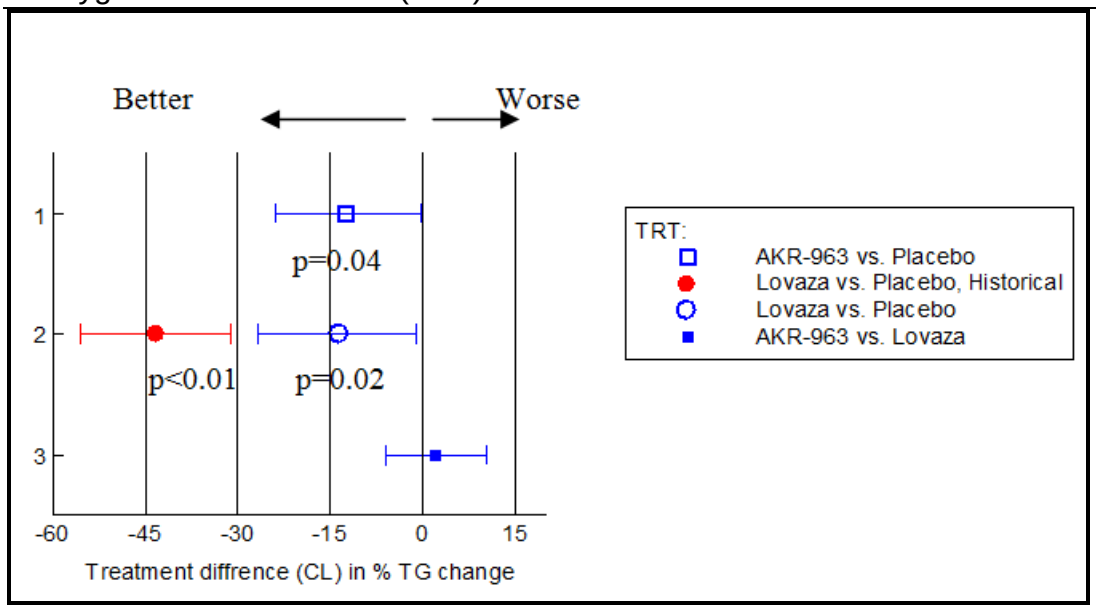


Figure 2: Treatment Difference in TG % Change in TRGG-963-002 (blue) and Historical Lovaza Trials (red) in Severe Hypertriglyceridemia

In a letter dated May 21, 2013, the Division requested the applicant's opinion on why the effects of AKR-963 and Lovaza were less than expected in their efficacy trial. The applicant responded that TRGG-963-002 data were not intended to support a *de novo* efficacy claim such as that sought for a 505(b)(1) application. The applicant claimed that the efficacy data generated need to be considered in the context of the bridging approach for a 505(b)(2) application.

The applicant stated that the sensitivity analyses conducted during the review were post-hoc analyses. The applicant conducted their own post-hoc analysis which they claimed supported the robustness of TRGG-963-002 results. The statistical review team concluded that applicant's reanalysis supported the primary efficacy analysis of active treatment vs. placebo; however, the sponsor's analyses were also post-hoc analyses (see statistical review further details).

With regard to the constancy assumption, the applicant listed 14 published clinical trials conducted with Lovaza 4g dose. From these trials, the unweighted median TG change from baseline was -27% with minimum and maximum reported changes of -45% and -15%, respectively. In the subset of studies with mean or median baseline TG >400 mg/dL, the median change from the baseline was -38% with minimum and maximum reported mean or median values of -45% and -24%, respectively. In the MARINE trial with 4g/day Vascepa (ethyl EPA) the median change from baseline TG was -27%.

Because the two Lovaza trials from which the non-inferiority margin was calculated showed a median percent change from baseline that was at least 50% greater than any of the controlled studies that have been reported since, the applicant believes that the constancy assumption is fulfilled if data beyond the two original Lovaza trials are considered. That is, the applicant believes that the effect of Lovaza in their non-inferiority trial was similar to the effect of Lovaza in trials in the literature; therefore the constancy assumption is fulfilled.

In response to the applicant's claim that other Lovaza trials should be considered when deriving the NI margin, the statistical team analyzed the treatment differences between Lovaza and placebo with seven of the trials submitted in NDA 021654. Trial K85-95009 was excluded because of significant heterogeneity.

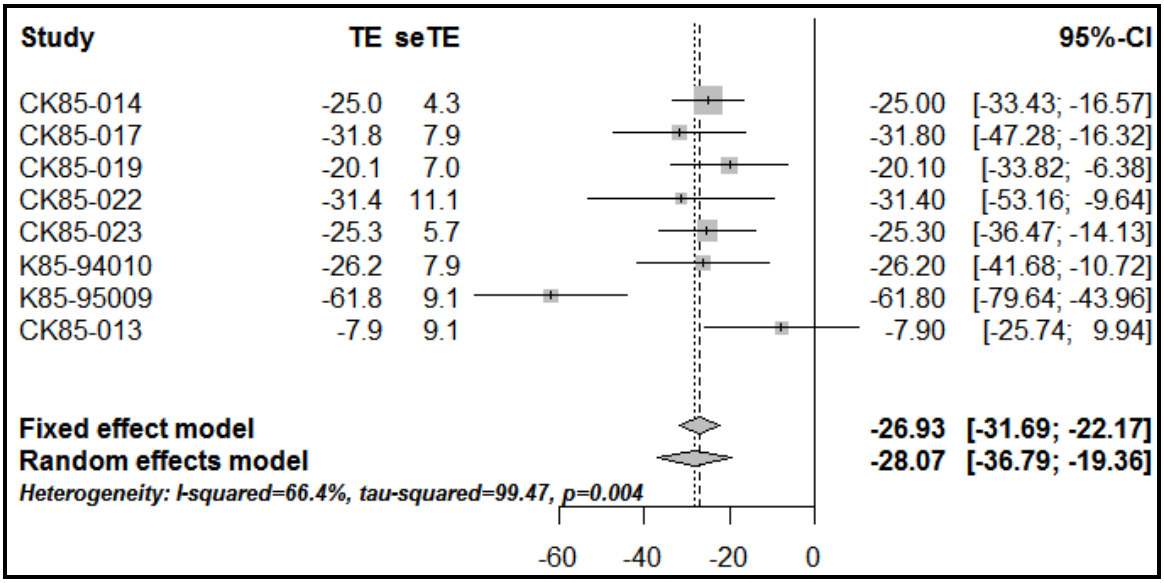


Figure 3: Meta-analysis of Lovaza NDA Trials

Using the random effects model (due to significant heterogeneity between trials, p=0.004), the TG lowering point estimate was -28.07 (36.79, -19.36). Based on half of the -19.36% upper bound of the confidence interval, a non-inferiority margin of +9.7% was calculated.

Using the +9.7% non-inferiority margin, and considering that the study treatment difference of AKR-963 and Lovaza was +2.3% (-6%, +10.5%), AKR-963 still slightly exceeded this new NI margin (+10.5% vs. +9.7%). Therefore, AKR-963 could not be considered non-inferior using this post-hoc analysis of a new NI margin.

6.1 Indication

The applicant proposes the following indication for this product:

"OMTRYG is a combination of ethyl esters of omega-3 fatty acids, principally EPA and DHA, indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia."

The proposed indication is the same as the reference listed drug (RLD), Lovaza, being used as the basis for this 505(b)(2) NDA application. A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)).

According to the applicant, both Lovaza and AKR-963 have the same strength (at least 900 mg of total omega-3-acid ethyl esters and approximately 465 mg of EPA and 375 mg of DHA), although the expression of strength is different (0.9 g for AKR-963 and 1 g for Lovaza). According to CMC, AKR-963 is less concentrated than Lovaza.

6.1.1 Methods

Protocol TRGG-963-002: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Assess Efficacy and Safety of AKR-963 Therapy in Subjects with Severe Hypertriglyceridemia"

Primary Objective: To evaluate the efficacy of AKR-963 as adjunctive therapy to diet for the treatment of severe hypertriglyceridemia (TG ≥ 500 mg/dL).

In reference to TG, the following null hypotheses were tested for Period A (12-Week Double-Blind Period):

- H01: There was no difference between the AKR-963 and placebo treatment groups in the percent change in TG from baseline to endpoint.

- H02: There was no difference between the Lovaza and Placebo treatment groups in the percent change in TG from baseline to endpoint.

- H03: The AKR-963 treatment group was inferior to the Lovaza treatment group (using a 15% margin) in the percent change in TG from baseline to endpoint.

Secondary Objective: To evaluate the safety of AKR-963 as adjunctive therapy to diet for the treatment of severe hypertriglyceridemia, and to assess the effects of AKR-963

on other lipid parameters, cardiovascular risk markers, body weight, blood pressure, and homeostatic model assessment for insulin resistance (HOMA-IR, among subjects not receiving hypoglycemic medication).

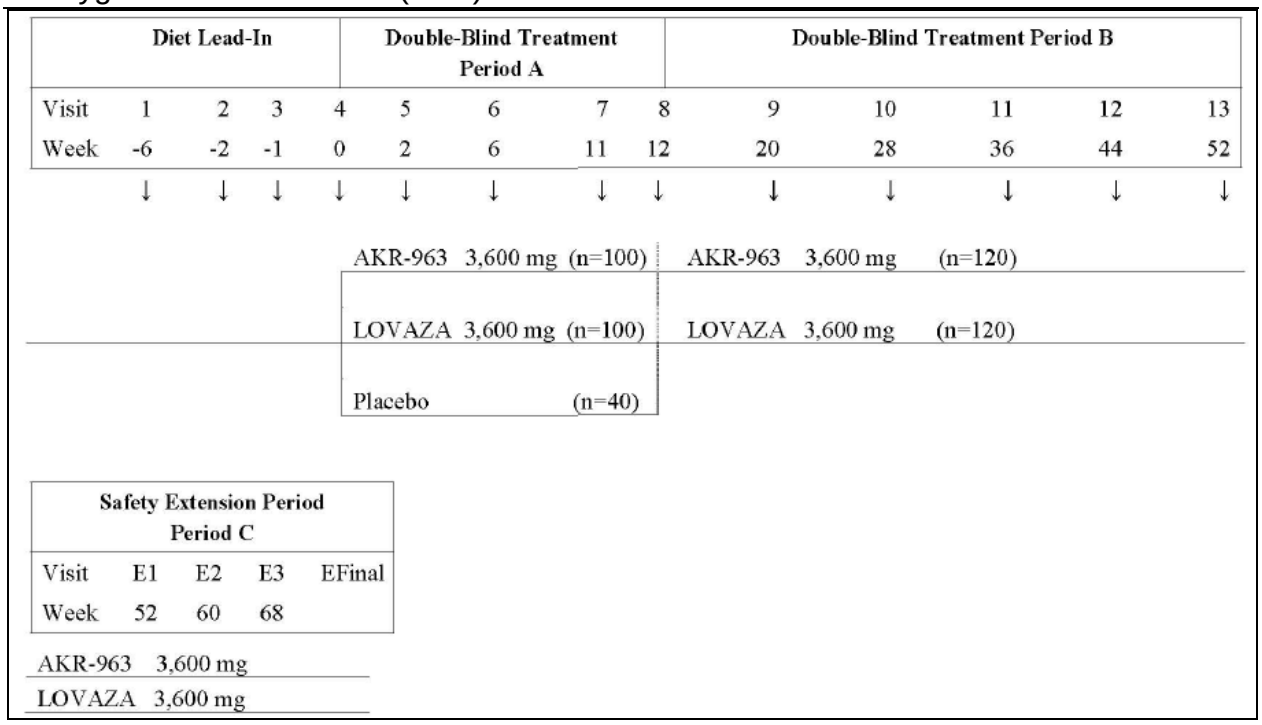
Population: Men and women between 18 and 79 years of age, inclusive, with fasting TG levels ≥500 mg/dL and <1500 mg/dL and body mass index (BMI) ≥25 kg/m2 and ≤43 kg/m^2.

Design: This trial consisted of a 6-Week Diet Lead-In Period, a 12-Week double-blind treatment period (Period A), a 40-Week double-blind treatment period (Period B), and an up to 24-Week double-blind safety extension (Period C).

Period A (12-Week Double-Blind Treatment Period): At Visit 4 (Week 0), qualifying patients were randomly assigned to one of three double-blind treatment groups: AKR-963, Lovaza, or Placebo (vegetable oil).

Period B (40-Week Double-Blind Treatment Period): At Visit 8 (Week 12), those patients initially randomized to Placebo were re-assigned equally to either AKR-963 or Lovaza. Patients already assigned to AKR-963 or Lovaza in Period a remained on their treatment.

Period C (Double-Blind Safety Extension Period): Patients who completed the first 52 weeks of treatment (Periods A and B) were eligible to enter a double-blind safety extension period (Period C). Patients completed a separate informed consent form prior to participating in Period C. Patients remained on the treatment they received during Period B for up to an additional 24 weeks.



Source: Study Report, TRGG-963-002, pg. 28.

Figure 4:Protocol TRGG-963-002 Study Design

Inclusion Criteria:

- Adult male or female subjects 18 to 79 years of age, inclusive;
- Fasting TG levels ≥500 mg/dL and <1500 mg/dL (based on an average of Visit 2 [Week -2] and Visit 3 [Week -1]). Note: In cases in which a subject's average TG level from Visit 2 and Visit 3 fell outside the required range for entry into the study, an additional TG measurement could have been taken. If a third TG measurement was taken, entry into the study was based on the average of the values from the 3 visits (Visit 2 [Week -2], Visit 3 [Week -1], and the repeat value);
- Body mass index (BMI) ≥25 kg/m2 and ≤45 kg/m2 at Visit 1 (Week -6);
- Willing to follow a low saturated fat diet throughout the study period and maintain the current level of physical activity throughout;
- For smokers, no plans to change smoking habits during the study period;
- Normal activity levels and judged by the Investigator to be in good health on the basis of medical history, directed physical examination, electrocardiogram, and routine laboratory tests; and
- Understanding of the study procedures and protocol requirements, documented by providing written informed consent and authorization for protected health information disclosure.

Exclusion Criteria

- Use of any non-study marine-oil-based omega-3 fatty acid product or any niacin product (or niacin analogues) at doses >400 mg/day after Visit 1 (Week -6). The following supplements were permitted during the study only if they had been taken at a dose unchanged for at least 1 month prior to Visit 1 (Week -6) and were to be continued at the same dose throughout the study (i.e., supplements were to not be discontinued or have their dosage adjusted during the study unless medically warranted for safety reasons):
  - − Sterol/stanol products; dietary fiber supplements (including >2 teaspoons/day of Metamucil® or psyllium-containing supplements or other such viscous fiber-containing products) and
  - − Flax seed oil; red rice yeast, garlic, soy isoflavone supplements, or others at the Investigator's discretion;
- Use of any lipid-altering medications, including bile acid sequestrants, cholesterol absorption inhibitors, fibrates, etc. after Visit 1 (Week -6), which were not provided by the Sponsor as study medication. Unless deemed unsafe by the Investigator, all subjects were to discontinue statin therapy at screening. Note: Treatment with statins was permitted after Week 12 at the Investigator's discretion;
- Change in the use of cyclic sex hormone therapy or cyclic hormonal contraceptives or a plan to initiate therapy or modify the dose during the study. Note: Subjects must have been on stable-dose sex hormone therapy or cyclic hormonal contraceptive therapy for 2 months prior to Week -6;
- Use of warfarin (Coumadin®);
- Use of cyclosporine, androgens, phenytoin, isotretinoin, or thyroid hormones (except for the use of stable-dose thyroid replacement therapy ≥2 months prior to Visit 1 [Week -6]). Subjects who required any of these medications during the study were permitted to initiate therapy with approval from the Medical Monitor;
- Routine or anticipated use of all systemic corticosteroids and high-dose topical corticosteroids (>1500 mg/day). Use of local or low-dose topical corticosteroids was permitted;
- Use of any prescription or over-the-counter weight loss medications or plans to lose weight or participate in a weight loss program after Visit 1 (Week -6);
- Use of tamoxifen, estrogens, or progestins at doses that have not been stable for ≥4 weeks prior to screening;
- Use of any investigational agent within 30 days prior to Visit 1 (Week -6);
- Known sensitivity to omega-3 fatty acid products (including EPA or DHA), constituents of the placebo product, or known sensitivity or allergy to fish or shellfish;
- Known lipoprotein lipase impairment or deficiency, apolipoprotein (apo) c-2 deficiency, or familial dysbeta lipoproteinemia (Type III hyperlipidemia);
- History of pancreatitis;

- Uncontrolled or poorly controlled hypertension at 2 consecutive screening visits, defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg. Subjects with hypertension adequately controlled with medication were eligible for entry into the study if their dose of antihypertensive therapy had been stable for ≥2 months prior to Visit 1 (Week -6);
- Recent history of (within 6 months prior to Visit 1 [Week -6]) or current significant renal, hepatic, pulmonary, biliary, or gastrointestinal disease;
- History of symptomatic gallstone disease unless treated with cholecystectomy;
- History of cancer (except non-melanoma skin cancer) within 2 years prior to Visit 1 (Week -6);
- Poorly controlled diabetes mellitus, defined as HbA1c >9.5%;
- Presence of type 1 diabetes. Subjects with type 2 diabetes on stable doses of insulin or other hypoglycemic agents for ≥2 months prior to Visit 1 (Week -6) were eligible for the study;
- Current or recent history (within the past 12 months) of drug abuse or alcohol abuse. Alcohol abuse was defined as >21 drinks per week (1 drink = 12 oz. beer, 5 oz. wine, or 1.5 oz. hard liquor);
- Clinically significant abnormal laboratory values at Visit 1 (Week -6);
- Serum creatinine >2 mg/dL at Visit 1 (Week -6);
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN);
- Total MEDFICTS final score ≥70 at Visit 4 (Week 0); Unwilling to abstain from the use of alcoholic beverages within 48 hours prior to each study visit;
- Pregnant or lactating females, females who planned to become pregnant during the study, or women of childbearing potential who were not using a medically approved method of contraception; or
- Any other condition which the Investigator believed would interfere with evaluation of the subject or would put the subject at undue risk.

Prior and Concomitant Medications

The use of any non-study marine-oil-based omega-3 fatty acid product was prohibited after Visit 1 (Week -6). Subjects were also not permitted to use niacin or its analogs at doses >400 mg/day after Visit 1 (Week -6).

Other medications excluded after Visit 1 (Week -6) included the following:

- Lipid-altering medications including bile acid sequestrants, cholesterol absorption inhibitors, and fibrates, which were not provided by the Sponsor. Statins were tp be discontinued at screening unless deemed unsafe by the Investigator. The use of statins was permitted during Periods B and C.
- Warfain (Coumadin)
- Systemic use of corticosteroids or topical use of corticosteroids >1500 mg/day (the use of local or low-dose topical corticosteroids was permitted); or
- Prescription or over-the-counter weight-loss medications

The following supplements were permitted by the protocol, provided the subject had been on a stable dose for at least 1 month prior to Visit 1 (Week -6) and dosage changes were not anticipated during the study:

- Sterol/stanol products;
- Dietary fiber supplements, including >2 teaspoons Metamucil or other psyllium-containing supplements per day (or other such viscous fiber products);
- Flax seed oil;
- Red rice yeast, garlic, or soy isoflavone supplements; or
- Any other products at the discretion of the Investigator.

Medications for hypertension, type 2 diabetes, or thyroid replacement therapy were permitted by the protocol, provided the subject had been on a stable dose for at least 2 months prior to Visit 1 (Week -6). Treatment with tamoxifen, estrogens, or progestins was permitted, provided the subject had been on a stable dose for ≥4 weeks prior to screening.

6.1.2 Demographics

The randomized population in study TRGG-963-002 was mostly Caucasian (92%), male (72%), with a mean age of 51 years and a mean BMI of 33 kg/m2. Approximately 79% of patients were not on a statin at randomization. Thirty-eight percent of the population had a history of diabetes mellitus.

Table 7: Summary of Baseline Demographics-Randomized Population

Characteristic	Placebo N=43	Lovaza N=105	AKR-963 N=106	Total
Age (years)				
n	43	105	106	254
Mean (SD)	52 (11)	51(9)	50 (10)	51 (10)
P-value				0.7027
Age group (n, %)				
<65 years	39 (91)	97 (92)	101 (95)	237 (93)
≥65 years	4 (9)	8 (8)	5 (5)	17 (7)
P-value				0.4761
Sex (n,%)				
Male	32 (74)	77 (73)	75 (71)	184 (72)
Female	11 (26)	28 (27)	31 (29)	70 (28)
P-Value				0.4761
Race (n, %)				
White/Caucasian	38 (88)	94 (90)	101 (95)	233 (92)
African American	2 (5)	6 (6)	3 (3)	11 (4)
Asian	1 (2)	3 (3)	0	4 (2)

Characteristic	Placebo N=43	Lovaza N=105	AKR-963 N=106	Total
P-Value				0.1755
Diabetes status (n, %)				
No diabetes	28 (65)	65 (62)	66 (62)	159 (63)
Diabetes with HbA1c <8.0%	11 (26)	25 (24)	27 (26)	63 (25)
Diabetes with HbA1c ≥8.0%	4 (9)	15 (14)	13 (12)	32 (13)
P-Value				0.9460
Statin Use (n, %)				
No	33 (77)	84 (80)	84 (79)	201 (79)
Yes	10 (23)	21 (20)	22 (21)	53 (21)
P-value				0.9061
Body mass index (kg/m2)				
n	43	105	106	254
Mean (SD)	32 (5)	32 (5)	33 (5)	33 (5)
P-value				0.1545

Source: CSR, Table 14.1.4, pg. 121. P-values for continuous variables are from a one-way analysis of variance with treatment as a factor. If the normality assumption is not satisfied (Shapiro-Wilk p<0.01), ranks will be used in the ANOVA model to calculate p-values. P-values for categorical variables are from a chi-square test (or Fisher's exact test when the expected value of any cell is <5). Note the p-valuefor race is based on White vs. Non-White.

The mean baseline TG was 759 mg/dL, with approximately 43% of the randomized population having a TG >750 mg/dL. The following table summarizes baseline lipid parameters.

Table 8: Summary of Baseline Lipid Parameters-Randomized Population

Characteristic	Placebo N=43	Lovaza N=105	AKR-963 N=106	Total
TG (mg/dL)				
n	43	105	106	254
Mean (SD)	751 (253)	732 (236)	789 (257)	759 (248)
Median	624	655	715	675
P-Value				0.2492
non-HDL-C (mg/dL)				
n	43	105	106	254
Mean (SD)	223 (65)	217 (62)	243 (83)	229 (73)

Characteristic	Placebo N=43	Lovaza N=105	AKR-963 N=106	Total
Median	222	210	239	223
P-Value				0.0395
VLDL-C (mg/dL)				
n	43	105	106	254
Mean (SD)	129 (65)	127 (54)	162 (84)	142 (71)
Median	114	117	155	128
P-Value				.0020
LDL-C (mg/dL)				
n	43	105	106	254
Mean (SD)	95 (47)	90 (42)	81 (34)	87 (40)
Median	94	84	78	82
P-Value				0.1992
HDL-C (mg/dL)				
n	43	105	106	254
Mean (SD)	30 (8)	30 (8)	29 (8)	30 (8)
Median	30	30	28	28
P-Value				0.3032
TG category (n, %)				
<750 mg/dL	24 (56)	65 (62)	57 (54)	146 (58)
≥750 mg/dL	19 (44)	40 (38)	49 (46)	108 (43)
P-Value				0.4757

Source: CSR, Table 14.1.4, pg. 123. P-values for continuous variables are from a one-way analysis of variance with treatment as a factor. If the normality assumption is not satisfied (Shapiro-Wilk p<0.01), ranks will be used in the ANOVA model to calculate p-values. P-values for categorical variables are from a chi-square test (or Fisher's exact test when the expected value of any cell is <5).

Reviewer Comment: In general, baseline demographic characteristics were well matched between treatment groups.

Concomitant Medications

The following table summarizes concomitant medications by WHO ATC classification that were taken by ≥10% of patients in any treatment group in the safety population during Period A. Overall, the most commonly used class of concomitant medications was platelet aggregation inhibitors (32%). Other commonly used classes included biguanides (24%), angiotensin-converting enzyme inhibitors (21%); multivitamins (20%), propionic acid derivatives (20%); and selective serotonin reuptake inhibitors (20%). The proportion of patients using these classes of concomitant medications was similar across the treatment groups.

Table 9: Summary of Concomitant Medications Taken During Period A (≥10% in any Treatment Group)- Safety Population

	Placebo N=43 n (%)	Lovaza N=105 n(%)	AKR-963 N=106 n(%)	Total N=254 n(%)
Patient with any concomitant med	43 (100)	98 (93)	98 (93)	239 (94)
Platelet aggregation inhibitors, excluding heparin	10 (23)	36 (34)	34 (32)	80 (32)
Biguanides	7 (16)	26 (25)	28 (26)	61 (24)
ACE inhibitors, plain	10 (23)	23 (22)	20 (19)	53 (21)
Multivitamins, plain	9 (21)	21 (20)	20 (19)	50 (20)
Propionic acid derivatives	10 (23)	18 (17)	22 (21)	50 (20)
Selective serotonin reuptake inhibitors	9 (21)	21 (20)	20 (19)	50 (20)
Proton pump inhibitors	5 (12)	20 (19)	15 (14)	40 (16)
Benzodiazepine derivatives	7 (16)	16 (15)	16 (15)	39 (15)
Anilides	5 (12)	13 (12)	17 (16)	35 (14)
Natural opium alkaloids	5 (12)	18 (17)	11 (10)	34 (13)
Beta blocking agents, selective	4 (9)	13 (12)	15 (14)	32 (13)
HMG-CoA reductase inhibitors	4 (9)	15 (14)	13 (12)	32 (13)
Other antidepressants	4 (9)	14 (13)	11 (10)	29 (11)
Vitamin D analogues	1 (2)	12 (11)	14 (13)	27 (11)
Thyroid hormones	2 (5)	11 (11)	13 (12)	26 (10)
Sulfonamides, urea derivatives	3 (7)	10 (10)	12 (11)	25 (10)
Angiotensin II antagonists, plain	4 (9)	12 (11)	7 (7)	23 (9)
ACE inhibitors and diuretics	3 (7)	8 (8)	11 (11)	22 (9)
Preparations inhibiting uric acid production	1 (2)	11 (11)	8 (8)	20 (8)
Other antiepileptics	1 (2)	6 (6)	11 (10)	18 (7)
Unspecified herbal	1 (2)	4 (4)	12 (11)	17 (7)

Source: CSR, Table 7; pg. 63.

6.1.3 Subject Disposition

Of the 1,212 patients screened, 79% or 958 patients failed to be randomized mainly because they did not satisfy inclusion or exclusion criteria. This may be a reflection of the prevalence of patients with severe hypertriglyceridemia.

Table 10: Summary of Patient Disposition-Study TRGG-963-002

Disposition	Placebo n (%)	Lovaza n (%)	AKR-963 n (%)	Total n (%)
Screened				1212 (100.0)
Withdrew prior to randomization				958 (79.0)
Did not satisfy inclusion/exclusion criteria				860 (71.0)
Withdrawal of consent				65 (5.4)
Adverse event				2 (0.2)
Death				1 (0.1)
Other				30 (2.5)
Randomized	43 (100.0)	105 (100.0)	106 (100.0)	254 (100.0)
Withdrew during Period A	4 (9.3)	14 (13.3)	9 (8.5)	27 (10.6)
Withdrawal of consent	2 (4.7)	5 (4.8)	4 (3.8)	11 (4.3)
Adverse event	0 (0.0)	2 (1.9)	2 (1.9)	4 (1.6)
Protocol violation	1 (2.3)	3 (2.9)	0 (0.0)	4 (1.6)
Other	1 (2.3)	4 (3.8)	3 (2.8)	8 (3.1)
Completed Period A	39 (90.7)	91 (86.7)	97 (91.5)	227 (89.4)
Continued in Period B		112 (100.0)	115 (100.0)	227 (100.0)
Withdrew during Period B		18 (16.1)	25 (21.7)	43 (18.9)
Adverse event		6 (5.4)	8 (7.0)	14 (6.2)
Withdrawal of consent		3 (2.7)	6 (5.2)	9 (4.0)
Death		0 (0.0)	1 (0.9)	1 (0.4)
Other		9 (8.0)	10 (8.7)	19 (8.4)
Completed Period B		94 (83.9)	90 (78.3)	184 (81.1)
Continued in Period C		15 (100.0)	16 (100.0)	31 (100.0)
Withdrew during Period C		0 (0.0)	2 (12.5)	2 (6.5)
Withdrawal of consent		0 (0.0)	1 (6.3)	1 (3.2)
Other		0 (0.0)	1 (6.3)	1 (3.2)
Completed Period C		15 (100.0)	14 (87.5)	29 (93.5)

The number of all screened subjects was used as the denominator for percentages of screen failures. The number of randomized subjects was used as the denominator for calculating the percentages of subjects who completed Period A or withdrew from the study during Period A following randomization. The numbers of subjects who continued in Period B and Period C were used as the denominator for calculating the percentages of subjects who completed or withdrew from the study during each respective treatment period.
Source: Post-text Table 14.1.1

Source: CSR Study 002, Table 4, pg. 58.

Of the 254 patients randomized into the trial, slightly more patients (13%) from the Lovaza treatment arm withdrew in Period A than from Placebo (9.3%) or AKR-963 (8.5%) treatment arms, mainly due to more patients withdrawing due to “Other” reasons and “Protocol Violations”. Consequently, 87% of patients in the Lovaza treatment group completed Period A compared to 92% in AKR-963 and 91% in Placebo.

Withdrawal from Period A due to “Adverse Events” was similar between Lovaza (1.9%) and AKR-963 (1.9%).

Period B and C

Of the 227 patients who continued on to Period B, 22% in the AKR-963 treatment group and 16% in the Lovaza treatment group withdrew from the study mainly due to a higher incidence of patients withdrawing due to an "Adverse Event" (7% -AKR-963 vs. 5.4%-Lovaza). There were also more patients in AKR-963 who withdrew consent (5.2%) vs. 2.7% for Lovaza. Consequently, 78% of patients in AKR-963 completed Period B as compared to 84% in the Lovaza treatment group.

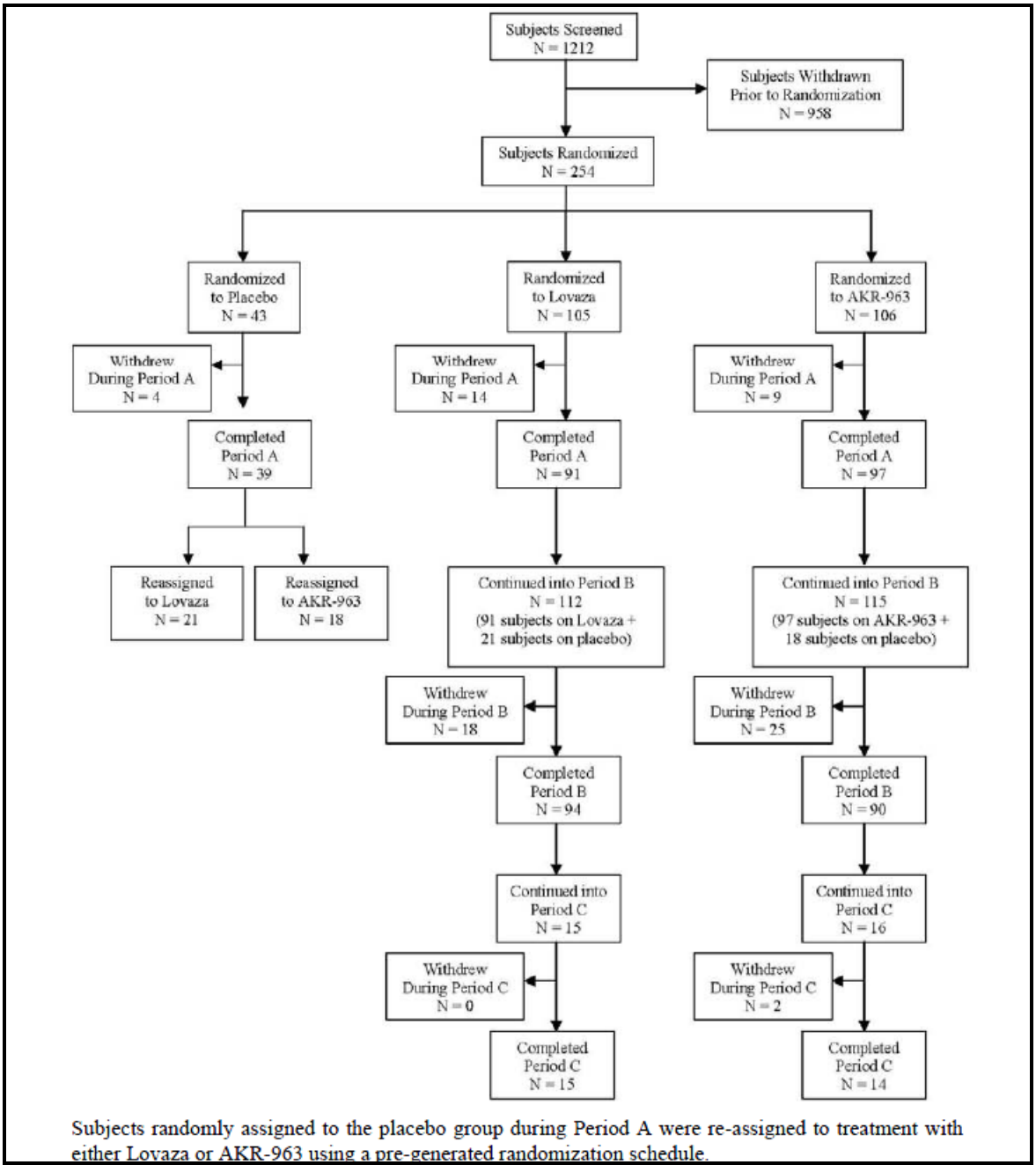


Figure 5: Patient Disposition in Study TRGG-963-002

Protocol Violations

During the course of the study there were instances of deviation from the protocol. The majority of these protocol violations were due to discontinuation of the study medication prior to Visit 7 (Week 11). Other protocol violations were due to the use of restricted medication, <80% compliance with study medication, missing TG endpoint value, and violation of the inclusion /exclusion criteria.

In total, the numbers of patients in each arm excluded due to protocol violations were:

- 14 patients in the AKR-963 group (13.5%)
- 19 patients in the Lovaza group (18.4%)
- 6 patients in the Placebo group (14.0%)

Patients with protocol violations were excluded in the Per-Protocol Population, but not from the Intent-to-Treat population.

Reviewer Comment: The proportion of protocol deviations were similar between the three treatment arms and would not be expected to influence the major efficacy and safety findings from the study.

Study Populations

The following table summarizes the number of patients in the various analysis populations in Period A and B/C.

Table 11: Number (%) of Patients in Various Analysis Populations by Period

Study Period Analysis Population	Placebo n (%)	Lovaza n (%)	AKR-963 n (%)	Total n (%)
Period A	N = 43	N = 105	N = 106	N = 254
Safety Population	43 (100.0)	105 (100.0)	106 (100.0)	254 (100.0)
MITT Population	43 (100.0)	103 (98.1)	104 (98.1)	250 (98.4)
Per-protocol Population	37 (86.0)	86 (81.9)	92 (86.8)	215 (84.6)
Period B/C		N = 112	N = 115	N = 227
Safety Population		112 (100.0)	115 (100.0)	227 (100.0)
MITT Population		112 (100.0)	115 (100.0)	227 (100.0)

For definitions of the analysis populations, see Section 9.7.1.1.
MITT = Modified Intent-to-Treat.
Source: Post-text Table 14.1.3

Source: CSR, Study TRGG-963-002, Table 5, pg.59.

6.1.4 Analysis of Primary Endpoint(s)

Period A (12 Week Double-Blind Period)

The following null hypotheses were tested during Period A, the 12-Week double-blind period:

- H01: There was no difference between AKR-963 and placebo treatment groups in the percent change in TG from baseline to endpoint.

- H02: There was no difference between the Lovaza and placebo treatment groups in the percent change in TG from baseline to endpoint.

- H03: The AKR-963 treatment group was inferior to the Lovaza treatment group (using a 15% margin) in the percent change in TG from baseline to endpoint.

For percent change in TG from Baseline to Period A Endpoint, adjusted p-values from Dunnett's test were used to compare each test medication to placebo (H01 and H02). If both test medications were superior to placebo (Dunnett's test p-value <0.05, 2-sided), a test for non-inferiority was performed.

The non-inferiority test (H03) used a 2-sided 95% CI (with an upper limit that was equivalent to the upper limit of a 1-sided 97.5% CI) and a non-inferiority margin of 15%. Non-inferiority was inferred if the response to AKR-963 minus that of Lovaza had a 2-sided 95% CI with an upper limit that did not include 15%.

Baseline TG was defined as the average of measurements taken at Visit 2 (Week-2), Visit 3 (Week -1), a repeat of Visit 3 (if applicable), and Visit 4 (Week 0). If any of these measurements were missing, the average of the available measurements was used to determine the baseline TG value.

Endpoint TG was defined as the average of the measurements taken at Visit 7 (Week 11) and Visit 8 (Week 12). If either of these measurements were missing, the other measurement was used as the endpoint TG value. If both of these measurements were missing, the last measurement taken during Period A (last observation carried forward [LOCF]) was used as the endpoint TG value.

Efficacy Overview- Lipid Parameters-TRGG-963-002

The following table summarizes lipid changes across the three treatment arms for Period A.

Table 12: Median Percent Change in Lipid Parameters from Baseline to Period A Endpoint, mITT Population

	AKR-963 N=104	Lovaza N=103	Placebo N=43	Median Difference AKR-963 -Placebo	P-Value (AKR-963 vs. Placebo)
Triglyceride	-24.7%	-26.8%	-17.4%	-12.2	0.0412
LDL-C	+20.3%	+12.8%	-5.9%	+24.7	0.0002
Non-HDL-C	-9.2%	-3.6%	-0.8%	-8.5	0.0258
VLDL-C	-21.2%	-18.1%	+5.6%	-28.7	0.0008
ApoB	+3.8%	+5.3%	0%	+3.2	0.2088
HDL-C	0.0%	0%	0.0%	+3.6	0.3502
Total Cholesterol	-8.1%	-1.0%	-0.8%	-6.9	0.0331

Source: CSR, TRGG-963-002, Tables 8-12, 14, 16.

As shown in the table above, all three treatment arms decreased TG, including the placebo treatment group---approximately -25% for AKR-963, -27% for Lovaza and -17% for placebo. AKR-963 was also efficacious in reducing VLDL-C, non-HDL-C, and TC. However, LDL-C increased in both the AKR-963 (20%) and Lovaza (13%) treatment arms, but not in placebo (-6%).

The following figures are from Dr. Lee Ping Pian's statistical review.

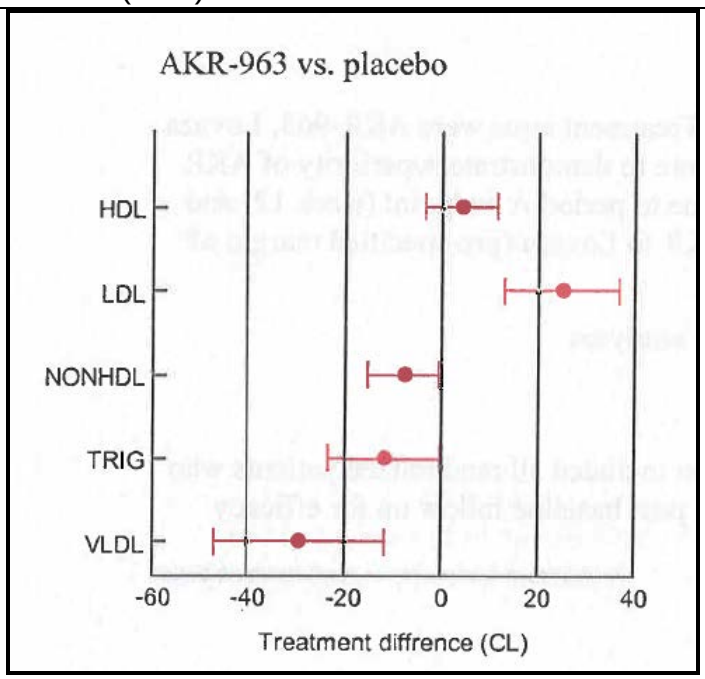


Figure 6: Median of Treatment Differences (Percent Change) of Lipid Parameters of AKR-963 vs. Placebo

The figure above displays the median treatment difference of the percent change in lipid parameters between AKR-963 and placebo. For TG and non-HDL-C, the upper bound of the 95% confidence interval (CI) is very close to zero. In the case of TG, the upper bound of the 95% CI is -0.4 and in the case of non-HDL-C, the upper bound is -0.9. If the CI had crossed zero, the median treatment difference of the percent change would not be statistically significant.

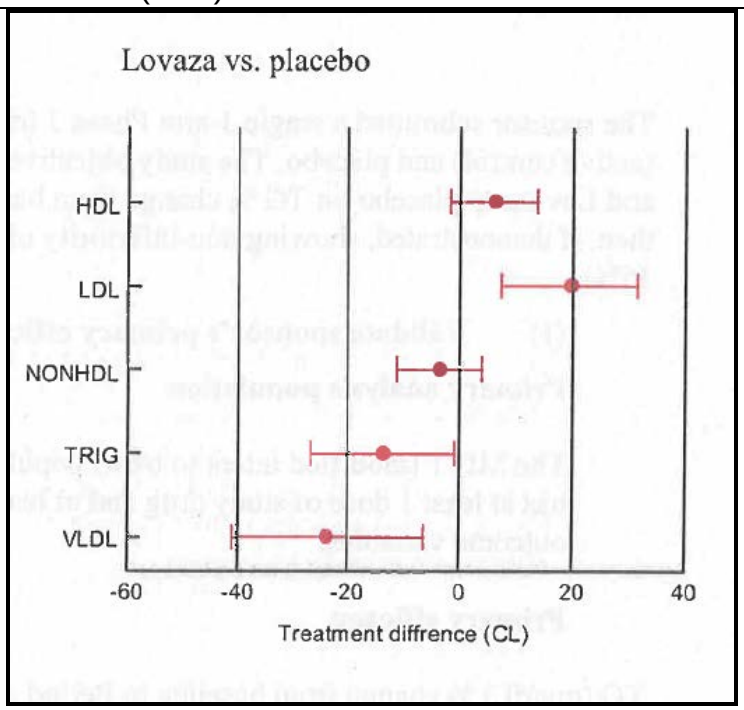


Figure 7: Median of Treatment Differences (Percent Change) of Lipid Parameters of Lovaza vs. Placebo

The figure above displays the median treatment difference of the percent change in lipid parameters between Lovaza and placebo. In this comparison, the upper bound of the 95% CI for TG is -1.1. For non-HDL-C, the upper bound of the 95% CI crosses zero.

Triglycerides
The effect of AKR-963 treatment on TG levels is summarized in the following table.

Table 13: Percent Change in TG (mg/dL) from Baseline to Period A Endpoint, mITT Population

	Placebo N=43	Lovaza N=103	AKr-963 N=104
Baseline median (Q1, Q3)	624 (555, 948)	655 (546, 879)	702 (577, 949)
Endpoint median (Q1, Q3)	611 (459, 779)	495 (338, 693)	514 (398, 766)
Median (Q1, Q3) Percent Change	-17.4 (-32, 16)	-26.8 (-47, -7)	-24.7 (-39, -6)
Median of differences relative to placebo		-14 (-27, -1)	-12.2 (-24, -0.4)
p-value		0.0234	0.0412
Median of differences relative to Lovaza			2.3 (-6, 10.5)
p-value			0.5768

Source: CSR, TRGG-963-002, Table 8; pg. 65.

The table above summarizes the median percent change in TG from Baseline to Period A Endpoint for the mITT Population. Median baseline TG levels were 624 mg/dL for the placebo group, 655 mg/dL for the Lovaza group, and 702 mg/dL for the AKR-963 group.

The median percent change in TG from baseline to Period A endpoint was -17.4% for the placebo group, -26.8% for the Lovaza group, and -24.7% for the AKR-963 group.

The median of the differences in percent change between placebo and AKR-963 was -12.2%, p=0.0412.The median of the differences in percent change between placebo and Lovaza was -14.0%, p=0.0234.

However, as discussed above, the upper bound of the 95% CI was close to zero when AKR-963 is compared to placebo (-0.4), similar to the comparison between Lovaza and placebo (-1.1).

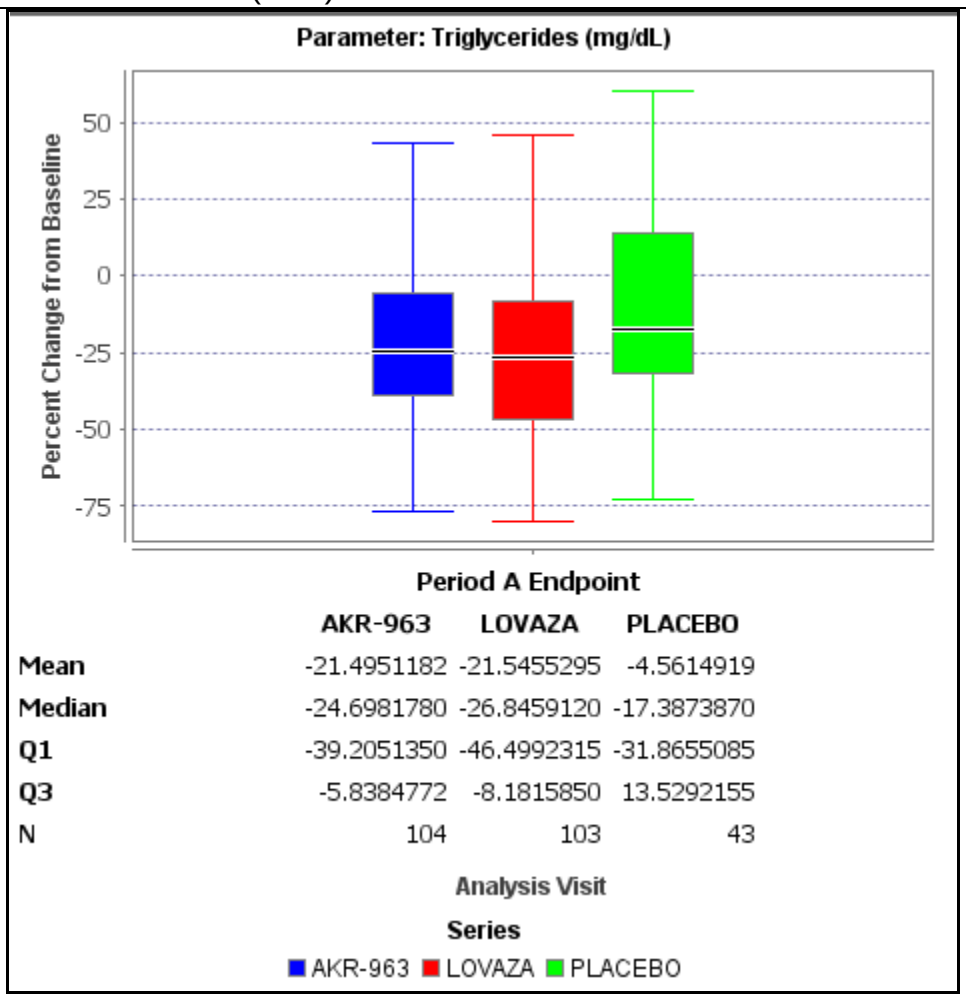


Figure 8: Mean and Median Percent Change in TG from Baseline to Period A Endpoint, mITT Population

The figure above graphically displays the mean and median percent change from Baseline to Period A Endpoint.

NCEP ATPIII treatment goal achievement

NCEP ATPIII treatment goals for patients with severe hypertriglyceridemia are to achieve a TG < 500 mg/dL. The table below shows the number and percent of patients in each treatment arm who achieved TG <500 mg and those who still had TG ≥500mg at Period A Endpoint. With AKR-963, approximately 46% reached TG<500 mg/dL, 51% with Lovaza and 30% with placebo.

Table 14: Triglyceride levels at Period A Endpoint (TG <500 or ≥500 mg/dL)

	AKR-963 N=104	Lovaza N=103	Placebo N=43
n	104	103	43
TG<500 mg/dL	48 (46%)	53 (51%)	13 (30%)
TG≥500 mg/dL	56 (54%)	50 (49%)	30 (70%)

Reviewer Comment: At the end of Period A, AKR-963 and Lovaza had similar percentage of patients who achieved TG <500 mg/dL.

The following table shows the number and percent of patients in each treatment arm who had a TG <500 mg/dL and those with TG≥ 500 mg/dL at Period B Endpoint.

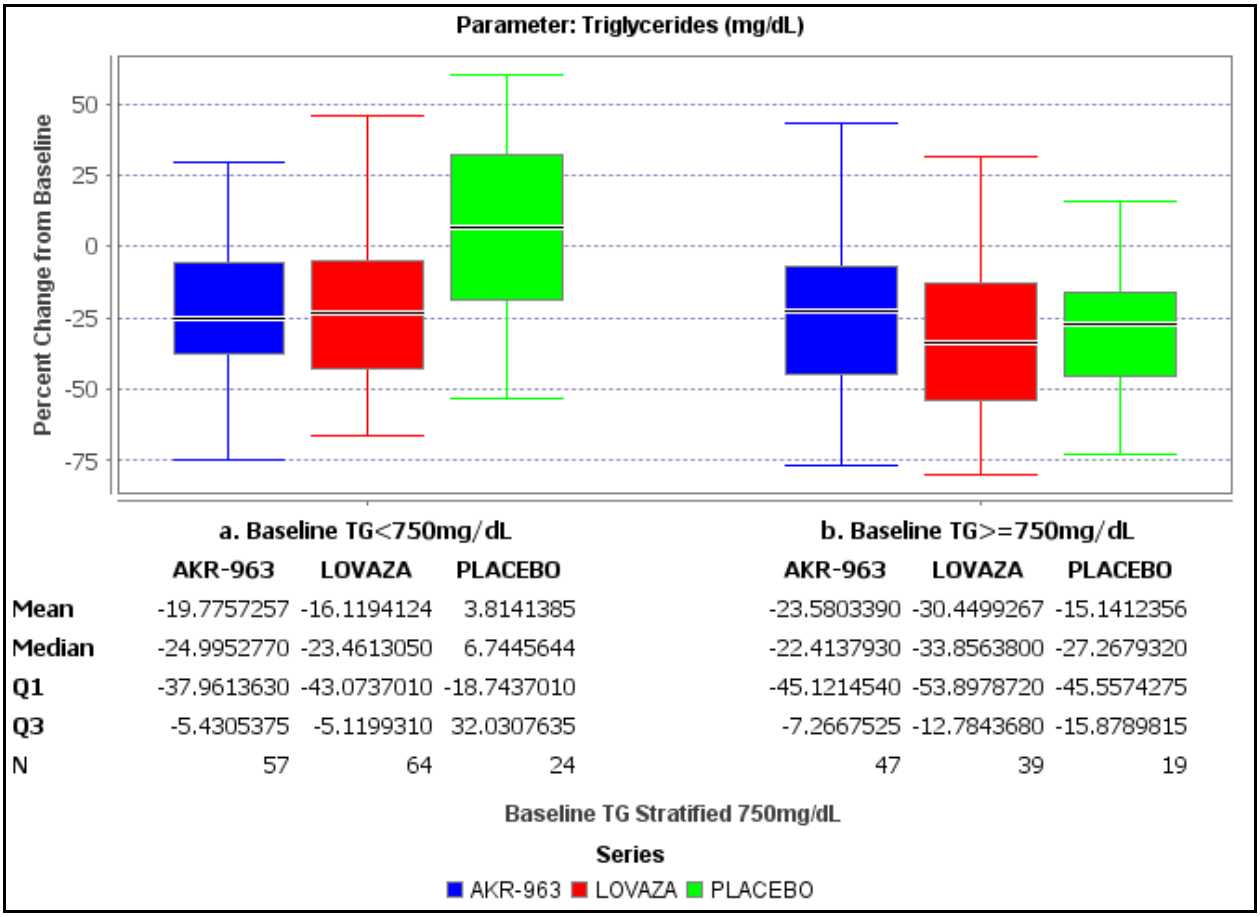
Table 15: Triglyceride levels at Period B Endpoint (TG <500 or ≥500 mg/dL)

	AKR-963 N=115	Lovaza N=112
n	109	109
TG<500 mg/dL	60 (52%)	70 (63%)
TG≥500 mg/dL	49 (43%)	39 (35%)

At Period B Endpoint, approximately 52% of patients on AKR-963 reached NCEP ATPIII treatment goals of TG <500 mg/dL. For Lovaza approximately 63% reached this goal by Period B Endpoint.

Reviewer Comment: At the end of Period B, there was a higher percentage of patients who achieved TG<500 mg/dL with Lovaza as compared to AKR-963.

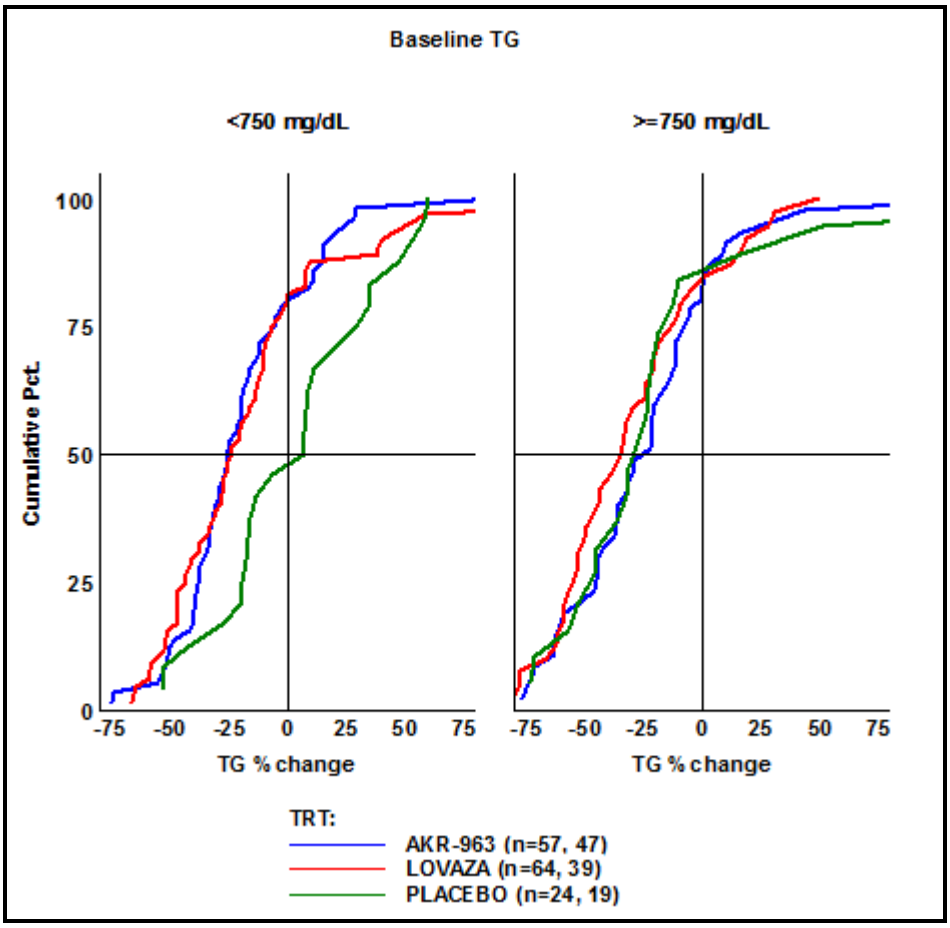
Table 16: Mean and Median Percent Change in TG from Baseline to Period A Endpoint by Baseline TG <750 mg/dL or ≥750 mg/dL



	a. Baseline TG<750mg/dL			b. Baseline TG>=750mg/dL		
	AKR-963	LOVAZA	PLACEBO	AKR-963	LOVAZA	PLACEBO
Mean	-19.7757257	-16.1194124	3.8141385	-23.5803390	-30.4499267	-15.1412356
Median	-24.9952770	-23.4613050	6.7445644	-22.4137930	-33.8563800	-27.2679320
Q1	-37.9613630	-43.0737010	-18.7437010	-45.1214540	-53.8978720	-45.5574275
Q3	-5.4305375	-5.1199310	32.0307635	-7.2667525	-12.7843680	-15.8789815
N	57	64	24	47	39	19

In subjects with baseline TG <750 mg/dL, the median percent change in TG from Baseline to Period A Endpoint was 6.7% for the placebo group, -23.5% for the Lovaza group, and -25.0% for the AKR-963 group. The difference in median percent change between placebo and Lovaza was -23.6%, p=0.0058.The difference in median percent change between placebo and AKR-963 was -23.5%, p=0.0027.

In subjects with baseline TG ≥750 mg/dL, the median percent change in TG from Baseline to Period A endpoint was -27.3% for the placebo group, -33.9% for the Lovaza group and -22.4% for the AKR-963 group. The difference in median percent change between placebo and Lovaza was -5.8%, p=0.4660. The difference in median percent change between placebo and AKR-963 was 1.4%, p=0.7770.



Source: Dr. Lee Ping Pian, Statistical Reviewer

Figure 9: Cumulative Distribution of Percent Change from Baseline to Endpoint by Baseline TG strata

The figure above shows the cumulative distribution of TG percent change from Baseline to Period A Endpoint by TG stratification <750 mg/dL and ≥750 mg/dL in the three treatment arms.

The placebo treatment group showed a substantive response in TG reduction by baseline TG stratification. Those patients with baseline TG ≥750 mg/dL on placebo showed as much reduction in TG as those patients on active study drug treatment. It is unknown to this reviewer why the placebo treatment group would demonstrate a 27% reduction in TG.

The following table summarizes the median difference in percent change in TG by baseline TG.

Table 17: Median Difference in Percent Change in TG by Baseline TG Strata

Baseline TG n(%) (AKR, Lovaza, placebo)	AKR vs. Placebo	Lovaza vs. Placebo
<750 mg/dL n=145 (58%) (57, 64, 24)	-24% (-40, -9)	-24% (-40, -7)
≥750 mg/dL n=105 (42%) (47, 39, 19)	**+1% (-15, +18)**	**-6% (-23, +12)**
All n=250 (100%) (104, 103, 43)	-12% (-24, +0.4)	-14% (-27, +1)

Source: Dr. Pian, statistical review, NDA 204977.

According to the summary table above, the median difference in TG percent change between AKR-963 and placebo in the TG strata ≥750 mg/dL was only 1%.

Reviewer Comment: These analyses show that placebo treatment substantially reduced TG in the subgroup strata TG ≥750 mg/dL at Baseline. Therefore the placebo subtracted treatment of the active study drugs was affected or diminished by comparison.

6.1.5 Analysis of Secondary Endpoints(s)

LDL-C

Median baseline LDL-C levels were 94.0 mg/dL for the placebo group, 85.0 mg/dL for the Lovaza group, and 78.0 mg/dL for the AKR-963 group. The median percent change in LDL-C from Baseline to Period A Endpoint was -5.9% for the placebo group, 12.8% for the Lovaza group, and 20.3% for the AKR-963 group.

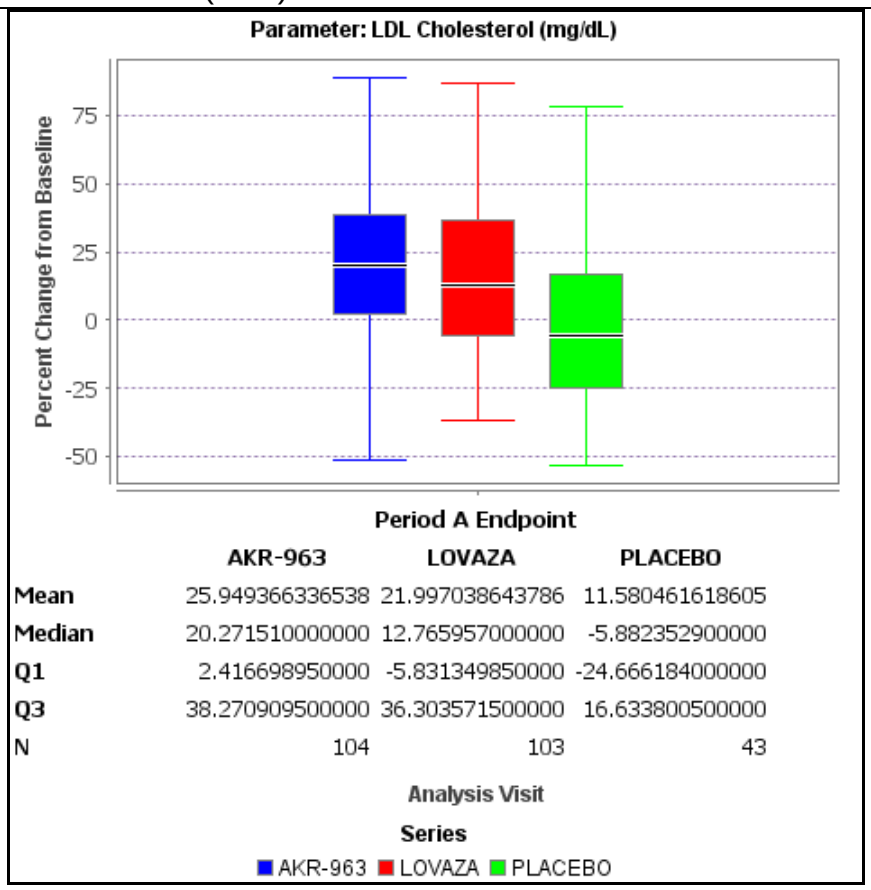


Figure 10: Mean and Median Percent Change in LDL-C from Baseline to Period A Endpoint, mITT population

For LDL-C, the median of the differences in percent change between placebo and AKR-963 was 25%, p=0.0002. The median of the differences in percent change between placebo and Lovaza was 19%, p=0.0025. The median of the differences in percent change between Lovaza and AKR-963 was 6%, p=0.2101.

HDL-C
The following figure shows the mean and median percent change from Baseline to Period A Endpoint in HDL-C.

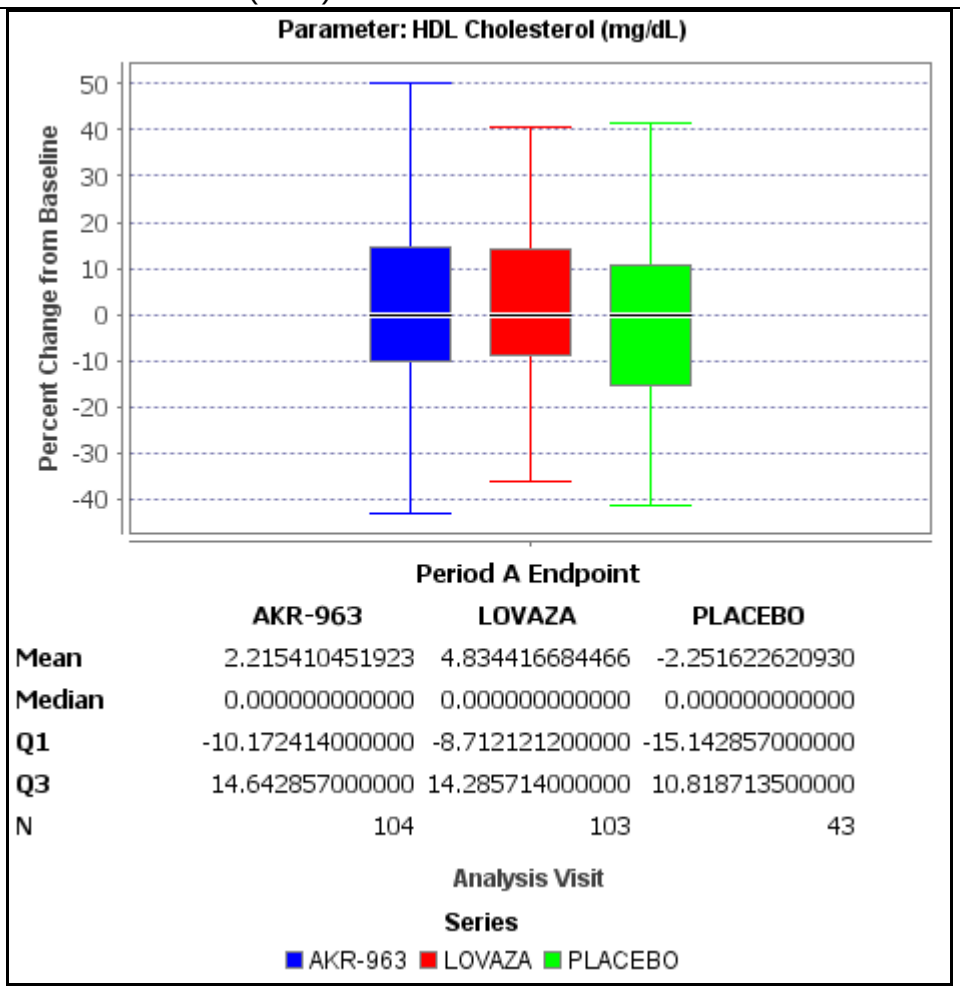


Figure 11: Mean and Median Percent Change in HDL-C from Baseline to Period A Endpoint, mITT Population

Essentially, the median percent change was 0% for all three treatment arms.

VLDL-C
The following figure shows the median and mean percent change from Baseline to Period A Endpoint. Median baseline VLDL-C levels were 114 mg/dL for the placebo group, 117 mg/dL for the Lovaza group, and 153 mg/dL for the AKR-963 group.

The median percent change in VLDL-C from Baseline to Period A Endpoint was 5.6% for the placebo group, -18.1% for the Lovaza group, and -21.2% for the AKR-963 group.

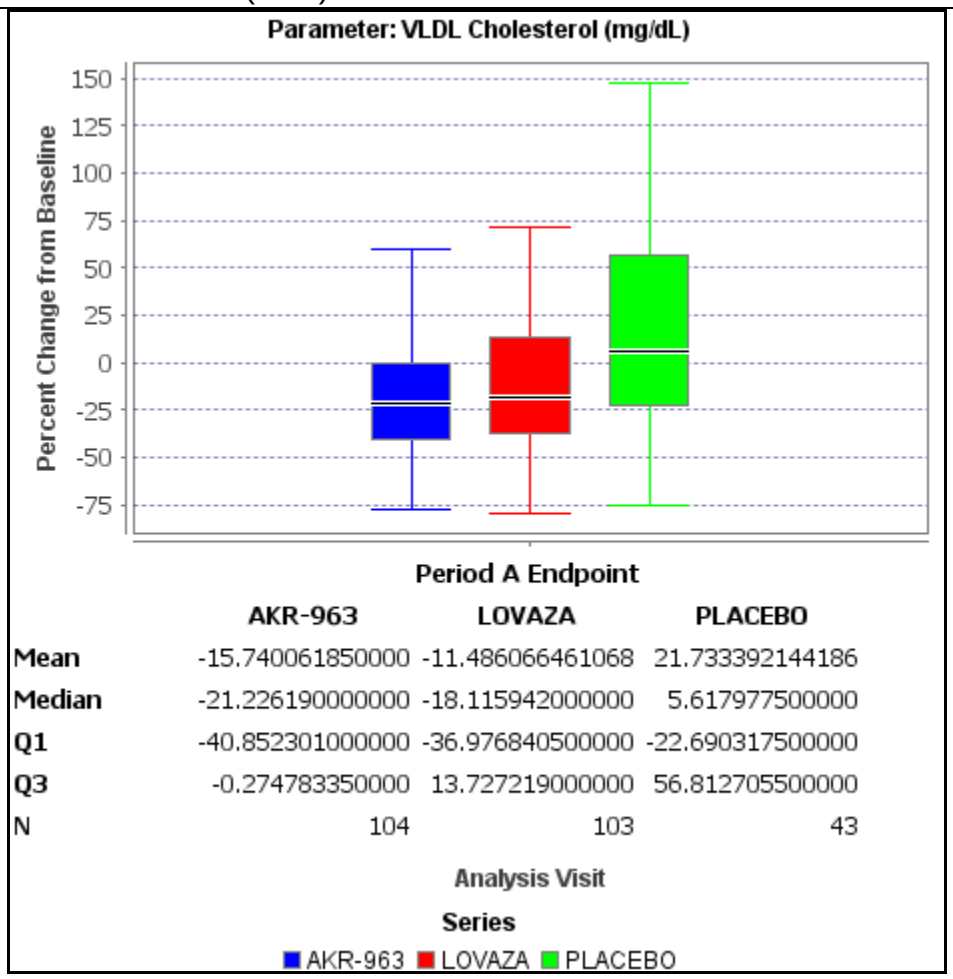
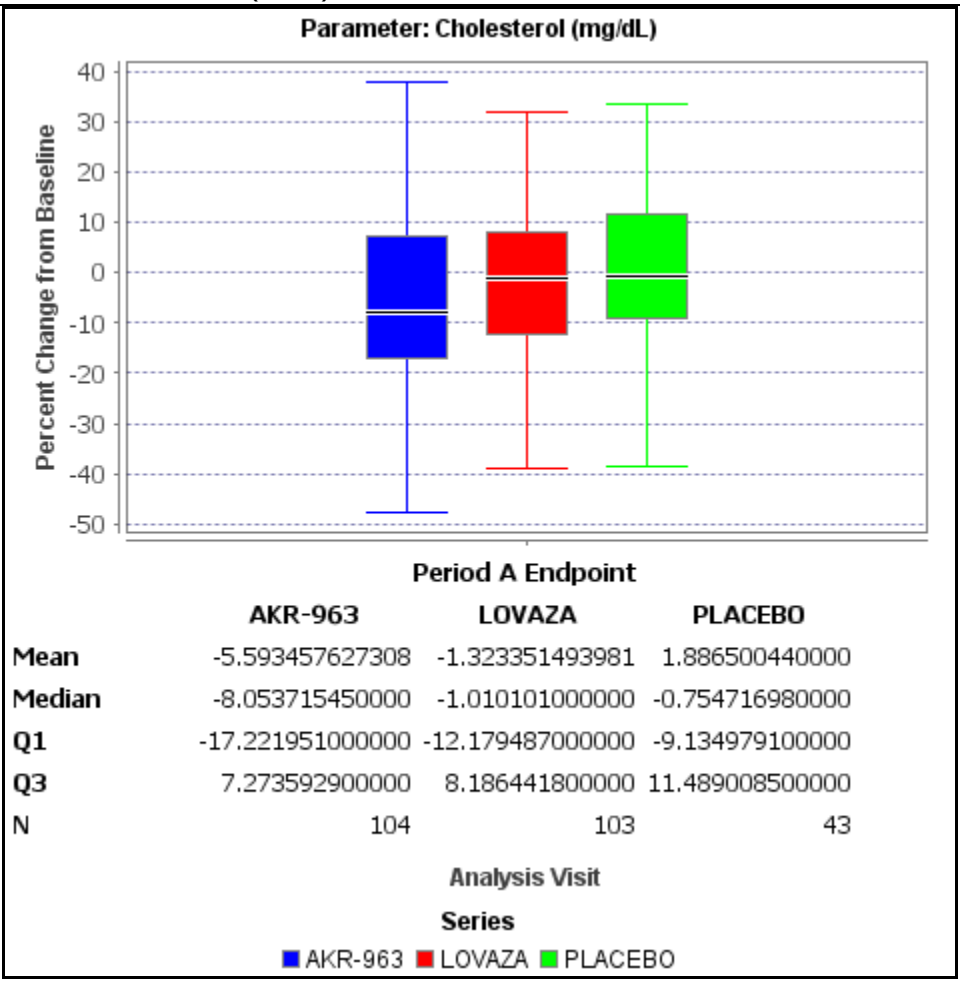


Figure 12: Mean and Median Percent Change in VLDL-C from Baseline to Period A Endpoint, mITT Population

The median of the differences in percent change between placebo and AKR-963 was -29%, p=0.0008. The median of the differences in percent change between placebo and Lovaza was -24%, p=0.0057. The median of the differences in percent change between Lovaza and AKR-963 was -6%, p=0.2039.

Total Cholesterol
The following figure presents the median percent change in TC from Baseline to Period A Endpoint for the mITT Population. Median baseline TC levels were 250 mg/dL for the placebo group, 244 mg/dL for the Lovaza group, and 270 mg/dL for the AKR-963 group.

The median percent change in TC from baseline to Period A Endpoint was -0.8% for the placebo group, -1.0% for the Lovaza group, and -8.1% for the AKR-963 group.



	AKR-963	LOVAZA	PLACEBO
Mean	-5.593457627308	-1.323351493981	1.886500440000
Median	-8.053715450000	-1.010101000000	-0.754716980000
Q1	-17.221951000000	-12.179487000000	-9.134979100000
Q3	7.273592900000	8.186441800000	11.489008500000
N	104	103	43

Figure 13: Mean and Median Percent Change in TC from Baseline to Period A Endpoint, mITT Population

The median of the differences in percent change between placebo and AKR-963 was -6.9%, p=0.0331. The median of the differences in percent change between placebo and Lovaza was -1.9%, p=0.5168. The median of the differences in percent change between Lovaza and AKR-963 was -4.7%, p=0.0465.

Non-HDL-C

The following figure presents the mean and median percent change in non-HDL-C from Baseline to Period A Endpoint for the mITT population.

Median baseline non-HDL-C levels were 222 mg/dL for the placebo group, 210 mg/dL for the Lovaza group, and 237 mg/dL for the AKR-963 group. The median percent change in non-HDL-C from Baseline to Period A Endpoint was -0.8% for the placebo group, -3.6% for the Lovaza group, and -9.2% for the AKR-963 group.

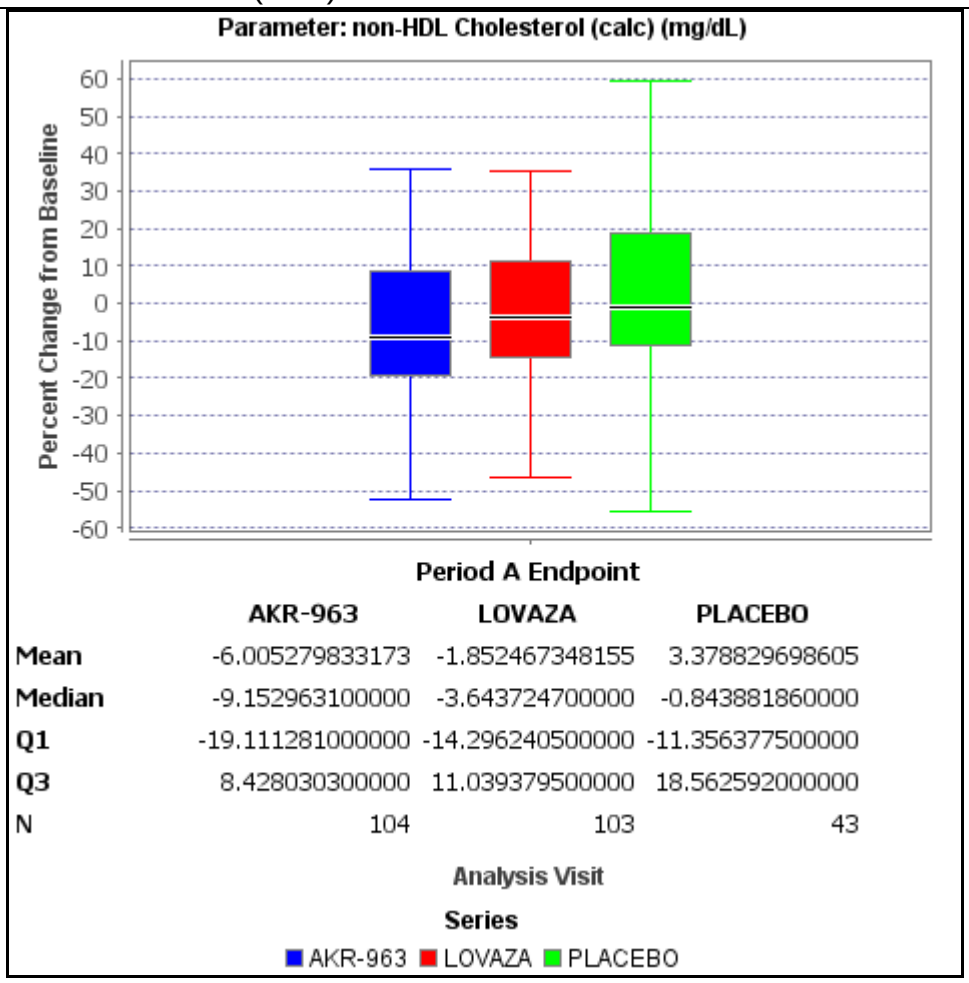


Figure 14: Mean and Median Percent Change in non-HDL-C from Baseline to Period A Endpoint, mITT Population

The median of the differences in percent change between placebo and AKR-963 was -8.5%, p=0.0258. The median of the differences in percent change between placebo and Lovaza was -3.5%, p=0.2870. The median of the differences in percent change between Lovaza and AKR-963 was -4.5%, p=0.0964.

6.1.6 Other Endpoints

Homeostatic model assessment for insulin resistance (HOMA-IR)

The following table presents the median percent change in HOMA-IR from Baseline to Period A Endpoint for patients not on hypoglycemic medications. Median baseline HOMA-IR levels were 3.5 for the placebo group, 4.5 for the Lovaza group, and 4.4 for the AKR-963 group. The median percent change in HOMA-IR from baseline to Period A endpoint was -3.9% for the placebo group, -7.5% for the Lovaza group, and -3.4% for the AKR-963 group.

The median of the differences in percent change between placebo and Lovaza was -12.7%. This treatment difference was not statistically significant (p=0.4115). The median of the differences in percent change between placebo and AKR-963 was -7.9%. This treatment difference was not statistically significant (p=0.5647). Adjusted p-values for each treatment comparison were not statistically significant (p=0.5647 for both comparisons). The median of the differences in percent change between Lovaza and AKR-963 was 3.2%. This treatment difference was not statistically significant (p=0.7217).

Table 18: Median Percent Change in HOMA-IR from Baseline to Period A Endpoint, mITT Population

Analysis Variable	Placebo (N = 43)	Lovaza (N = 103)	AKR-963 (N = 104)
n [1]	24	52	58
Baseline [2] median (Q1, Q3)	3.5 (2.0, 6.0)	4.5 (2.5, 7.3)	4.4 (2.6, 7.2)
Endpoint [3] median (Q1, Q3)	3.7 (2.2, 6.9)	4.1 (2.4, 6.4)	4.5 (2.2, 7.4)
Median (Q1, Q3) percent change	-3.9 (-23.3, 49.0)	-7.5 (-41.3, 29.0)	-3.4 (-27.3, 28.9)
Median of differences relative to placebo			
Estimate		-12.7	-7.9
95% CI		(-35.8, 13.2)	(-33.8, 16.1)
p-value		0.4115	0.5647
Adjusted p-value		0.5647	0.5647
Median of differences relative to Lovaza			
Estimate			3.2
95% CI			(-14.9, 22.6)
p-value			0.7217

HOMA-IR was only measured in subjects not receiving hypoglycemic medication.
95% CIs were estimated with the Hodges-Lehmann method. P-values were from the Wilcoxon rank-sum test.
Adjusted p-values were calculated using Hommel's procedure.
1. Includes subjects with non-missing values at baseline and Period A endpoint.
2. Baseline was defined as the Visit 4 (Week 0) measurement. If this measurement was missing, the last measurement taken prior to randomization was used as the baseline value.
3. Endpoint was defined as the measurement taken at Visit 8 (Week 12). If this measurement was missing, the last available measurement taken during Period A (last observation carried forward) was used as the endpoint value.

CI = confidence interval; Q1 = first quartile; Q3 = third quartile.
Source: Post-text Table 14.2.15

hsCRP

Median baseline hsCRP levels were 2.2 mg/L for the placebo group, 2.8 mg/L for the Lovaza group, and 3.1 mg/L for the AKR-963 group. The median change in hsCRP from baseline to Period A endpoint was 0.1 mg/L for the placebo and Lovaza groups and 0.0 mg/L for the AKR-963 group.

The median of the differences in change between placebo and Lovaza was -0.2 mg/L, p=0.5291. The median of the differences in change between placebo and AKR-963 was -0.2 mg/L, p=0.4214.

Period B/C Lipid Endpoints

Table 19: Median Percent Change in Lipids from Period B Baseline to Study Endpoint, Excluding Patients on Placebo During Period A, mITT Population

Parameter Statistic	Lovaza (N = 91)	AKR-963 (N = 97)
Triglycerides		
n [1]	88	93
Baseline [2] median (Q1, Q3)	486.5 (353.0, 637.5)	518.0 (405.0, 769.5)
Endpoint [3] median (Q1, Q3)	403.5 (291.0, 573.5)	433.0 (321.0, 692.0)
Median (Q1, Q3) percent change	-7.5 (-35.2, 24.3)	-8.9 (-36.9, 21.3)
Non-high-density lipoprotein cholesterol		
n [1]	88	93
Baseline [2] median (Q1, Q3)	197.0 (163.0, 234.0)	217.0 (188.0, 252.0)
Endpoint [3] median (Q1, Q3)	200.0 (162.0, 232.0)	211.0 (171.0, 248.0)
Median (Q1, Q3) percent change	2.3 (-10.8, 11.8)	1.4 (-14.7, 13.5)
Very low-density lipoprotein cholesterol		
n [1]	88	93
Baseline [2] median (Q1, Q3)	88.0 (68.0, 127.0)	106.0 (80.0, 157.0)
Endpoint [3] median (Q1, Q3)	82.0 (57.5, 107.5)	93.0 (60.0, 130.0)
Median (Q1, Q3) percent change	-12.5 (-37.8, 24.7)	-12.4 (-38.3, 15.8)
Low-density lipoprotein cholesterol		
n [1]	88	93
Baseline [2] median (Q1, Q3)	96.0 (76.0, 122.0)	93.0 (79.0, 123.0)
Endpoint [3] median (Q1, Q3)	107.5 (69.5, 142.5)	102.0 (81.0, 137.0)
Median (Q1, Q3) percent change	11.2 (-9.3, 29.2)	11.9 (-9.1, 30.8)
High-density lipoprotein cholesterol		
n [1]	88	93
Baseline [2] median (Q1, Q3)	30.0 (26.0, 36.0)	28.0 (24.0, 32.0)
Endpoint [3] median (Q1, Q3)	33.0 (26.0, 38.0)	30.0 (24.0, 35.0)
Median (Q1, Q3) percent change	4.8 (-7.2, 17.2)	3.3 (-7.1, 20.0)
Total cholesterol		
n [1]	88	93
Baseline [2] median (Q1, Q3)	230.0 (196.0, 267.0)	244.0 (217.0, 276.0)
Endpoint [3] median (Q1, Q3)	230.5 (195.0, 266.0)	243.0 (199.0, 280.0)
Median (Q1, Q3) percent change	1.9 (-8.6, 10.8)	0.0 (-13.5, 10.5)

1. Includes subjects with non-missing values at Period B/C baseline and study endpoint.
2. For TG, baseline was defined as the average of the measurements taken at Visit 7 (Week 11) and Visit 8 (Week 12). If either of these measurements were missing, the other measurement was used as the baseline value. If both of these measurements were missing, the last TG measurement taken during Period A was used as the baseline TG value for Period B/C. For all other lipid parameters, baseline was defined as the Visit 8 (Week 12) measurement. If this measurement was missing, the last measurement taken during Period A was used as the baseline value.
3. Endpoint was defined as the last measurement taken during Period B/C.

Q1 = first quartile; Q3 = third quartile; TG = triglycerides.
Sources: Post-text Tables 14.2.19, 14.2.20, and 14.2.21

AKR-963 and Lovaza had similar lipid lowering effects during Period B/C. For instance,

- the median percent change in TG was -7.5% for Lovaza and -8.9% for the AKR-963,
- the median percent change in VLDL-C was -12.5% for Lovaza and -12.4% for AKR-963, andthe median percent change in LDL-C was 11.2% for Lovaza and 11.9% for AKR-963.

6.1.7 Subpopulations

Diabetes

The figure below shows the mean and median percent change from Baseline to Period A Endpoint in TG in patients with and without diabetes.

In subjects without diabetes, the median percent change in TG from Baseline to Period A Endpoint was -13% for the placebo group, -28% for the Lovaza group, and -26% for the AKR-963 group.

In subjects with diabetes, the median percent change in TG from Baseline to Period A Endpoint was -19% for placebo, -25% for Lovaza, and -22% for AKR-963.

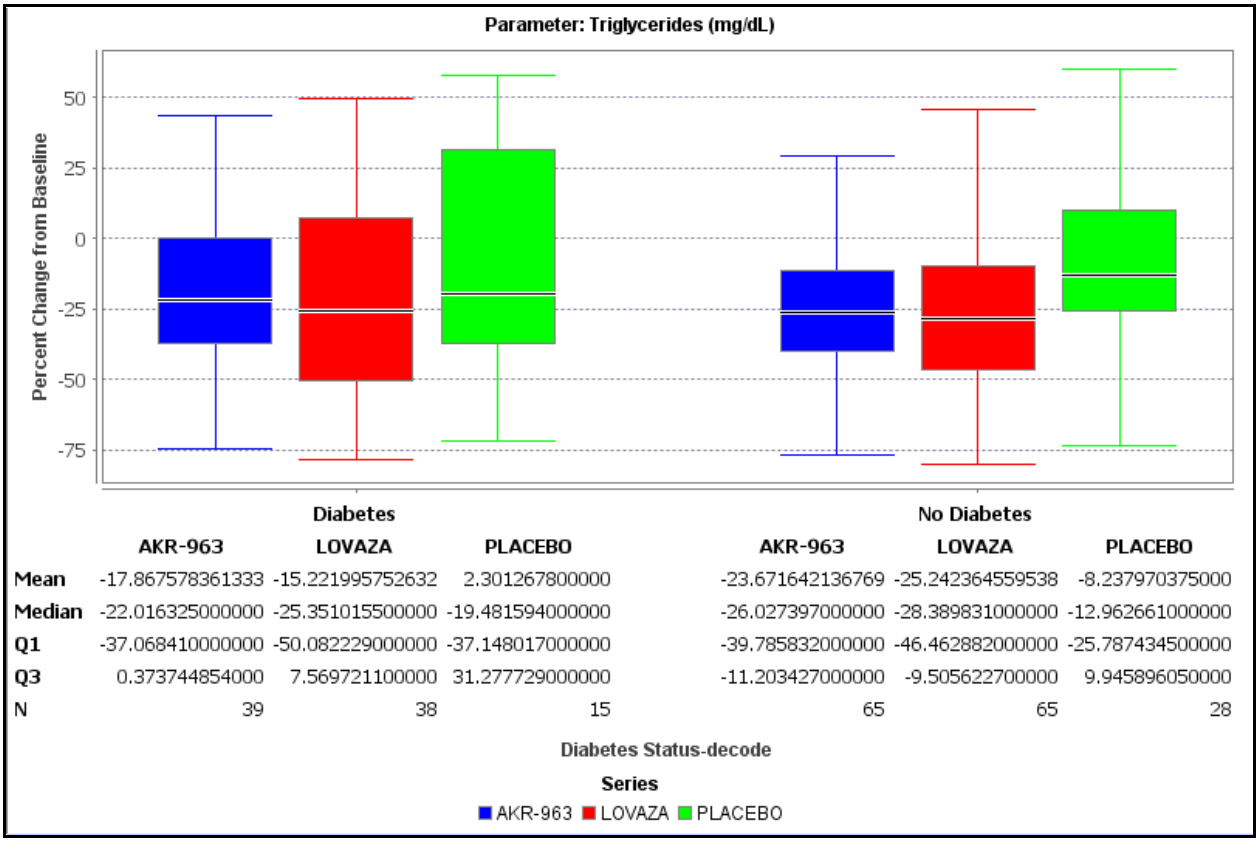
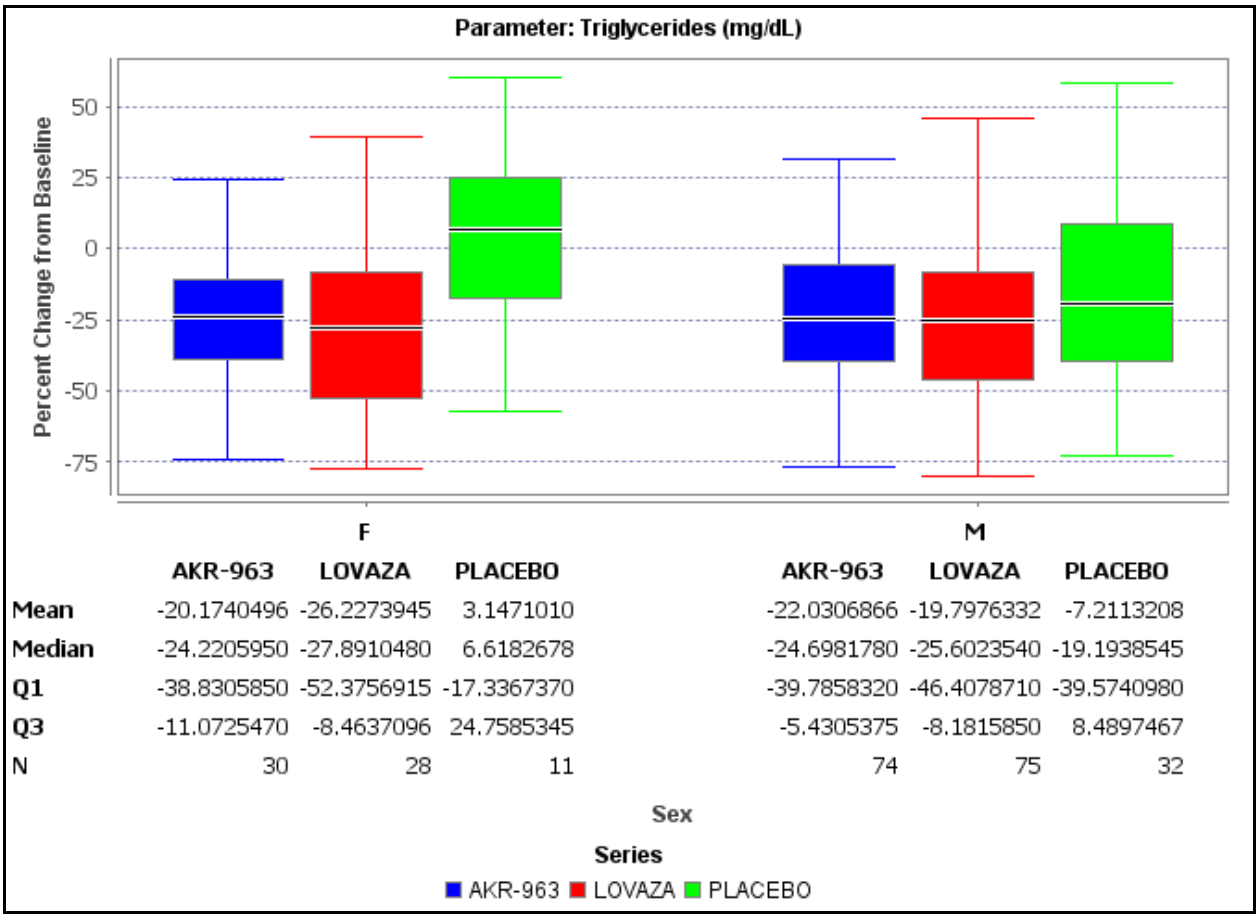


Figure 15: Mean and Median Percent Change from Baseline to Period A Endpoint in TG by Diabetes Status, mITT Population

Reviewer Comment: In this trial, TG reduction with AKR-963 and Lovaza was greater in non-diabetics than in diabetics. However, results are not generalizable due to small patient populations.

Sex
The following figure shows the mean and median percent change in TG from Baseline to Period A Endpoint by sex.



	F			M		
	AKR-963	LOVAZA	PLACEBO	AKR-963	LOVAZA	PLACEBO
Mean	-20.1740496	-26.2273945	3.1471010	-22.0306866	-19.7976332	-7.2113208
Median	-24.2205950	-27.8910480	6.6182678	-24.6981780	-25.6023540	-19.1938545
Q1	-38.8305850	-52.3756915	-17.3367370	-39.7858320	-46.4078710	-39.5740980
Q3	-11.0725470	-8.4637096	24.7585345	-5.4305375	-8.1815850	8.4897467
N	30	28	11	74	75	32

Figure 16: Mean and Median Percent Change from Baseline to Period A Endpoint by Sex, mITT Population

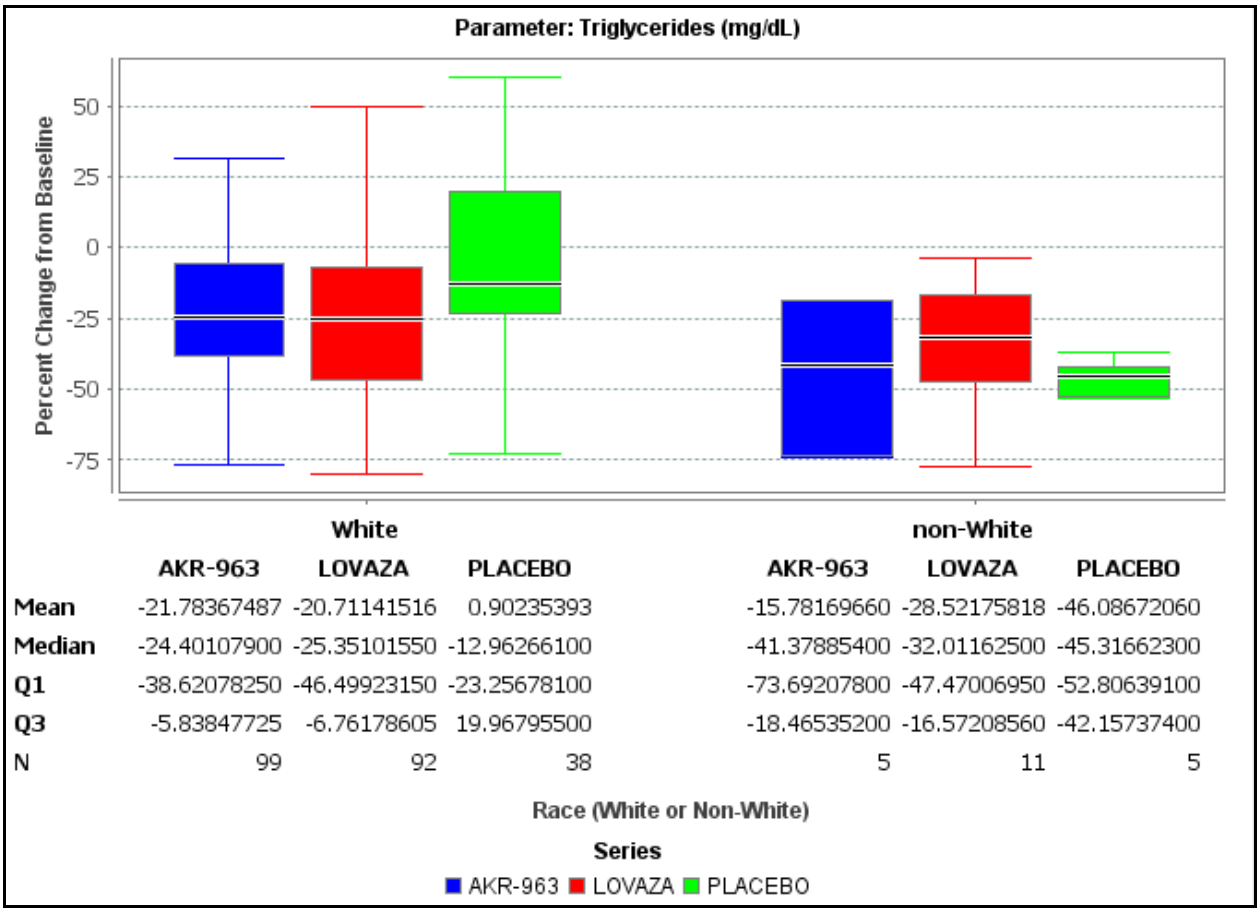
In men, the median percent change in TG from Baseline to Period A endpoint was -19% for the placebo group, -26% for the Lovaza group, and -25% for the AKR-963 group. The difference in median percent change between placebo and Lovaza was -7.7%, p=0.2118. The difference in median percent change between placebo and AKR-963 was -7.2%, p=0.3200. The difference in median percent change between Lovaza and AKR-963 was 1.3, p=0.7860.

In women, the median percent change in TG from Baseline to Period A Endpoint was7% for the placebo group, -28% for the Lovaza group, and -24% for the AKR-963 group. The difference in median percent change between placebo and Lovaza was -30.5%, p=0.0237. The difference in median percent change between placebo and AKR-963 was -26.3%. This treatment difference was statistically significant, p=0.0306. The difference in median percent change between Lovaza and AKR-963 was 5.2%, p=0.4598.

Reviewer Comment: Subgroup analysis by sex showed that the median percent differences between each active medication and placebo was statistically significant in women, but not in men. However, care must be taken not to over interpret these results as the sample size is small.

Race

White/Caucasians made up approximately 92% of the trial; therefore a meaningful analysis for non-whites is difficult given the small sample size. The following figure shows the mean and median percent change from Baseline to Period A Endpoint in TG according to race.



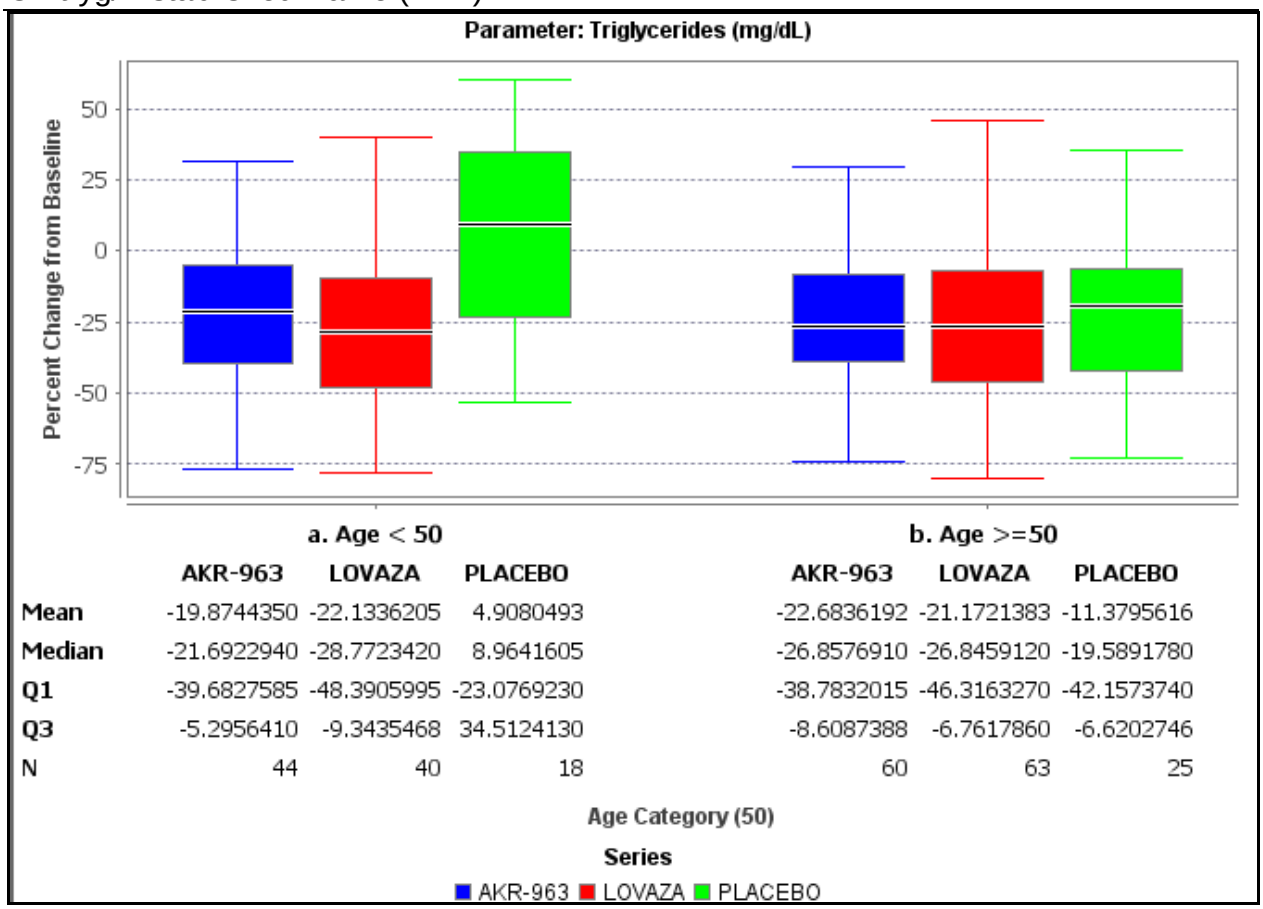
	White			non-White		
	AKR-963	LOVAZA	PLACEBO	AKR-963	LOVAZA	PLACEBO
Mean	-21.78367487	-20.71141516	0.90235393	-15.78169660	-28.52175818	-46.08672060
Median	-24.40107900	-25.35101550	-12.96266100	-41.37885400	-32.01162500	-45.31662300
Q1	-38.62078250	-46.49923150	-23.25678100	-73.69207800	-47.47006950	-52.80639100
Q3	-5.83847725	-6.76178605	19.96795500	-18.46535200	-16.57208560	-42.15737400
N	99	92	38	5	11	5

Figure 17: Mean and Median Percent Change from Baseline to Period A Endpoint in TG by Race, mITT Population

In Whites, the median percent change in TG from Baseline to Period A Endpoint was -13% for the placebo group, -25% for the Lovaza group, and -24% for the AKR-963 group. The difference in median percent change between placebo and Lovaza was -20%, p=0.0045. The difference in median percent change between placebo and AKR-963 was -17%, p=0.0038. The difference in median percent change between Lovaza and AKR-963 was 2.3%, p=0.5940.

In non-Whites, large median percent reductions were seen in all three treatment arms, including placebo. However, the sample size was too small to make definitive conclusions.

Age
The following figure shows the mean and median percent change in TG from Baseline to Period A Endpoint by age <50 and ≥50 years.



	a. Age < 50			b. Age >=50		
	AKR-963	LOVAZA	PLACEBO	AKR-963	LOVAZA	PLACEBO
Mean	-19.8744350	-22.1336205	4.9080493	-22.6836192	-21.1721383	-11.3795616
Median	-21.6922940	-28.7723420	8.9641605	-26.8576910	-26.8459120	-19.5891780
Q1	-39.6827585	-48.3905995	-23.0769230	-38.7832015	-46.3163270	-42.1573740
Q3	-5.2956410	-9.3435468	34.5124130	-8.6087388	-6.7617860	-6.6202746
N	44	40	18	60	63	25

Figure 18: Mean and Median Percent Change from Baseline to Period A Endpoint in TG by Age, <50 or ≥50 years, mITT Population

In patients <50 years, the median percent change in TG from Baseline to Period A Endpoint was -9% for the placebo group, -29% for the Lovaza group, and -22% for the AKR-963 group.

In patients ≥50 years, the median percent change in TG from Baseline to Period A Endpoint was -20% for placebo, -27% for Lovaza, and -27% for AKR-963.

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Reviewer Comment: In this trial, placebo patients older than 50 years had a reduction in TG similar to active treatment arms.

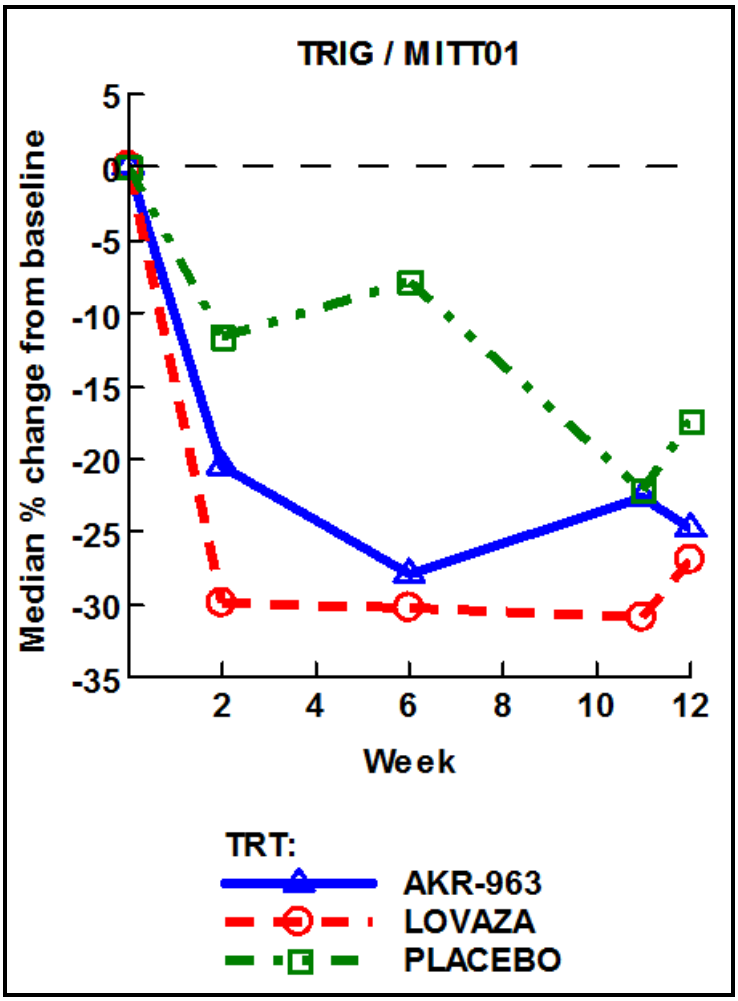
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose, four 1 g capsules at one time, was administered in study TRGG-963-002. However, no clear instructions were given in the study as to whether the capsules should be taken in a fed or fast state.

The applicant did conduct pharmacokinetic studies in both the fasting and fed conditions to determine the comparative bioavailability of AKR-963 (studies TRGG-963-005 and 006). Results showed that concentrations of EPA and DHA were increased in a fed state as compared to a fasted state.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

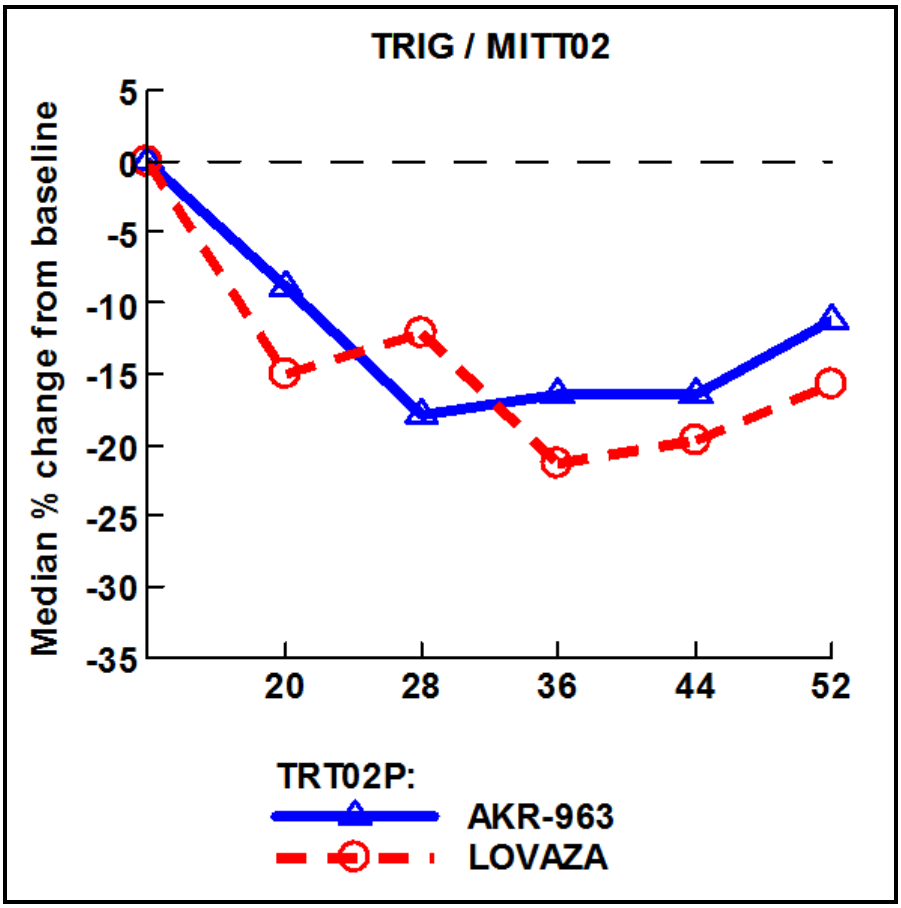
The following two figures show the mean percent change from baseline (either Baseline A or Baseline B) in TG at different time points. There are two baselines because there are two periods, A and B. Period C is not considered here for efficacy analysis because of the small sample size during that period.



Source: Dr. Lee Ping Pian, statistical reviewer

Figure 19: Median Percent Change in TG from Period A Baseline to Different Time Points, mITT Population

Weekly analysis of the median percent change from Period A Baseline in TG shows that both AKR-963 and Lovaza reduced TG, although Lovaza showed a more pronounced effect (approximately -30% vs. -22%) at Week 2. By Week 12, the median percent change in TG was approximately -27% for AKR-963 and -30% for Lovaza. Patients on placebo also had reductions in TG, although not as striking as the active treatments---approximately -12% at Week 2 and -9% at Week 6. However, by the end of Period A, placebo reductions in TG reached approximately -23 to -18%.
It is evident that patients on placebo had more fluctuating TG levels than patients on AKR-963 or Lovaza, but at the Week 11 timepoint, placebo had similar reductions in TG as AKR-963.



Source: Dr Lee Ping Pian

Figure 20: Median Percent Change in TG from Period B Baseline to Different Time Points, mITT Population

After the maximum reductions obtained in Period A with AKR-963 and Lovaza, there were no further dramatic reductions in TG (Figure 13). In Period B, further reductions in TG ranged from approximately -13% to -20% with Lovaza and -8% to -17% with AKR-963.

The following two figures show the mean TG levels at various time points by treatment arms.

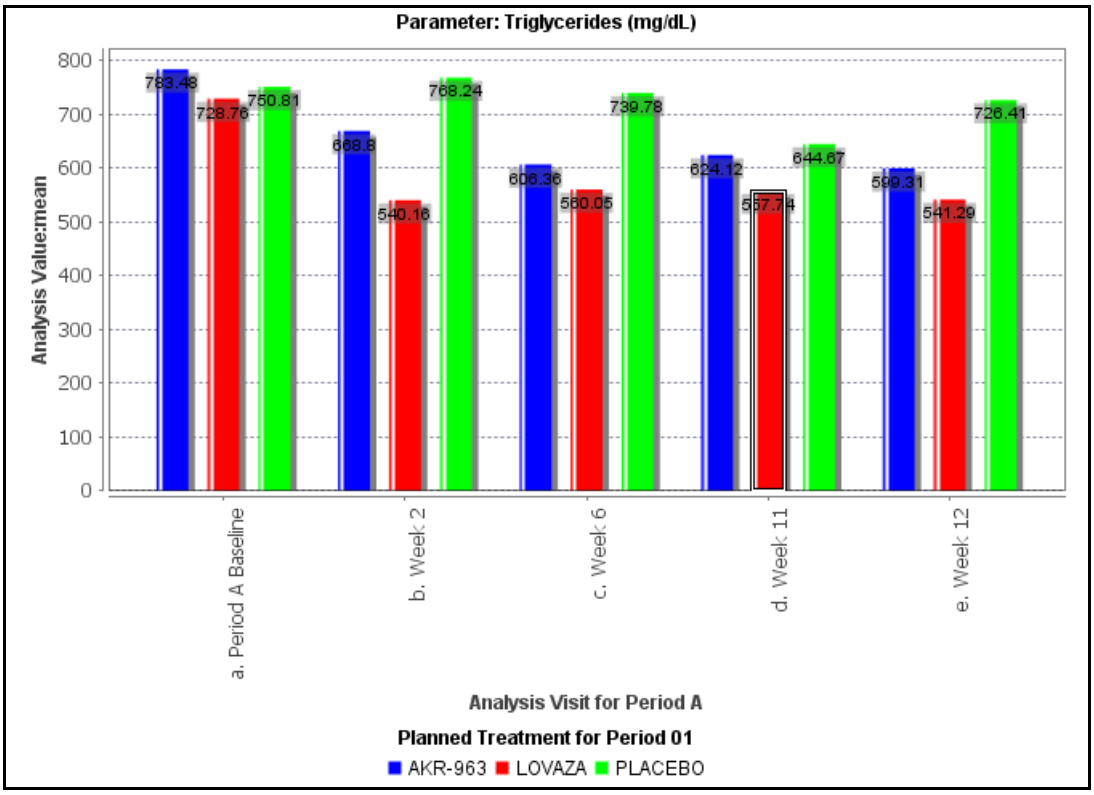


Figure 21: Mean TG (mg/dL) Levels at Various Timepoints, Period A, by Treatment Arm, mITT Population

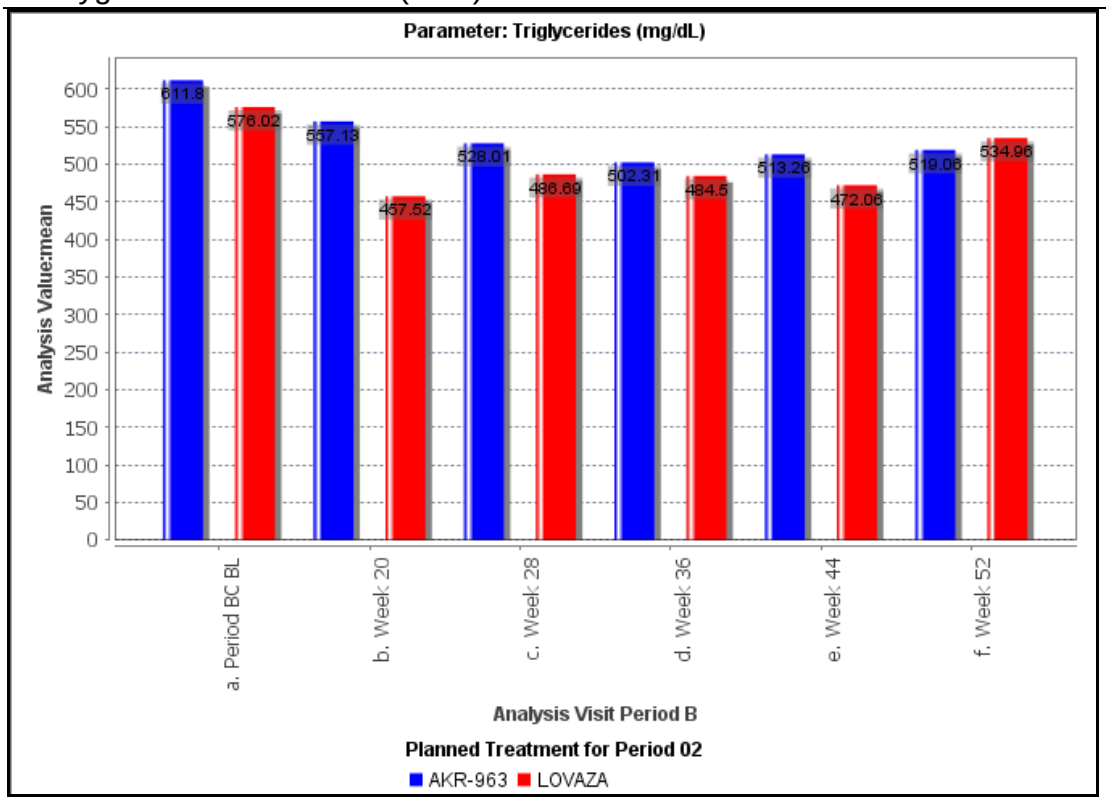


Figure 22: Mean TG (mg/dL) Levels at Various Timepoints, Period B, mITT Population

As shown in the figure above, the therapeutic effects of AKR-963 are fairly consistent up to Week 52.

6.1.10 Additional Efficacy Issues/Analyses

As part of the 74-Day Filing Letter, the applicant was requested to provide a rationale for assuming the applicability of foreign data in the submission (bioequivalence trials) to the US population.

In response, the applicant submitted key demographic data from the bioequivalence studies TRGG-963-005 and TGGG-963-006 and compared it to the US population from the US 2010 census. The applicant also noted that these studies were conducted at a site in Canada.

Table 20: Comparison of Demographic Data from Studies TRGG-963-005 and TRGG-963-006 to the US Population 2010 Census Data

Parameter	Subgroup	Study TRGG-963-005		Study TRGG-963-006		US 2010 Census Data[a,b]	Conclusions
		Safety Dataset (N = 44)	Pharmacokinetic Dataset (N = 39)	Safety Dataset (N = 50)	Pharmacokinetic Dataset (N = 49)		
Gender Number (Percent)	Male	25 (56.8)	25 (64.1)	34 (68.0)	33 (67.3)	49.2%	Higher representation of males in studies compared to US population but females still had significant representation
	Female	19 (43.2)	14 (35.9)	16 (32.0)	16 (32.7)	50.8%	
Race and Ethnicity Number (Percent)	White	16 (36.4)	15 (38.5)	19 (38.0)	18 (36.7)	65.1%	Racially, non-white races over-represented. Ethnically, Hispanic representation similar to proportion in US population
	Black	9 (20.5)	8 (20.5)	13 (26.0)	13 (26.5)	12.9%	
	Asian	10 (22.7)	8 (20.5)	11 (22.0)	11 (22.4)	4.6%	
	Hispanic	9 (20.5%)	8 (20.5%)	7 (14.0)	7 (14.3)	15.8%	
Age Group Number (Percent)	< 18	0	0	0	0	23.7%	
	18 to 40	32 (72.7)	27 (69.2)	26 (52.0)	25 (51.0)	36.4%[c]	Younger age range proportionally higher than US population but consistent with median age of 37.3 years of US population [a]
	41 to 64	12 (27.3)	12 (30.8)	24 (48.0)	24 (49.0)	26.5%[d]	
	65 to 74	0	0	0	0	7.2%	
	≥ 75	0	0	0	0	6.1%	

[a] = Source: http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_11_1YR_S0201&prodType=table
[b] = Source: http://www.census.gov/compendia/statab/2012/tables/12s0006.pdf
[c] = Represents age range of 18 to 44 years since exact range to study statistic not available
[d] = Represents age range of 45 to 64 years since exact range to study statistic not available

Source: NDA 204977 submission, SN006, May 2013.

The applicant made the following three points:

1. Although studies were conducted at a study site in Canada, these studies were conducted under US IND 107259 and met Health Canada requirements.
2. Demographically, the population of subjects in the 2 key bioequivalence studies compared well to the US population in general with in fact an over-representation of minority races, which is a more conservative approach.
3. Based on an extensive literature search (summarized in Section 1.12.11 in NDA 204977), there was no suggestion that the absorption of Lovaza is different on the basis of differences in gender, race, ethnicity, or age.

Reviewer Comment: Based on the provided rationale, I am in agreement that the results from studies TRGG-963-005 and TRGG-963-006 are applicable to the US population.

7 Review of Safety

Safety Summary

The safety information in this NDA was based on one Phase 3 trial, TRGG-963-002, and was divided into Period A and Period B/C.

The safety population during Period A consisted of all randomized patients who took at least one dose of study medication: 106 patients in the AKR-963 group, 105 subjects in the Lovaza group, and 43 subjects in the placebo group.

In Period B/C, the safety population consisted of all randomized patients who took at least one dose of study medication: 115 patients in the AKR-963 group and 112 patients in the Lovaza group.

During Period A, approximately 49% of patients on Placebo, 44% on Lovaza, and 48% on AKR-963 reported any AE. During Period B/C approximately 53% of patients on Lovaza and 60% reported any AE.

Previously approved fish oil products have a statement in the warnings and precautions section of the labeling to periodically monitor ALT and AST in patients with hepatic impairment. There is also a statement about the increase in LDL-C with treatment. This safety review focuses on these issues as well as a possibly increased risk of bleeding.

7.1 Methods

The materials submitted by the sponsor for this review are summarized in Section 5. The review involved analysis of the files submitted electronically as part of the sponsor's original submission, the 4-month safety update, and patient/study information as requested by this clinical reviewer during the review process.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety analysis was based on trials from the applicant's development program and included not only their Phase 3 trial, TRGG-963-002, but also the four PK trials -003, 004, 005, and 006. The safety analyses of the four PK trials are reviewed in Section 5, while the safety analysis for TRGG-963-002 is discussed in Section 7.

7.1.2 Categorization of Adverse Events

This reviewer assessed the applicant's coding of events by comparing the applicant's preferred terms (dictionary –derived terms in the table below) to the verbatim terms (reported term for the adverse event) used by the investigators and patients. In general the reported adverse event term was mapped to an appropriate dictionary-derived term.

Table 21: Comparison of Reported Term for Adverse Event with Dictionary-Derived Term-

Dictionary –Derived Term	Reported Term for the Adverse Event
Diarrhoea	Loose Stools
Alanine Aminotransferase Increased	Increased ALTPer Protocol Definition
Back Pain	Exacerbation of Chronic Back Pain
Carpal Tunnel Syndrome	Exacerbation of Carpal Tunnel Synderome
Cerumen Impaction	Left Ear Impacted Cerumen
Eructation	Fish Burps
Furuncle	Boil

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Mean exposure to study medication during Period A was 11.8 weeks for the placebo group, 11.5 weeks for the Lovaza group, and 11.6 weeks for the AKR-963 group. Mean exposure to study medication during Period B/C was 37.1 weeks for the Lovaza group and 36.2 weeks for the AKR-963 group.

The following table summarizes the overall exposure to study medications during the entire study. Approximately 56% of patients in AKR-963 group had greater than 12 months of exposure as compared to 53% of patients in the Lovaza treatment group.

Table 22: Overall Exposure to Study Medications- Safety Population – TRGG-963-002

Exposure Categories	Placebo N=43 n (%)	Lovaza N=126 n (%)	AKR-963 N=124 n (%)
>0 to ≤3 months	41 (95)	13 (10)	14 (11)
>3 to ≤6 months	2 (5)	11 (8)	9 (7)
>6 to ≤12 months	0	35 (28)	32 (26)
>12 months	0	67 (53)	69 (56)

Source: TRGG-963-002 Study Report, Table 26, pg. 94

7.2.2 Explorations for Dose Response

The applicant did not conduct dose response studies.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

In Study TRGG-963-002, safety laboratory tests (chemistry, hematology, and urinalysis) were evaluated at Week -6, Week 0, Week 12, Week 36, Week 52 and at the final visit of the extension period.

Algorithm for elevated liver function tests

The following were defined as elevations in liver tests:

- ALT and/or AST or bilirubin measurement >3 × ULN and an increase of at least 30% above the baseline value;
- ALT and/or AST or bilirubin measurement >2 × ULN and an increase of at least 70% above the baseline value; or
- Alkaline phosphatase measurement >2 × ULN with an ALT, AST, and/or bilirubin measurement >ULN.

In the event of any of these elevations in liver tests, the initial measurement was to be confirmed by repeat blood draw and retest (using the same central laboratory) as soon as possible. If the elevations were confirmed by repeat testing, the following procedures were to be followed:

- An SAE form was to be completed immediately
- The Investigator was to contact the Medical Monitor to discuss any additional laboratory testing
- The subject was to return to the site for follow-up
- Repeat clinical laboratory testing until abnormal values returned to baseline or a confirmation of a diagnosis. The follow-up schedule was to be agreed upon between the Investigator and the Medical Monitor
- If a diagnosis of hepatotoxicity was made secondary to factors not related to study medication, the Medical Monitor was to be contacted. Per Investigator judgment, the subject was to either continue in the study or be discontinued from the study

If any elevations in the above laboratory parameters were not confirmed by repeat testing, the test was to be repeated according the schedule of assessments. An Adverse Event form was to be completed.

Reviewer Comment: The inclusion of elevated liver tests as a serious adverse event is unique to this NDA. Usually, elevated liver tests are followed as events of special interest. As shown in more detail in other sections, liver test elevations made up most of the SAEs throughout the study periods.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the Clinical Pharmacology review for the adequacy assessment of the in vitro and in vivo metabolism, excretion and drug-drug interaction testing.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hemorrhagic diathesis

Omega-3 FA such as EPA and DHA can inhibit cyclo-oxygenase and thereby decrease platelet aggregation.[6] Platelet derived growth factor–like protein and syntheses of the platelet activation factor are also decreased with omega-3 FA.[7] Theoretically, it is possible that long-term dietary enrichment with omega-3 FA can increase the risk for bleeding.

Post-marketing reports for Lovaza have identified bleeding complications or a "hemorrhagic diathesis" with the use of Lovaza. According to case reports with Lovaza, the onset of apparent bleeding related AEs occur after several weeks to longer than one year of exposure. [8]

Current prescribing information for Lovaza states:
"Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Lovaza and concomitant anticoagulants. Patients receiving treatment with Lovaza and an anticoagulant or other drug affecting coagulation should be monitored periodically (e.g., aspirin, NDAIDS, warfarin, coumarin)."

PT/PTT and INR were not collected during this study. There was one case of "increased tendency to bleed" reported in a patient on Lovaza during this study.

6 Thorngren M et al. Effects of Acetylsalicylic Acid and Dietary Intervention on Primary Hemostasis. Am J of Medicine 1983; June 14: 66-71.
7 Bays HE et al. Safety Considerations with Omega-3 Fatty Acid Therapy. Am J Cardiol 2007; 99[supp]: 35C-43C.
8 GlaxoSmithKline, submission to FDA. Global Clinical Safety and Pharmacovigilance, Safety Evaluation and Risk Management: Lovaza-Hemorrhagic Diathesis 2008, pg. 7.

7.3 Major Safety Results

7.3.1 Deaths

A total of 2 deaths were reported during this study. Subject 127-005 died prior to randomization (i.e., during the diet lead-in period) due to multiple injuries from a motor vehicle accident. Subject 111-019 in the AKR-963 group died during Period B due to esophageal carcinoma. The following table summarizes these fatalities.

Table 23: Listing of All Deaths, All Randomized Patients

ID	Treatment Group	Age	Gender	Days on Medication	Onset of AE	Day of Death	Reported Cause of Death	Cause of Death on Narrative Review
127-005/ (b) (6)	Prior to Randomization	60	Male	N/A	N/A	(b) (6)	Motor Vehicle Accident	Multiple trauma due to Motor vehicle accident
111-019/ (b) (6)	AKR-963	52	Male	In March 2012, study med discontinued on unknown date	Day 281	Day (b) (6)	Esophageal Carcinoma	Esophageal Carcinoma

Reviewer Comment: Based on review of the case narrative, the reported causes of death appear accurate.

7.3.2 Nonfatal Serious Adverse Events

An adverse event was defined as any untoward medical occurrence in a patient following the patient's written informed consent that did not necessarily have a causal relationship with the treatment. An adverse event could be any unfavorable or unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it was related to the medicinal (investigational) product.

A serious adverse event (SAE) was any adverse experience that results in any of the following: death, life-threatening adverse event, persistent or significant disability, in-patient hospitalization, or congenital anomaly or birth defect.

In Period A, twelve patients reported a non-fatal SAE:

- 3 (2.83%) on AKR-963

- 8 (7.62%) on Lovaza
- 1 (2.33%) on Placebo

According to protocol, repeated elevations in liver enzymes were also considered SAEs (see section 7.2.4).

The following table summarizes the SAEs reported in Period A.

Table 24: Summary of All Nonfatal Serious Adverse Events by Treatment Arm Reported in Period A

System Organ Class/ Preferred Term	AKR-963 N=106	Lovaza N=105	Placebo N=43
Patient Reporting any Serious Adverse Event	3 (2.83%)	8 (7.62%)	1 (2.33%)
Gastrointestinal Disorders			
Abdominal Pain Upper	0	1 (0.95%)	0
Infections and Infestations			
Cellulitis	0	1 (0.95%)	0
Gastroenteritis	0	0	1 (2.33%)
Osteomyelitis	0	1 (0.95%)	0
Investigations			
Alanine Aminotransferase Increased	1(0.94%)	1(0.95%)	0
Hepatic Enzyme Test Abnormal	1 (0.94%)	2(1.90%)	0
Liver Function Test Abnormal	0	1 (0.95%)	0
Metabolism and Nutritional Disorders			
Gout	0	1 (0.95%)	0
Musculoskeletal and Connective Tissue Disorders			
Osteoarthritis	1 (0.94%)	0	0
Psychiatric Disorders	0	1 (0.95%)	0
Depression			
Reproductive System and Breast Disorders			
Uterine Prolapse	0	1 (0.95%)	0
Vascular Disorders			
Hypotension	0	0	1 (2.33%)

Reviewer Comment: In Period A, there were no SAEs which occurred in ≥1% more patients in the AKR-963 group versus the Lovaza treatment group or the Placebo treatment group.

In Period B/C, thirteen patients reported a non-fatal SAE:

- 7 (6.09%) on AKR-963
- 6 (5.36%) on Lovaza

Table 25: Summary of All Nonfatal Serious Adverse Events by Treatment Arm in Periods B/C

System Organ Class/ Preferred Term	AKR-963 N=115	Lovaza N=112
Patient Reporting any Serious Adverse Event	7 (6.09%)	6 (5.36%)
Cardiac Disorders		
Angina Pectoris	0	1 (0.89%)
Coronary Artery Disease	1 (0.87%)	1 (0.89%)
Injury, Poisoning and Procedural Complications		
Intentional Overdose	0	1 (0.89%)
Limb Traumatic Amputation	0	1 (0.89%)
Investigations		
Alanine Aminotransferase Increased	2 (1.74%)	1 (0.89%)
Aspartate Aminotransferase Increased	0	1 (0.89%)
Hepatic Enzyme Test Abnormal	1 (0.87%)	2 (1.79%)
Liver Function Test Abnormal	1 (0.87%)	0
Metabolism and Nutrition Disorders		
Gout	1 (0.87%)	0
Musculoskeletal and Connective Tissue Disorders		
Muscular weakness	0	1 (0.89%)
Rotator cuff syndrome	1 (0.87%)	0
Psychiatric Disorders		
Depression	0	1 (0.89%)

Reviewer Comment: In Period B/C, there were no SAEs which occurred in ≥1% more patients in the AKR-963 group versus the Lovaza treatment group.

Serious Adverse Events Related to Liver Enzyme Elevation

Liver enzyme abnormalities made up most of the reported SAEs in Periods A and B/C. In Period A, 1.89% of patients on AKR-963 vs. 3.81% of patients on Lovaza vs. 0% of patients on Placebo reported a liver enzyme related abnormality.

In Period B/C, 3.48% of patients on AKR-963 vs. 3.57% of patients on Lovaza reported a liver enzyme related SAE.

Overall, 14 patients had an SAE related to a liver enzyme elevation. The patients with an SAE related to liver enzyme elevations were not necessarily reported also with an abnormal/elevated ALT/AST. Only seven of the 14 patients with an SAE also had a reported ALT and/or AST value >3XULN during the study: 4 patients in the Lovaza group and 3 patients in the AKR-963 group (see following table).
These inconsistencies made it difficult to adequately report the incidence of patients with liver-related issues.

Table 26: Identification of Patients Reported with an SAE Related to Liver Enzyme Elevation and Patients Reported with an ALT/AST >3XULN

Patients with SAEs related to liver enzyme elevation		**Patients with ALT and/or AST >3XULN**	
On Lovaza		**On Lovaza**	
106-012	SAE of Hepatic enzyme increased		
112-028	SAE of Hepatic enzyme increased	112-028	ALT >3XULN
112-030	SAE of Hepatic enzyme increased	112-030	ALT >3XULN
112-033	SAE of Liver function test abnormal	112-033	ALT >3XULN
121-003	SAE of Hepatic enzyme increased		
123-003	SAE of ALT increased		
132-016	SAE of ALT increased		
105-020	SAE of AST increased	105-020	AST >3xULN
		137-009	ALT >3XULN
		142-033	ALT >3XULN
		101-001	ALT>3XULN
		106-012	AST>3XULN
		142-013	ALT >3XULN

Patients with SAEs related to liver enzyme elevation		Patients with ALT and/or AST >3XULN	
On AKR-963		**On AKR-963**	
132-019	ALT increased		
141-010	ALT increased	141-010	ALT >3XULN
155-012	Hepatic enzyme increased	155-012	ALT and AST >3XULN
161-001	Hepatic enzyme increased		
172-004	ALT increased		
174-009	Liver function test abnormal	174-009	ALT and AST >3XULN

Overall there were thirteen patients on Lovaza who were reported with either an SAE related to liver enzyme abnormalities or an ALT/AST >3XULN. For AKR-963 there were six patients with either an SAE related to liver enzyme abnormalities or ALT/AST >3XULN (see table above).

Review of Serious Adverse Event Narratives Related to Liver Enzyme Elevations

The following are excerpts from the narratives of the 14 patients with a SAE related to liver enzyme elevations.

Subject 105-020/ (b) (6), a 59-year-old Caucasian male with a history of severe hypertriglyceridemia and minor elevation of liver functions, signed informed consent on 27-Dec-2010 with an alanine aminotransferase (ALT) of 57 U/L (normal range [NR] 6-41 U/L), aspartate aminotransferase (AST) of 55 U/L (NR 9-34 U/L), alkaline phosphatase of 72 U/L (NR 37-116 U/L), and total bilirubin of 0.64 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **Lovaza** on 07-Feb-2011 with an ALT of 81 U/L, AST of 66 U/L, alkaline phosphatase of 81 U/L, and total bilirubin of 0.69 mg/dL. Per protocol, the last dose of study medication was taken on Study Day 364 (05-Feb-2012). On Study Day 365 (06-Feb-2012), laboratory testing at Visit 13 (Week 52) revealed an ALT of 104 U/L, elevated AST of 117 U/L, alkaline phosphatase of 83 U/L, and total bilirubin of 1.17 mg/dL. On the same date, a physical examination revealed the subject to be asymptomatic. On 06-Mar-2012, laboratory testing at an Unscheduled Visit revealed an ALT of 134 U/L, AST of 135 U/L, alkaline phosphatase of 81 U/L, and a total bilirubin of 1.16 mg/dL. There was no treatment reported for the event. Additional medical history included hypertension, gout, hyperlipidemia, and hypercholesterolemia. Concomitant medications included allopurinol, simvastatin, triamterene/hydrochlorothiazide, and lisinopril. On 21-Aug-2012, the subject was considered lost to follow-up after multiple unsuccessful contact attempts. The event remained ongoing. The Investigator

considered the event of worsening of elevated AST/SGOT as moderate and not related to study medication, and reported fatty liver as a possible cause.

Subject 106-012 (b) (6), a 71-year-old Caucasian female with a history of severe hypertriglyceridemia, fatty liver, and elevated liver enzymes, signed informed consent on 18-May-2011 with an ALT of 75 U/L (normal range: 6-41 U/L), AST of 76 U/L (normal range: 9-34 U/L), alkaline phosphatase of 72 U/L (normal range 37-116 U/L), and total bilirubin of 0.44 mg/dL (normal range 0.10-1.10 mg/dL). The subject was randomized to **Lovaza** on 27-Jun-2011 with an ALT of 45 U/L, AST of 37 U/L, alkaline phosphatase of 77 U/L, and total bilirubin of 0.49 mg/dL.

On Study Day 85 (19-Sep-2011), laboratory testing at Visit 8 (Week 12) revealed an elevated ALT of 94 U/L, elevated AST of 92 U/L, alkaline phosphatase of 68 U/L, and total bilirubin of 0.52 mg/dL. On Study Day 93 (27-Sep-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 100 U/L, AST of 118 U/L, alkaline phosphatase of 72 U/L, and total bilirubin of 0.40 mg/dL. The study medication was permanently discontinued on Study Day 95 (29-Sep-2011) due to the event of worsening of elevated hepatic enzymes and the subject was subsequently withdrawn from the study on Study Day 96 (30-Sep-2011).

On the same date, laboratory testing at the Early Termination Visit revealed an ALT of 75 U/L, AST of 69 U/L, alkaline phosphatase of 65 U/L, and total bilirubin of0.48 mg/dL. On 20-Oct-2011, laboratory testing at an Unscheduled Visit revealed an ALT of 97 U/L, AST of 126 U/L, alkaline phosphatase of 63 U/L, and total bilirubin of 0.56 mg/dL. On 22-Nov-2011, laboratory testing at an Unscheduled Visit revealed an ALT of 79 U/L, AST of 109 U/L, alkaline phosphatase of 63 U/L, and total bilirubin of 0.40 mg/dL. On 11-Jan-2012, laboratory testing at an Unscheduled Visit revealed an ALT of 56 U/L, AST of 64 U/L, alkaline phosphatase of 66 U/L, and total bilirubin of 0.31 mg/dL. On 29-Feb-2012, laboratory testing at an Unscheduled Visit revealed an ALT of 36 U/L, AST of 34 U/L, alkaline phosphatase of 68 U/L, and total bilirubin of 0.30 mg/dL. Treatment of the event included treatment of other possible causes (hyperglycemia and elevated triglycerides) with rosuvastatin, fish oil, Lovaza, insulin aspart, and insulin lispro.

Subject 112-028 (b) (6), a 38-year-old Caucasian male with a history of severe hypertriglyceridemia, fatty liver disease, and abnormal liver function test, signed informed consent on 26-Apr-2011 with an ALT of 58 U/L (normal range [NR] 6-41 U/L), AST of 48 U/L (NR 9-34 U/L), alkaline phosphatase of 60 U/L (NR 37-116 U/L), and total bilirubin of 0.88 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **Lovaza** on 09-Jun-2011 with an ALT of 80 U/L, AST of 48 U/L, alkaline phosphatase of 92 U/L, and total bilirubin of 0.38 mg/dL.

On Study Day 86 (02-Sep-2011), laboratory testing at Visit 8 (Week 12) revealed a worsening of elevated hepatic enzymes with an elevated ALT of 125 U/L, elevated AST of 88 U/L, alkaline phosphatase of 91 U/L, and total bilirubin of 0.96 mg/dL. On Study Day 93 (09-Sep-2011), laboratory testing at an Unscheduled Visit revealed an ALT of

137 U/L, AST of 103 U/L, alkaline phosphatase of 86 U/L, and a total bilirubin of 0.82 mg/dL. The study medication was permanently discontinued on Study Day 96 (12-Sep-2011) due to the event of worsening of elevated hepatic enzymes. On the same date, a telephone interview revealed the subject was asymptomatic and feeling well. There was no treatment required for the event.

Subject 112-030/ (b) (6) a 32-year-old Caucasian male with a history of severe hypertriglyceridemia, signed informed consent on 05-May-2011 with an ALT of 49 U/L (normal range 6-41 U/L), aspartate aminotransferase (AST) of 27 U/L (NR 9-34 U/L), alkaline phosphatase of 81 U/L (NR 37-116 U/L), and total bilirubin of 0.96 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **Lovaza** on 23-Jun-2011 with an ALT of 47 U/L, AST of 27 U/L, alkaline phosphatase of 74 U/L, and total bilirubin of 1.19 mg/dL. On Study Day 86 (16-Sep-2011), laboratory testing at Visit 8 (Week 12) revealed an elevated ALT of 103 U/L, AST of 51 U/L, alkaline phosphatase of 67 U/L, and total bilirubin of 1.01 mg/dL.

On Study Day 93 (23-Sep-2011), laboratory testing at an Unscheduled Visit revealed an improved ALT of 70 U/L, AST of 35 U/L, alkaline phosphatase of 64 U/L, and total bilirubin of 0.62 mg/dL. On Study Day 125 (25-Oct-2011), laboratory testing at an Unscheduled Visit revealed an elevated ALT of 96 U/L, AST of 55 U/L, alkaline phosphatase of 70 U/L, and total bilirubin of 0.96 mg/dL. On Study Day 133 (02-Nov-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 125 U/L, AST of 52 U/L, alkaline phosphatase of 65 U/L, and total bilirubin of 1.36 mg/dL.

On the same date, physical examination revealed clear sclera and a benign abdomen and the subject was noted to be asymptomatic. There was no treatment required for the event. On Study Day 142 (11-Nov-2011), per protocol, the study medication was permanently discontinued due to the event of elevated liver enzymes. On Study Day 163 (02-Dec-2011), the subject was withdrawn from the study due to the event of elevated liver enzymes. The subject recovered from the event of elevated liver enzymes on 03-Jan-2012.

Subject 112-033/ (b) (6), a 34-year-old Caucasian male with a history of severe hypertriglyceridemia and fatty liver disease, signed informed consent on 09-Jun-2011 with an ALT of 101 U/L (normal range [NR] 6-41 U/L), AST of 48 U/L (NR 9-34 U/L), alkaline phosphatase of 64 U/L (NR 37-116 U/L), and total bilirubin of 1.00 mg/dL (NR 0.10-1.10 mg/dL).The subject was randomized to **Lovaza** on 19-Jul-2011 with an ALT of 104 U/L, AST of 50 U/L, alkaline phosphatase of 71 U/L, and total bilirubin of 0.76 mg/dL. On Study Day 86 (12-Oct-2011), laboratory testing at Visit 8 (Week 12) revealed an elevated ALT of 151 U/L, AST of 71 U/L, alkaline phosphatase of 67 U/L, and total bilirubin of 0.85 mg/dL. On Study Day 95 (21-Oct-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 159 U/L and AST of 93 U/L. On Study Day 99 (25-Oct-2011), the study medication was permanently discontinued due to the event of elevated liver function test, and the subject was subsequently withdrawn from

the study on Study Day 108 (03-Nov-2011). The subject recovered from the event of elevated liver function test on 14-Feb-2012.

Subject 121-003 (b) (6) a 57-year-old Caucasian male with a history of severe hypertriglyceridemia, signed informed consent on 13-Dec-2010 with an ALT of 33 U/L (normal range [NR] 6-41 U/L), an AST of 31 U/L (NR 9-34 U/L), alkaline phosphatase of 51 U/L (NR 37-116 U/L), and total bilirubin of 0.60 mg/dL (NR 0.10-1.10 mg/dL), and was randomized to **Lovaza** on 26-Jan-2011 with an ALT of 44 U/L, AST of 37 U/L, alkaline phosphatase of 54 U/L, and total bilirubin of 0.42 mg/dL. On Study Day 253 (05-Oct-2011), laboratory testing at Visit 11 (Week 36) revealed an elevated ALT of 106 U/L, AST of 76 U/L, alkaline phosphatase of 50 U/L, and total bilirubin of 0.44 mg/dL. On Study Day 258 (10-Oct-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 96 U/L, AST of 55 U/L, alkaline phosphatase of 49 U/L, and total bilirubin of 0.41 mg/dL.

On Study Day 261 (13-Oct-2011), per protocol, the study medication was permanently discontinued due to the event of elevated liver enzymes. On Study Day 262 (14-Oct-2011), physical examination revealed no changes and the subject denied any symptoms of hepatotoxicity. Treatment of the event included discontinuation of vitamin B12, vitamin E, multivitamin, and HA joint formula. On Study Day 288 (09-Nov-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 79 U/L, an AST of 52 U/L, an alkaline phosphatase of 47 U/L, and a total bilirubin of 0.59 mg/dL. On Study Day 296 (17-Nov-2011), the subject was withdrawn from the study due to the event. On 18-Jan-2012, the subject recovered with sequelae from the event of elevated liver enzymes.

Subject 123-003 (b) (6) a 36-year-old Native Hawaiian or Pacific Islander male with a history of severe hypertriglyceridemia and fatty infiltration of liver, signed informed consent on 30-Nov-2010 with an ALT of 48 U/L (normal range: 6-41 U/L), AST of 23 U/L (NR 9-34 U/L), alkaline phosphatase of 95 U/L (NR 37-116 U/L), and total bilirubin of 0.68 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **Lovaza** on 12-Jan-2011 with an ALT of 49 U/L, AST of 23 U/L, alkaline phosphatase of 85 U/L, and total bilirubin of 0.84 mg/dL. On Study Day 92 (13-Apr-2011), laboratory testing at Visit 8 (Week 12) revealed an elevated ALT of 83 U/L, AST of 36 U/L, alkaline phosphatase of 117 U/L, and total bilirubin of 0.65 mg/dL. On Study Day 134 (25-May-2011), laboratory testing at Visit 9 (Week 20) revealed an ALT of 92 U/L, AST of 40 U/L, alkaline phosphatase of 104 U/L, and total bilirubin of 0.66 mg/dL. The subject was reportedly asymptomatic.

On Study Day 183 (13-Jul-2011), the study medication was permanently discontinued due to the event of elevated ALT. On Study Day 190 (20-Jul-2011), laboratory testing at Visit 10 (Week 28) revealed an ALT of 60 U/L, AST of 29 U/L, alkaline phosphatase of 102 U/L, and total bilirubin of 0.91 mg/dL. On Study Day 225 (24-Aug-2011), computed tomography revealed probable fatty infiltration of the liver. On Study Day 253 (21-Sep-

2011), the subject recovered from the event of elevated ALT and was withdrawn from the study.

Subject 132-016/ (b) (6), a 40-year-old Caucasian male with a history of non-alcoholic steatohepatitis (NASH) and severe hypertriglyceridemia, signed informed consent on 11-Jan-2011 with an ALT of 40 U/L (normal range 6-41 U/L), AST of 17 U/L (NR 9-34 U/L), alkaline phosphatase of 90 U/L (NR 37-116 U/L), and total bilirubin of 0.39 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **Lovaza** on 22-Feb-2011 with an ALT of 46 U/L, AST of 24 U/L, alkaline phosphatase of 89 U/L, and total bilirubin of 0.26 mg/dL. On Study Day 85 (17-May-2011), laboratory testing at Visit 8 (Week 12) revealed an ALT of 52 U/L, AST of 22 U/L, alkaline phosphatase of 72 U/L, and total bilirubin of 0.71 mg/dL.

On Study Day 365 (21-Feb-2012), laboratory testing at Visit 13 (Week 52) revealed an ALT of 83 U/L, AST of 43 U/L, alkaline phosphatase of 65 U/L, and total bilirubin of 0.75 mg/dL. On Study Day 367 (23-Feb-2012), the Investigator reported there were no signs of hepatotoxicity. On Study Day 430 (26-Apr-2012), laboratory testing at an Unscheduled Visit revealed an ALT of 90 U/L and AST of 41 U/L. On Study Day 449 (15-May-2012), laboratory testing at an Unscheduled Visit revealed an elevated ALT of 82 U/L, AST of 48 U/L, alkaline phosphatase of 73 U/L, and total bilirubin of 0.71 mg/dL. The Investigator advised the subject to decrease alcohol consumption and recommended a gastroenterology consultation. Per protocol, the last dose of study medication was taken on Study Day 477 (12-Jun-2012). The subject recovered from the event of elevated ALT on Study Day 478 (13-Jun-2012).

Subject 141-010/ (b) (6) a 51-year-old Caucasian male with a history of severe hypertriglyceridemia, signed informed consent on 27-Dec-2010 with an ALT of 45 U/L (normal range [NR] 6-41 U/L), AST of 26 U/L (NR 9-34 U/L), alkaline phosphatase of 86 U/L (NR 37-116 U/L), and total bilirubin of 0.73 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **AKR-963** on 07-Feb-2011 with an ALT of 51 U/L, AST of 35 U/L, alkaline phosphatase of 98 U/L, and total bilirubin of 0.68 mg/dL.

On Study Day 85 (02-May-2011), laboratory testing at Visit 8 (Week 12) revealed an elevated ALT of 94 U/L, AST of 57 U/L, alkaline phosphatase of 87 U/L, and total bilirubin of 0.77 mg/dL. On Study Day 88 (05-May-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 112 U/L, AST of 65 U/L, alkaline phosphatase of 86 U/L, and total bilirubin of 0.44 mg/dL. The Investigator reported there were no signs and symptoms related to the event. There was no treatment reported for the event. The study medication was permanently discontinued on Study Day 92 (09-May-2011). The subject recovered from the event of increased ALT per protocol definition on 20-Sep-2011.

Subject 155-012/ (b) (6), a 62-year-old Caucasian female with a history of severe hypertriglyceridemia, signed informed consent on 07-Apr-2011 with ALT of 37 U/L (normal range [NR] 6-41 U/L), AST of 29 U/L (NR 9-34 U/L), alkaline phosphatase of

113 U/L (NR 37-116 U/L), and total bilirubin of 0.23 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **AKR-963** on 25-May-2011 with an ALT of 37 U/L, AST of 29 U/L, alkaline phosphatase of 99 U/L, and total bilirubin of 0.42 mg/dL. On Study Day 254 (02-Feb-2012), laboratory testing at the subject's Visit 11 (Week 36) revealed an elevated ALT of 183 U/L, elevated AST of 233 U/L, alkaline phosphatase of 106 U/L, and total bilirubin of 0.61 mg/dL. On Study Day 255 (03-Feb-2012), the study medication was permanently discontinued due to the event of elevated hepatic enzymes (elevated AST and ALT). Physical examination revealed the subject to be asymptomatic and no findings consistent with hepatotoxicity. The subject was instructed to avoid acetaminophen and alcohol. On Study Day 275 (23-Feb-2012), laboratory testing at an Unscheduled Visit revealed an ALT of 125 U/L, AST of 137 U/L, alkaline phosphatase of 99 U/L, and total bilirubin of 0.44 mg/dL. On Study Day 283 (02-Mar-2012), laboratory testing at an Unscheduled Visit revealed an ALT of 114 U/L, AST of 115 U/L, alkaline phosphatase of 102 U/L, and total bilirubin of 0.34 mg/dL. The subject was unresponsive to multiple follow-up attempts made by the site and considered lost to follow-up. The outcome of the event of elevated hepatic enzymes (elevated AST and ALT) was unknown.

Subject 161-001/ (b) (6), a 42-year-old Caucasian female with a history of severe hypertriglyceridemia, signed informed consent on 08-Mar-2011 and completed the screening visit on 16-Mar-2011 with an AST of 75 U/L (normal range [NR] 9-34 U/L), ALT of 110 U/L (NR 6-41 U/L), alkaline phosphatase of 98 U/L (NR 37-116 U/L), and total bilirubin of 0.37 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **AKR-963** on 27-Apr-2011 with an AST of 47 U/L, ALT of 52 U/L, alkaline phosphatase of 91 U/L, and total bilirubin of 0.28 mg/dL. On Study Day 85 (20-Jul-2011), laboratory testing at Visit 8 (Week 12) revealed an elevated AST of 80 U/L, ALT of 62 U/L, alkaline phosphatase of 105 U/L, and total bilirubin of 0.42 mg/dL. On Study Day 93 (28-Jul-2011), laboratory testing at an Unscheduled Visit revealed an AST of 80 U/L, ALT of 81 U/L, alkaline phosphatase of 101 U/L, and total bilirubin of 0.48 mg/dL.
On Study Day 99 (03-Aug-2011), it was reported that the subject was asymptomatic. On the same date, per protocol, the event met SAE criteria; the study medication was permanently discontinued; and the subject was withdrawn from the study due to the event of elevated liver enzymes. The subject had not recovered from the event at the time of study withdrawal.

Subject 172-004/ (b) (6), a 62-year-old Caucasian male with a history of severe hypertriglyceridemia, signed informed consent on 31-May-2011 with an ALT of 34 U/L (normal range [NR] 6-41 U/L), AST of 34 U/L (NR 9-34 U/L), alkaline phosphatase of 103 U/L (NR 37-116 U/L), and total bilirubin of 0.93 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **AKR-963** on 13-Jul-2011 with an ALT of 30 U/L, AST of 29 U/L, alkaline phosphatase of 88 U/L, and total bilirubin of 0.93 mg/dL. On Study Day 240 (08-Mar-2012), laboratory testing at Visit 11 (Week 36) revealed an elevated ALT of 92 U/L, AST of 54 U/L, alkaline phosphatase of 89 U/L, and total bilirubin of 1.24 mg/dL. On Study Day 246 (14-Mar-2012), laboratory testing at an Unscheduled Visit revealed an ALT of 83 U/L, AST of 58 U/L, alkaline phosphatase of 95 U/L, and total bilirubin of

0.82 mg/dL. Physical examination revealed the subject to be asymptomatic. On Study Day 254 (22-Mar-2012), the study medication was permanently discontinued due to the event of increased ALT lab value.

On Study Day 260 (28-Mar-2012), laboratory testing at an Unscheduled Visit revealed an ALT of 77 U/L, AST of 48 U/L, alkaline phosphatase of 94 U/L, and total bilirubin of 0.87 mg/dL. On Study Day 279 (16-Apr-2012), the subject was withdrawn from the study. On the same date, laboratory testing at the Early Termination Visit revealed an ALT of 95 U/L, AST of 61 U/L, alkaline phosphatase of 99 U/L, total bilirubin of 0.83 mg/dL, and triglyceride of 1920 mg/dL (NR 50-150 mg/dL). On 02-May-2012, laboratory testing at an Unscheduled Visit revealed an ALT of 86 U/L, AST of 63 U/L, alkaline phosphatase of 96 U/L, total bilirubin of 0.65 mg/dL, triglyceride of 1663 mg/dL, and blinded hemoglobin A1c (NR 4.0-6.0%). Physical examination revealed no acute findings and no physical signs/symptoms consistent with hepatic dysfunction. The Investigator noted the subject's signs/symptoms may reflect undiagnosed diabetes mellitus. On 15-May-2012, the subject declined further study-related follow-up and informed the site that any follow-up would be conducted by the primary care physician. There was no treatment reported for the event. The outcome of the event of increased ALT lab value was unknown.

Subject 174-009 (b) (6), a 38-year-old Caucasian female with a history of severe hypertriglyceridemia and fatty liver disease, signed informed consent on 13-Jun-2011 with an ALT of 46 U/L (normal range [NR] 6-41 U/L), ASTof 33 U/L (NR 9-34 U/L), alkaline phosphatase of 94 U/L (NR 37-116 U/L), and total bilirubin of 0.40 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **AKR-963** on 28-Jul-2011 with an ALT of 42 U/L, AST of 37 U/L, alkaline phosphatase of 90 U/L, and total bilirubin of 0.45 mg/dL. On Study Day 82 (17-Oct-2011), laboratory testing at Visit 8 (Week 12) revealed an elevated ALT of 139 U/L, elevated AST of 102 U/L, alkaline phosphatase of 87 U/L, and total bilirubin of 0.37 mg/dL. On Study Day 89 (24-Oct-2011), laboratory testing at an Unscheduled Visit revealed an improved ALT of 79 U/L, improved AST of 51 U/L, alkaline phosphatase of 77 U/L, and total bilirubin of 0.25 mg/dL. On Study Day 314 (05-Jun-2012), laboratory testing at an Unscheduled Visit revealed an ALT of 56 U/L, AST of 42 U/L, alkaline phosphatase of 77 U/L, and total bilirubin of 0.43 mg/dL. Per protocol, the last dose of study medication was taken on Study Day 355 (16-Jul-2012). On Study Day 356 (17-Jul-2012), laboratory testing at Visit 13 (Week 52) revealed an ALT of 58 U/L, AST of 52 U/L, alkaline phosphatase of 74 U/L, and total bilirubin of 0.32 mg/dL. There was no treatment reported for the event. The subject recovered from the event of increased liver function test on Study Day 356 (17-Jul-2012).

Subject 132-019 (b) (6), a 35-year-old Caucasian male with a history of severe hypertriglyceridemia, signed informed consent on 25-Jan-2011 with an ALT of 55 U/L (normal range [NR] 6-41 U/L), AST of 47 U/L (NR 9-34 U/L), alkaline phosphatase of 86

U/L (NR 37-116 U/L), and total bilirubin of 0.32 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to **AKR-963** on 08-Mar-2011 with an ALT of 53 U/L, AST of 35 U/L, alkaline phosphatase of 113 U/L, and total bilirubin of 0.48 mg/dL.

On Study Day 260 (22-Nov-2011), laboratory testing at Visit 11 (Week 36) revealed an elevated ALT of 100 U/L, AST of 70 U/L, alkaline phosphatase of 72 U/L, and a total bilirubin of 0.80 mg/dL. On Study Day 281 (13-Dec-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 95 U/L, AST of 58 U/L, alkaline phosphatase of 68 U/L, and total bilirubin of 0.71 mg/dL. On the same date, the study medication was permanently discontinued due to the event of elevated ALT and the subject was withdrawn from the study on Study Day 295 (27-Dec-2011). On 17-Jan-2012, laboratory testing at an Unscheduled Visit revealed an ALT of 51 U/L, AST of 35 U/L, alkaline phosphatase of 85 U/L, and total bilirubin of 0.38 mg/dL. There was no treatment required for the event. The subject recovered from the event on 17-Jan-2012.

Reviewer Comment: The protocol specified identification of ALT and AST elevations as SAEs was more hindrance than help in the safety evaluation. After review of the SAEs flagged for liver enzyme elevations, it was clear the cases were not real SAEs in the standard definition for SAEs in clinical trials. Furthermore, no pattern was apparent on review of these cases as to what subset of the population was more likely to get elevated liver enzymes.

Of the eight patients on Lovaza reported with an SAE related to elevations in liver enzymes, six were discontinued from their treatment, one recovered from the event, and one was lost to follow-up.

Of the six patients on AKR-963 reported with an SAE related to elevations in liver enzymes, five were discontinued from their treatment and one recovered from the event.

It is unclear if the patients were followed instead of discontinued from treatment, whether their liver enzymes would have normalized. Some of these patients had mild elevations in liver tests prior to starting study medication and some had history of fatty liver at baseline.

Review of All Serious Adverse Event Narratives

Reviewer Comment: This clinical reviewer read all serious adverse event narratives to assess for accuracy of event term assignment and to search for additional serious events. For the majority of narratives, I concurred with the assigned event term and no additional adverse events were found within the narrative. The following table lists only those cases where this reviewer did not concur with the assigned event term or where an additional serious event that had not been reported elsewhere was noted in the narrative. For each listed case, a brief summary of the case narrative follows the table.

Table 27: Serious Adverse Events: Narrative Cases Consistent with a Different Event Term, or an Additional Serious Adverse Event Noted Within Narrative

Patient ID	Treatment Group	Applicant's SAE Term	Clinical Reviewer's SAE Term	Additional Terms Within Narrative
122-001/ (b) (6)	Prior to Randomization	Acute non- ST segment elevation MI, multivessel coronary artery disease	Same	Coronary artery bypass graft (CABG) surgery
161-008/ (b) (6)	Prior to Randomization	Urinary tract infection	Sepsis	Metabolic encephalopathy
113-005/ (b) (6)	Placebo	Gastroenteritis, hypotension	Same	Hyponatremia, hypomagnesemia
139-027/ (b) (6)	AKR-963	Exacerbation of right hip osteoarthritis	Same	Right total hip arthroplasty

Source: Narrative for deaths and nonfatal serious adverse events, TRGG-963-002 Study Report, beginning pg. 539.

Patient 122-001/ (b) (6), a 62-year-old American Indian/Alaskan Native male with a history of severe hypertriglyceridemia, signed informed consent on 01-Nov-2010 and was not randomized at the time of the event. On (b) (6), the subject presented to a primary care physician with a one week history of intermittent nausea, light-headedness, burning sensation in chest, shortness of breath, diaphoresis, and chest pain. At that time, an electrocardiogram reportedly revealed nonspecific ST segment depression and nonspecific T wave abnormality. Laboratory testing reportedly revealed an elevated troponin level (value unknown). The subject was sent to the emergency room and was subsequently admitted to the hospital for evaluation and treatment. The subject was diagnosed with an acute non-ST segment elevation myocardial infarction. On (b) (6), a coronary angiography and left ventriculography revealed multi-vessel coronary artery disease and the subject underwent a coronary artery bypass graft (CABG) surgery with repair of four vessels on (b) (6).

Patient 161-008/ (b) (6): a 52-year-old Caucasian female with a history of severe hypertriglyceridemia, signed informed consent on 21-Apr-2011 and was not randomized at the time of the event. On (b) (6), the subject presented to the emergency room with a two day history of confusion and generalized weakness which was determined to be secondary to a urinary tract infection. On (b) (6), an electroencephalogram revealed mild diffuse slowing. It was felt by the neurologist that the subject experienced "transient metabolic encephalopathy possibly related to urinary tract infection."

Patient 113-005/ (b) (6): a 71-year-old Caucasian male with a history of severe hypertriglyceridemia, signed informed consent on 21-Dec-2010 and was randomized to placebo on 04-Feb-2011 with a blood pressure of 120/71 mmHg. On Study Day 50

(25-Mar-2011), the subject began experiencing vomiting and diarrhea. On Study Day (b) (6) the subject presented to the emergency room with complaints of weakness, dizziness, headache, posterior neck pain, and abdominal pain, and was subsequently admitted to the hospital for evaluation and treatment. Vital signs revealed a blood pressure of 93/53 mmHg and heart rate of 63 beats per minute. Liver function tests were reportedly normal and a urinalysis was reportedly unremarkable. The subject was diagnosed with viral gastroenteritis and hyponatremia (sodium of 122 mmol/L) secondary to dehydration from nausea, vomiting, and diarrhea. On Study Day (b) (6) additional labs revealed magnesium of 1.4 mg/dL. Treatment of the events included clear liquid diet (advance as tolerated), intravenous normal saline, intravenous magnesium sulfate, ondansetron, lorazepam, tramadol, acetaminophen, and meclizine.

Patient 139-027/ (b) (6): a 58-year-old Caucasian female with a history of severe hypertriglyceridemia, osteoarthritis (hips), and osteopenia, signed informed consent on 09-May-2011 and was randomized to AKR-963 on 22-Jun-2011. On Study Day 72 (01-Sep-2011), the subject began experiencing increasing pain and disability related to an exacerbation of right hip osteoarthritis. On Study Day (b) (6) the subject was admitted to the hospital and underwent an elective right total hip arthroplasty.

7.3.3 Dropouts and/or Discontinuations

The following table summarizes reasons for withdrawal from study from Period A, B and C respectively as well as the disposition following randomization.

Table 28: Disposition of Patients Following Randomization and Reasons for Withdrawal by Period- TRGG-963-002

	Placebo n (%)	Lovaza n (%)	AKR-963 n (%)	Total n (%)
Randomized	N=43	N=105	N=106	N=254
Withdrew During Period A	4 (9.3)	14 (13.3)	9 (8.5)	27 (10.6)
Adverse event	0	2 (1.9)	2 (1.9)	4 (1.6)
Death	0	0	0	0
Withdrawal of consent	2 (4.7)	5 (4.8)	4 (3.8)	11 (4.3)
Protocol violation	1 (2.3)	3 (2.9)	0	4 (1.6)
Other	1 (2.3)	4 (3.8)	3 (2.8)	8 (3.1)
Completed Period A	39 (90.7)	91 (86.7)	97 (91.5)	227 (89.4)
Continued into Period B		N=112	N=115	N=227
Withdrew During Period B		18 (16.1)	25 (21.7)	43 (18.9)

	Placebo n (%)	Lovaza n (%)	AKR-963 n (%)	Total n (%)
Randomized	N=43	N=105	N=106	N=254
Adverse event		6 (5.4)	8 (7.0)	14 (6.2)
Death		0	1 (0.9)	1 (0.4)
Withdrawal of consent		3 (2.7)	6 (5.2)	9 (4.0)
Protocol violation		0	0	0
Other		9 (8.0)	10 (8.7)	19 (8.4)
Completed Period B		94 (83.9)	90 (78.3)	184 (81.1)
Continued into Period C		N=15	N=16	N=31
Withdrew during Period C		0	2 (12.5)	2 (6.5)
Adverse event		0	0	0
Death		0	0	0
Withdrawal of Consent		0	1 (6.3)	1 (3.2)
Protocol Violation		0	0	0
Other		0	1 (6.3)	1 (3.2)
Completed Period C		15 (100)	14 (87.5)	29 (93.5)

Source: TRGG-963-002 Study Report, Table 14.1.1, pg. 116

Reviewer Comment: Eight patients in Period A and 20 patients in Period B/C withdrew from the study due to "Other" reasons. In order to determine whether these "Other" reasons might be due to an adverse event, I searched the verbatim term given by the patient which was then classified as "Other" by the applicant.

The following is a table with the verbatim terms given which were then classified under "Other" reasons for discontinuations:

Table 29: Verbatim Term for "Other" Reasons for Study Discontinuations

Treatment Arm	Patient ID	Verbatim Term Listed Under "Other" for Discontinuation
Placebo	126-002	Loss to follow-up
Lovaza	126-005	Loss to follow up
AKR-963	133-024	Lost to follow up
Lovaza	126-005	Lost to follow up
AKR-963	108-007	Lost to follow up. Subject did not return for early termination visit
AKR-963	134-012	Lost to follow up
Lovaza	112-015	Per MM d/t subject initiated Synthroid
Lovaza	114-007	Subject was a lost to follow up
Lovaza	137-009	Elevated TG

Treatment Arm	Patient ID	Verbatim Term Listed Under "Other" for Discontinuation
AKR-963	135-020	Insufficient therapeutic response
Lovaza	111-009	Lost to follow up
Lovaza	112-028	Lost to follow up
Lovaza	135-008	Lost to follow up
Lovaza	138-005	Lost to follow up
AKR-963	112-013	Lost to follow up
AKR-963	143-020	Lost to follow up
AKR-963	170-002	Lost to follow up
AKR-963	174-002	Lost to follow up
AKR-963	135-020	MM decision as the triglycerides were over 1500 several times
Lovaza	137-004	Non-compliance with visits
AKR-963	112-016	Patient had work conflicts, did not show for last two visits
AKR-963	115-010	Pt had trigs checked at PCP and they were 1500 and she started Trilipix
AKR-963	131-005	Pt is lost to follow up
AKR-963	147-013	Pt moving to another state
Lovaza	139-021	Recurrent exacerbation of depression
Lovaza	114-009	Subject enroll at another site
Lovaza	168-005	The subject continually had extremely elevated triglycerides and the investigator felt the subject should be withdrawn from the study
AKR-963	137-008	Per Instructions subject was discontinue

Reviewer Comment: Out of the 28 verbatim terms classified as "Other" reasons for discontinuations, I believe 6 terms could be re-classified as an adverse event leading to discontinuation (as highlighted in the above table)---three under Lovaza and three under AKR-963. Since an equal number of "Other" reasons for discontinuations are re-classified, the overall incidence for discontinuations remains the same as the applicant's original summary table.

Discontinuations due to an Adverse Event

Overall, twenty patients discontinued the study due to an adverse event; eleven patients on AKR-963 and nine patients on Lovaza. No patients on Placebo discontinued due to an adverse event.

The following table summarizes the incidence of adverse events leading to study discontinuation during Period A.

Table 30: Incidence of Treatment Emergent Adverse Events Leading to Study Discontinuation, Safety Population, Period A

System Organ Class/ Preferred Term	Placebo N=43 n (%)	Lovaza N=105 n (%)	AKR-963 N=106 n (%)
Subjects with any TEAE	**0**	**6 (5.7)**	**4 (3.8)**
Eye Disorders	0	0	1 (0.9)
Eye Swelling	0	0	1 (0.9)
Gastrointestinal Disorders	0	1 (1.0)	1 (0.9)
Abdominal Discomfort	0	1 (1.0)	0
Nausea	0	1 (1.0)	0
Pancreatitis Acute	0	0	1 (0.9)
Investigations	0	4 (3.8)	2 (1.9)
Hepatic Enzyme Increased	0	2 (1.9)	1 (0.9)
Alanine Aminotransferase Increased	0	1 (1.0)	1 (0.9)
Liver Function Test Abnormal	0	1 (1.0)	0
Metabolism and Nutrition Disorders	0	1 (1.0)	0
Gout	0	1 (1.0)	0

Source: CSR, TRGG-963-002, Table 14.3.1.11, pg. 523.

Table 31: Incidence of Treatment Emergent Adverse Events Leading to Study Discontinuation, Safety Population, Period B/C

System Organ Class/ Preferred Term	Lovaza N=112 n (%)	AKR-963 N=115 n (%)
Subjects with any TEAE	**3 (2.7)**	**7 (6.1)**
Cardiac Disorder	0	1 (0.9)
Coronary Artery Disease	0	1 (0.9)
Gastrointestinal Disorders	0	1 (0.9)
Nausea	0	1 (0.9)
Investigations	2 (1.8)	3 (2.6)
Hepatic Enzyme Increased	2 (1.8)	1 (0.9)
Alanine Aminotransferase Increased	0	2 (1.7)
Metabolism and Nutrition Disorders	0	1 (0.9)
Hypertriglyceridaemia	0	1 (0.9)
Neoplasms Benign,	0	1 (0.9)

System Organ Class/ Preferred Term	Lovaza N=112 n (%)	AKR-963 N=115 n (%)
Malignant and Unspecified (Including Cysts and Polyps)		
Oesophageal carcinoma	0	1 (0.9)
Skin and Subcutaneous Tissue Disorders	1 (0.9)	0
Rash	1 (0.9)	0

Source: CSR, TRGG-963-002, Table 14.3.1.12, pg. 524.

Reviewer Comment: Out of the 20 patients who discontinued the study, 11 (55%) were under the SOC Investigations and related to liver enzyme dysfunction. Six of these 11 patients were in the Lovaza treatment arm and 5 were on AKR-963.

7.3.4 Significant Adverse Events

The current Lovaza label contains a Warnings and Precaution to monitor for certain laboratory tests such as ALT and AST, particularly in patients with hepatic impairment.

A search was conducted for Hy's Law cases (e.g., patients with any elevated aminotransferase (AT) of >3x upper limit of normal (ULN), alkaline phosphotase (ALP) <2xULN, and associated with an increase in bilirubin ≥2xULN). However, in this NDA submission, there were no instances of combined elevation of liver transaminases and bilirubin to suggest drug-induced liver injury.

The following table summarizes ALT and AST elevations by Period and treatment arm:

Table 32: Summary of ALT/AST Elevation by Period and Treatment Arm

Parameter Study Period Abnormality	Placebo (N=43) n (%)	Lovaza (Period A, N=115 Period B/C, N=112) n (%)	AKR-963 (Period A, N=106 Period B/C, N=115) n (%)	Total (Period A, N=254 Period B/C, N=227) n (5)
ALT				
Period A	N'=39	N'=94	N'=98	N'=231
>1XULN	14 (35.9)	26 (27.7)	35 (35.7)	75 (32.5)
>2XULN	0	10 (10.6)	4 (4.1)	14 (6.1)
>3XULN	0	2 (2.1)	1 (1.0)	3 (1.3)
>3XULN, consecutive	0	0	0	0
Period B/C		N'=107	N'=106	N'=213
>1XULN		33 (30.8)	44 (41.5)	77 (36.2)

Parameter Study Period Abnormality	Placebo (N=43) n (%)	Lovaza (Period A, N=115 Period B/C, N=112) n (%)	AKR-963 (Period A, N=106 Period B/C, N=115) n (%)	Total (Period A, N=254 Period B/C, N=227) n (5)
>2XULN		13 (12.1)	5 (4.7)	18 (8.5)
>3XULN		6 (5.6)	3 (2.8)	9 (4.2)
>3XULN, consecutive		2 (1.9)	1 (0.9)	3 (1.4)
AST				
Period A	N'=39	N'=94	N'=98	N'=231
>1XULN	7 (17.9)	27 (28.7)	21 (21.4)	55 (23.8)
>2XULN	0	6 (6.4)	4 (4.1)	10 (4.3)
>3XULN	0	0	0	0
>3XULN, consecutive	0	0	0	0
Period B/C		N'=107	N'=106	N'=213
>1XULN		35 (32.7)	33 (31.1)	68 (31.9)
>2XULN		6 (5.6)	6 (5.7)	12 (5.6)
>3XULN		3 (2.8)	2 (1.9)	5 (2.3)
>3XULN, consecutive		0	1 (0.9)	1 (0.5)

N' = the number of subjects with non-missing values during the specified treatment period.
1. Subjects included in this category of laboratory abnormality are a subset of the subjects included in the >3 × ULN.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; Per. = Period; ULN = upper limit of normal.

ALT elevations:
A total of 12 patients were reported with an ALT elevations >3XULN; eight of these patients were on Lovaza and 4 patients were on AKR-963. No patient on Placebo had an ALT >3XULN.

Of the 12 patients with an ALT elevations >3XULN, and three had a consecutive >3XULN ALT elevation. Two of the three patients were on Lovaza and one was on AKR-963. All three of these patients discontinued the study.

The following is a narrative summary of the three patients with consecutive >3XULN ALT elevation:
Subject 112-028/ (b) (6), a 38-year-old Caucasian male with a history of severe hypertriglyceridemia, fatty liver disease, and abnormal liver function test, signed informed consent on 26-Apr-2011 with an ALT of 58 U/L (normal range [NR] 6-41 U/L), AST of 48 U/L (NR 9-34 U/L), alkaline phosphatase of 60 U/L (NR 37-116 U/L), and total bilirubin of 0.88 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to

Lovaza on 09-Jun-2011 with an ALT of 80 U/L, AST of 48 U/L, alkaline phosphatase of 92 U/L, and total bilirubin of 0.38 mg/dL.

On Study Day 86 (02-Sep-2011), laboratory testing at Visit 8 (Week 12) revealed a worsening of elevated hepatic enzymes with an elevated ALT of 125 U/L, elevated AST of 88 U/L, alkaline phosphatase of 91 U/L, and total bilirubin of 0.96 mg/dL. On Study Day 93 (09-Sep-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 137 U/L, AST of 103 U/L, alkaline phosphatase of 86 U/L, and a total bilirubin of 0.82 mg/dL. The study medication was permanently discontinued on Study Day 96 (12-Sep-2011) due to the event of worsening of elevated hepatic enzymes. On the same date, a telephone interview revealed the subject was asymptomatic and feeling well. There was no treatment required for the event.

Subject 112-033/ (b) (6), a 34-year-old Caucasian male with a history of severe hypertriglyceridemia and fatty liver disease, signed informed consent on 09-Jun-2011 with an ALT of 101 U/L (normal range [NR] 6-41 U/L), AST of 48 U/L (NR 9-34 U/L), alkaline phosphatase of 64 U/L (NR 37-116 U/L), and total bilirubin of 1.00 mg/dL (NR 0.10-1.10 mg/dL).The subject was randomized to Lovaza on 19-Jul-2011 with an ALT of 104 U/L, AST of 50 U/L, alkaline phosphatase of 71 U/L, and total bilirubin of 0.76 mg/dL. On Study Day 86 (12-Oct-2011), laboratory testing at Visit 8 (Week 12) revealed an elevated ALT of 151 U/L, AST of 71 U/L, alkaline phosphatase of 67 U/L, and total bilirubin of 0.85 mg/dL. On Study Day 95 (21-Oct-2011), laboratory testing at an Unscheduled Visit revealed an ALT of 159 U/L and AST of 93 U/L. On Study Day 99 (25-Oct-2011), the study medication was permanently discontinued due to the event of elevated liver function test, and the subject was subsequently withdrawn from the study on Study Day 108 (03-Nov-2011). The subject recovered from the event of elevated liver function test on 14-Feb-2012.

Subject 155-012 (b) (6), a 62-year-old Caucasian female with a history of severe hypertriglyceridemia, signed informed consent on 07-Apr-2011 with ALT of 37 U/L (normal range [NR] 6-41 U/L), AST of 29 U/L (NR 9-34 U/L), alkaline phosphatase of 113 U/L (NR 37-116 U/L), and total bilirubin of 0.23 mg/dL (NR 0.10-1.10 mg/dL). The subject was randomized to AKR-963 on 25-May-2011 with an ALT of 37 U/L, AST of 29 U/L, alkaline phosphatase of 99 U/L, and total bilirubin of 0.42 mg/dL. On Study Day 254 (02-Feb-2012), laboratory testing at the subject's Visit 11 (Week 36) revealed an elevated ALT of 183 U/L, elevated AST of 233 U/L, alkaline phosphatase of 106 U/L, and total bilirubin of 0.61 mg/dL. On Study Day 255 (03-Feb-2012), the study medication was permanently discontinued due to the event of elevated hepatic enzymes (elevated AST and ALT). Physical examination revealed the subject to be asymptomatic and no findings consistent with hepatotoxicity. The subject was instructed to avoid acetaminophen and alcohol. On Study Day 275 (23-Feb-2012), laboratory testing at an Unscheduled Visit revealed an ALT of 125 U/L, AST of 137 U/L, alkaline phosphatase of 99 U/L, and total bilirubin of 0.44 mg/dL. On Study Day 283 (02-Mar-2012), laboratory testing at an Unscheduled Visit revealed an ALT of 114 U/L, AST of 115 U/L, alkaline phosphatase of 102 U/L, and total bilirubin of 0.34 mg/dL. The subject was unresponsive to multiple follow-up attempts made by the site and considered lost to

follow-up. The outcome of the event of elevated hepatic enzymes (elevated AST and ALT) was unknown.

AST elevations:
A total of 5 patients were reported with an AST >3XULN---3 patients on Lovaza and 2 patients on AKR-963. No patients on Placebo reported an AST >3XULN.

7.3.5 Submission Specific Primary Safety Concerns

Changes in Blood Glucose
The following table and figure summarize both the mean change from Baseline to Period A Endpoint and the mean percent change from Baseline to Period A Endpoint in glucose and hemoglobin A1c (HbA1c).

Table 33: Mean Change in Glucose and Hemoglobin A1C from Baseline to Endpoint Period A, mITT Population

Parameter	Treatment Arm	Mean Change from Baseline (SD)	Minimum Change from Baseline	Maximum Change from Baseline
Glucose mg/dL	AKR-963 n=98	8.45 (34)	-106	162
	Lovaza n=94	-2.21 (47)	-243	199
	Placebo n=39	-0.28 (25)	-54	95
HbA1c (%)	AKR-963 n=97	0.163 (0.64)	-2.3	2.5
	Lovaza n=92	0.002 (0.52)	-2.3	1.4
	Placebo n=39	-0.021 (0.70)	-1.5	3.2

In Period A, treatment with AKR-963 increased both the mean change in glucose (8.45 mg/dL) and HbA1c (0.163%). Treatment with Lovaza seemed to slightly decrease glucose (-2.21 mg/dL), but showed a 0.002% change in HbA1c. Treatment with Placebo slightly decreased glucose (-0.28 mg/dL) and decreased HbA1c (-0.021%).

The following table summarizes the change in glucose and HbA1c from start of Period B to Period B Endpoint.

Table 34: Change in Glucose and Hemoglobin A1C from Period B Baseline to Period B Endpoint, mITT Population

Parameter	Treatment Arm	Mean Change from Baseline (SD)	Minimum Change from Baseline	Maximum Change from Baseline
Glucose mg/dL	AKR-963 n=106	-1.9 (39)	-175	94
	Lovaza n=106	-1.2 (42)	-263	96
HbA1c (%)	AKR-963 n=105	-0.04 (0.84)	-4.9	2.1
	Lovaza	0.11 (0.67)	-2.0	2.5

In Period B, treatment with AKR-963 decreased both the mean change in glucose (-1.9 mg/dL) and HbA1c (-0.04%). Treatment with Lovaza decreased glucose (-1.2 mg/dL), but increased HbA1c (0.11%).

Reviewer Comment: No consistent changes in glucose or HbA1c were noted with AKR-963 or with Lovaza treatment.

Increases in LDL-C

The increase in LDL-C seen with the use of omega 3 fatty acid products represents a cause for concern and long term studies assessing hard cardiovascular endpoints in patients are needed.

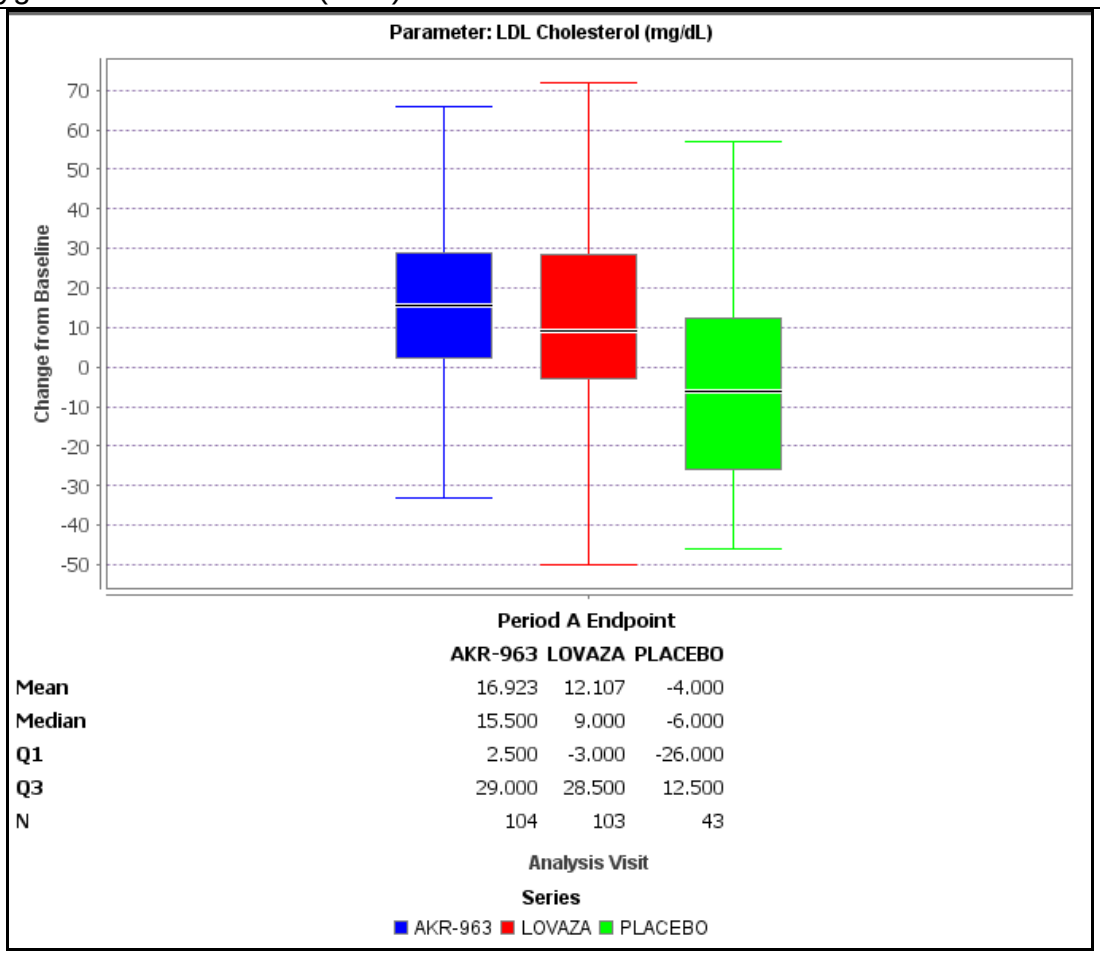


Figure 23: Mean Change from Baseline to Period A Endpoint in LDL-C by Treatment Arm

The mean change from Baseline to Period A Endpoint for LDL-C was +16.92 mg/dL for AKR-963, +12.10 mg/dL for Lovaza, and -4 mg/dL for Placebo.
In terms of mean percent change from Baseline to Period A Endpoint for LDL-C, there was a 25.94% increase over Baseline with AKR-963 (Standard Deviation 41.79), a 21.99% increase with Lovaza (SD 43.47) and a decrease of 11.58% with Placebo (SD 92.96) (See secondary efficacy endpoint analysis in Section 6).

Bleeding Diathesis

No PT/PTT/INR labs were drawn during the study. I looked for reports of bleeding or bruising and found one report of “Increased tendency to bruise” in a patient on Lovaza. There were no reports of bleeding or bruising in AKR-963 or Placebo.

The applicant proposes the following language for AKR-963 in regards to hemorrhagic/bleeding diathesis which is similar to language in the current Lovaza label:

7.1 Anticoagulants or Other Drugs Affecting Coagulation

Some studies with omega-3-acids demonstrated prolongation of bleeding time. (b) (4)

Clinical studies have not been done to thoroughly examine the effect of (b) (4) and concomitant anticoagulants. Patients receiving treatment with BRANDNAME and an anticoagulant or other drug affecting coagulation should be monitored periodically (b) (4)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Period A

The following table lists adverse events by preferred term for which the incidence was ≥2% in the AKR-963 or Lovaza group and greater than Placebo.

Table 35: Treatment-Emergent Adverse Events ≥2% in AKR-963 or Lovaza Group and Greater Than Placebo, Period A, Safety Population

System Organ Class/ Preferred Term	Placebo N=43 n (%)	Lovaza N=105 n (%)	AKR-963 N=106 n (%)
Gastrointestinal Disorders			
Eructation	0	3 (2.9)	9 (8.5)
Dyspepsia	0	3 (2.9)	0
Flatulence	0	0	2 (1.9)
Infections and Infestations			
Upper Respiratory Tract Infection	0	7 (6.7)	4 (3.8)
Nasopharyngitis	1 (2.3)	1 (1.0)	4 (3.8)
Bronchitis	0	0	3 (2.8)
Cellulitis	0	2 (1.9)	1 (0.9)
Injury, Poisoning and Procedural Complications			
Muscle Strain	0	0	2 (1.9)
Investigations			
Hepatic Enzyme Increased	0	2 (1.9)	1 (0.9)
Metabolism and Nutrition Disorders			

System Organ Class/ Preferred Term	Placebo N=43 n (%)	Lovaza N=105 n (%)	AKR-963 N=106 n (%)
Gout	1 (2.3)	4 (3.8)	2 (1.9)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	0	5 (4.8)	2 (1.9)
Nervous System Disorders			
Dizziness	0	2 (1.9)	2 (1.9)
Respiratory, Thoracic and Mediastinal Disorders			
Rhinitis Allergic	0	2 (1.9)	0

Source: CSR TRGG-963-002, Table 14.3.1.3, pg. 444-451.

From those AEs listed above, the terms that occurred more frequently in the AKR-963 group than in the Lovaza group are summarized below.

Table 36: Treatment-Emergent Adverse Events ≥2% in AKR-963 Group and Greater than in Lovaza or Placebo Groups, Period A, Safety Population

Preferred Term	Placebo N=43 n (%)	Lovaza N=105 n (%)	AKR-963 N=106 n (%)
Eructation	0	3 (2.9)	9 (8.5)
Flatulence	0	0	2 (1.9)
Nasopharyngitis	1 (2.3)	1 (1.0)	4 (3.8)
Bronchitis	0	0	3 (2.8)
Muscle Strain	0	0	2 (1.9)

Of the 5 AE terms in the table above, only eructation trended towards a statistically significant difference (p=0.06) between AKR-963 and Placebo (see MAED analysis below).

Period B/C

The following table lists adverse events by preferred term for which the incidence was ≥2% more in the AKR-963 group than in the Lovaza group during Period B/C.

Table 37: Treatment-Emergent Adverse Events ≥2% in AKR-963 or Lovaza Group and Greater Than Placebo, Period B/C, Safety Population

System Organ Class/ Preferred Term	Lovaza N=115 n (%)	AKR-963 N=115 n (%)
Any TEAE	59 (52.7)	69 (60.0)
Blood and Lymphatic System Disorders		
Anaemia	0	3 (2.6)
Gastrointestinal Disorders		
Diarrhoea	2 (1.8)	4 (3.5)
Abdominal Pain	1 (0.9)	3 (2.6)
General Disorders and Administration Site Conditions		
Asthenia	0	2 (1.7)
Infections and Infestations		
Upper Respiratory Tract Infection	4 (3.6)	8 (7.0)
Urinary Tract Infection	2 (1.8)	7 (6.1)
Gastroenteritis Viral	2 (1.8)	4 (3.5)
Sinusitis	1 (0.9)	4 (3.5)
Cellulitis	0	2 (1.7)
Tooth Infection	0	2 (1.7)
Injury, Poisoning and Procedural Complications		
Fall	0	3 (2.6)
Contusion	0	2 (1.7)
Investigations		
Blood Creatine Phosphokinase Increased	1 (0.9)	3 (2.6)
Metabolism and Nutrition Disorders		
Diabetes Mellitus	1 (0.9)	5 (4.3)
Gout	2 (1.8)	4 (3.5)
Musculoskeletal and Connective Tissue Disorders		
Pain in Extremity	3 (2.7)	5 (4.3)
Nervous System Disorders		
Headache	1 (0.9)	4 (3.5)
Dizziness	0	2 (1.7)

Source: CSR TRGG-963-002, Table 14.3.1.4, pg. 452-462.

From the terms listed above, the AE terms reported by 3% or more patients in the AKR-963 group over the Lovaza treatment group are summarized in the following table.

Table 38: Treatment –Emergent Adverse Events ≥3% in AKR-963 Group vs. Lovaza, Period B, Safety Population

Preferred Term	Lovaza N=115 n (%)	AKR-963 N=115 n(%)
Upper Respiratory Tract Infection	4 (3.6)	8 (7.0)
Urinary Tract Infection	2 (1.8)	7 (6.1)
Diabetes Mellitus	1 (0.9)	5 (4.3)

Reviewer Comment: There were 5 patients with diabetes mellitus reported in the AKR-963 group as compared with 1 patient in the Lovaza group. The complete study report was searched for additional cases of diabetes mellitus and none were found. There are conflicting associations between glucose metabolism and omega-3 FA products reported in the literature. A meta-analysis of 23 randomized controlled trials of 1075 patients with type 2 diabetes mellitus showed no significant increase in HbA1c, fasting glucose or fasting insulin and omega-3 FA intake.[9]

MedDRA Adverse Event (MAED) Analysis

A MedDra Adverse Event analysis was conducted for treatment emergent adverse events (TEAE) for Period A. The results of the analysis are shown in the following table. The top four adverse events reported in the AKR-963 group were diarrhea (8.5% incidence), eructation (8.5% incidence), nasopharyngitis (3.8% incidence) and upper respiratory tract infection (3.8%).

When comparing AKR-963 to Placebo, diarrhea RR =0.91 (0.3 - 2.8, 95% CI), p=1.00; eructation RR=7.8 (0.5 - 131.4., 95% CI), p=0.06; nasopharyngitis RR= 1.62 (0.2 – 14.1, 95% CI), p=1.00; upper respiratory tract infection RR=3.7 (0.2 to 67.3, 95% CI), p=0.3.

9 Hartweg J, Perera R, Montori V, et al. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. 2009 Cochrane Collaboration, Issue 1.

Table 39: Treatment Emergent Adeverse EventsPeriod A

	A	D	G	J	N	O	P	T
4		AKR-963 (N = 106)	LOVAZA (N = 105)	PLACEBO (N = 43)	AKR-963 vs. PLACEBO			
5	PT	Proportion (%)	Proportion (%)	Proportion (%)	RR	RR C.I. (lower bound	RR C.I. (upper bound	P-value
6	Diarrhoea	8.49	3.81	9.3	0.913	0.297	2.806	1
7	Eructation	8.49	2.86	0	7.813	0.465	131.35	0.06
8	Nasopharyngitis	3.77	0.95	2.33	1.623	0.187	14.105	1
9	Upper respiratory tract infection	3.77	6.67	0	3.701	0.204	67.3	0.325
10	Bronchitis	2.83	0	0	2.879	0.152	54.576	0.557
11	Arthralgia	1.89	4.76	0	2.056	0.101	41.964	1
12	Arthropod bite	1.89	0	2.33	0.811	0.076	8.715	1
13	Back pain	1.89	0.95	6.98	0.27	0.047	1.562	0.145
14	Dizziness	1.89	1.9	0	2.056	0.101	41.964	1
15	Flatulence	1.89	0	0	2.056	0.101	41.964	1
16	Gout	1.89	3.81	2.33	0.811	0.076	8.715	1
17	Muscle strain	1.89	0	0	2.056	0.101	41.964	1
18	Urinary tract infection	1.89	0.95	2.33	0.811	0.076	8.715	1

Reviewer Comment: Eructation in the AKR-963 group, with a p=0.06, trended towards statistical significance when compared with Placebo.

7.4.2 Laboratory Findings

Safety laboratory tests consisting of chemistry and hematology blood tests and a urinalysis were evaluated at Visit 1 (Week -6), Visit 4 (Week 0), Visit 8 (Week 12), Visit 11 (Week 36), Visit 13 (Week 52/early termination) and the final visit of the extension period.

Analyses Focused on Measures of Central Tendency

The following table summarizes the mean changes in different laboratory tests from Week 0 to Week 12 Endpoint. Over the course of the 12 week period, there were small numerical differences between the AKR-963 group and placebo of unknown clinical significance.

Table 40: Summary of Mean Laboratory Changes from Week 0 to Week 12 Endpoint

Laboratory Parameter	AKR-963 N=106	Lovaza N=105	Placebo N=43
ALT (U/L)			
n	106	105	43
Week 0, Mean (SD)	36.7 (17.9)	39.0 (19.4)	38.5 (23.1)
n	98	94	39
Week 12 Endpoint Mean (SD)	42.4 (22.7)	46.6 (26.6)	35.1 (16.5)

Laboratory Parameter	AKR-963 N=106	Lovaza N=105	Placebo N=43
n	98	94	39
Mean Change (SD)	5.9 (15.1)	7.1 (16.8)	-4.3 (19.0)
AST (U/L)			
n	106	105	43
Baseline mean (SD)	28.4 (10.1)	31.0 (12.5)	30.2 (16.0)
n	98	94	39
Week 12 Endpoint mean (SD)	31.6 (15.1)	33.9 (16.6)	27.0 (9.8)
n	98	94	39
Mean Change (SD)	3.2 (10.2)	3.2 (13.8)	-3.9 (13.5)
Creatine Kinase (U/L)			
n	106	105	43
Baseline mean (SD)	140 (112.6)	214.8 (455.9)	179.2 (164.9)
n	98	94	39
Week 12 Endpoint mean (SD)	132.1 (94.5)	178.0 (359.7)	171.1 (170.3)
n	98	94	39
Mean Change (SD)	-8.4 (64.8)	-37.2 (490.7)	-16.2 (112.0)
Glucose (mg/dL)			
n	106	105	43
Baseline mean (SD)	127.9 (46.7)	134.3 (58.8)	129.8 (51.5)
n	98	94	39
Week 12 Endpoint mean (SD)	136.4 (60.2)	134.5 (59.5)	125.2 (40.4)
n	98	94	39
Mean Change (SD)	8.5 (34.0)	-2.1 (47.2)	-0.3 (25.0)
Creatinine (mg/dL)			
n	106	105	43
Baseline mean (SD)	0.883 (0.19)	0.899 (0.16)	0.912 (0.18)
n	98	94	39
Week 12 Endpoint mean (SD)	0.874 (0.20)	0.913 (0.18)	0.904 (0.20)
n	98	94	39
Mean Change (SD)	-0.002 (0.11)	0.001 (0.11)	-0.014 (0.12)

Source: CSR, TRGG-963-002, Table 14.3.4.1.

From Visit 4 (Week 0) to Visit 8 (Week 12/ET) and from Visit 8 (Week 12) to Visit 13 (Week 52/ET), no clinically meaningful changes in hematology parameters were noted in the treatment groups.

From Visit 4 (Week 0) to Visit 8 (Week 12) and from Visit 8 (Week 12) to Visit 13 (Week 52), no clinically meaningful changes in urinalysis parameters were noted in the treatment groups.

Creatine Kinase
One patient in the Lovaza group (Subject 160-002) had a creatine kinase value >10XULN during Period A (3453 U/L at Visit 8 [Week 12]). The subject's creatine kinase value at Visit 4 (Week 0) was >5 and ≤10XULN (1339 U/L). The following is his narrative:

Subject 160-002 (b) (6), a 58 year-old Caucasian male with a history of severe hypertriglyceridemia, signed informed consent on 07-Mar-2011 with a creatine kinase (CK) of 230 U/L (normal range 25-210 U/L). The subject was randomized to Lovaza on 18-Apr-2011 with a CK of 1339 U/L. On Study Day 11 (28-Apr-2011), follow-up laboratory testing at an Unscheduled Visit revealed a CK of 170 U/L. On Study Day 87 (13-Jul-2011), laboratory testing at Week 12/Visit 8 revealed a CK of 3453 U/L. The subject reported "vigorous exercise just prior to having blood drawn" and was instructed by the investigative site to refrain from exercising prior to future laboratory testing. On Study Day 100 (26-Jul-2011), follow-up laboratory testing at an Unscheduled Visit revealed CK of 931 U/L. On Study Day 103 (29-Jul-2011), the Investigator reported, "Creatine Kinase is continuing to drop from its high after he stopped high level of exercise". Subsequent laboratory testing revealed CK levels of 328 U/L on Study Day 128 (23-Aug-2011), 225 U/L on Study Day 263 (05-Jan-2012), and 206 U/L on Study Day 367 (18-Apr-2012). There were no concurrent alanine aminotransferase or aspartate aminotransferase elevations of clinical significance. The study medication was continued. Additional medical history included high blood pressure, gout, and vasectomy. Concomitant medication included aspirin. The CK elevation was not recorded as an adverse event.

Another patient in the Lovaza group (Subject 142-013) had a creatine kinase value >10XULN during Period B/C (3782 U/L at Visit 11 [Week 36]). The patient's creatine kinase value at an unscheduled visit following Visit 11 was 37 U/L. The following is his narrative:

Subject 142-013 (b) (6), a 48 year-old Caucasian male with a history of severe hypertriglyceridemia, signed informed consent on 22-Nov-2010 with a creatine kinase (CK) of 102 U/L (normal range [NR] 25-210 U/L, ALT of 98 U/L (NR 6-41 U/L), and AST of 36 U/L (NR 9-34 U/L). The subject was randomized to Lovaza on 03-Jan-2011 with a CK of 129 U/L, ALT of 123 U/L, and AST of 61 U/L. On Study Day 239 (29-Aug-2011), laboratory testing at Week 36/Visit 11 revealed a CK of 3782 U/L, ALT of 125 U/L, and AST of 92 U/L. On Study Day 241 (31-Aug-2011), the subject was contacted by the investigative site regarding the elevations. The subject reported no symptoms, denied alcohol consumption, and stated that he played soccer for approximately four hours on the day prior to Visit 11. On Study Day 260 (19-Sep-2011), follow-up laboratory testing

at an Unscheduled Visit revealed CK of 37 U/L, ALT of 102 U/L, and AST of 52 U/L. On the same date, a physical examination revealed no clinically significant abnormalities. Additional medical history included presbyopia, hypertension, type 2 diabetes mellitus, and coronary artery disease. Concomitant medications included metformin, insulin glargine, aspirin, olmesartan, and glipizide. The study medication was continued. The subject recovered from the event of elevated creatine kinase on Study Day 260 (19-Sep-2011). The Investigator considered the event of elevated creatine kinase as mild and possibly related to study medication.

7.4.3 Vital Signs

Blood Pressure
Mean baseline systolic blood pressure was 125.5 mmHg for the placebo group, 128.6 mmHg for the Lovaza group, and 129.9 mmHg for the AKR-963 group. The LS mean change in systolic blood pressure from Baseline to Period A Endpoint was -1.0 mmHg for the placebo group, -2.8 mmHg for the Lovaza group, and -1.7 mmHg for the AKR-963 group.

The difference in LS mean change between Lovaza and placebo was -1.8 mmHg, p=0.42. The difference in LS mean change between AKR-963 and placebo was -0.7 mmHg, p=0.74. The difference in LS mean change between AKR-963 and Lovaza was 1.0 mmHg, p=0.53.

Mean baseline diastolic blood pressure was 79.1 mmHg for the placebo group, 81.5 mmHg for the Lovaza group, and 80.6 mmHg for the AKR-963 group. The LS mean change in diastolic blood pressure from Baseline to Period A Endpoint was -1.2 mmHg for the placebo group, -1.8 mmHg for the Lovaza group, and -0.0 mmHg for the AKR-963 group.

The difference in LS mean change between Lovaza and placebo was -0.6 mmHg, p=0.66. The difference in LS mean change between AKR-963 and placebo was 1.2 mmHg p=0.39. The difference in LS mean change between AKR-963 and Lovaza was 1.8 mmHg, p=0.092.

Body Weight
Median baseline body weight was 93 kg for the placebo group, 97 kg for the Lovaza group, and 101 kg for the AKR-963 group. The median change in body weight from Baseline to Period A Endpoint was -0.5 kg for the placebo group, -0.1 kg for the Lovaza group, and 0.1 kg for the AKR-963 group.

The median of the differences in change between Lovaza and placebo was 0.4 kg, p=0.34. The median of the differences in change between AKR-963 and placebo was 0.7 kg, p=0.07. The median of the differences in change between AKR-963 and Lovaza was 0.2 kg, p=0.37.

7.4.4 Electrocardiograms (ECGs)

There were no significant differences between the two treatment groups and placebo for changes in mean ECG intervals or emergence of ECG abnormalities.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Clinical trials with AKR-963 were only conducted with 4 capsules/day dosage. Therefore no analyses were conducted for dose-dependency.

7.5.2 Time Dependency for Adverse Events

The following is a summary table of the number of subjects with a reported AE by week of onset and by treatment arm in Period A.

Table 41: Number (%) of Subjects with a TEAE by Treatment Arm by Week in Period A

Weeks	AKR-963 N=106	Lovaza N=105	Placebo N=43
Week 1	11 (10.4%)	17 (16.2%)	5 (11.6%)
Week 2	11 (10.4%)	11 (10.5%)	3 (7.0%)
Week 3	9 (8.5%)	3 (2.9%)	3 (7.0%)
Week 4	8 (7.6%)	4 (3.8%)	2 (4.7%)
Week 5	6 (5.7%)	3 (2.9%)	2 (4.7%)
Week 6	6 (5.7%)	7 (6.7%)	4 (9.3%)
Week 7	7 (6.6%)	6 (5.7%)	4 (9.3%)
Week 8	3 (2.8%)	3 (2.9%)	2 (4.7%)
Week 9	4 (3.8%)	6 (5.7%)	4 (9.3%)
Week 10	3 (2.8%)	4 (3.8%)	2 (4.7%)
Week 11	3 (2.8%)	1 (1.0%)	4 (9.3%)
Week 12	7 (6.6%)	5 (4.7%)	2 (4.7%)
Week 13	10 (9.4%)	7 (6.7%)	3 (6.9%)
Week 14	1 (0.9%)	3 (2.9%)	0

All three treatment arms, Placebo, AKR-963 and Lovaza had a high number of subjects with a reported AE in the first week of starting the study. The reported AE dropped in the following weeks, but were similar in the AKR-963 and Lovaza treatment arms.

7.5.3 Drug-Demographic Interactions

Study TRGG-963-002 was stratified based upon the presence of diabetes---no diabetes, diabetes with HbA1c <8.0% or diabetes with HbA1c ≥8.0%. The percent change from Baseline to Period A Endpoint in TG was analyzed based on these diabetes categories.

In this study, the number of patients without diabetes in each treatment group included the following: 28 (placebo), 65 (Lovaza), and 65 (AKR-963). The number of diabetic patients with HbA1c <8.0% in each treatment group included the following: 11 (placebo), 24 (Lovaza), and 26 (AKR-963). The number of diabetic patients with HbA1c ≥8.0% included the following: 4 (placebo), 14 (Lovaza), and 13 (AKR-963).

Table 42: Median Percent Change in TG from Baseline to Period A Endpoint by Diabetes Status, mITT Population

	Placebo N=43	**Lovaza N=103**	**AKR-963 N=104**
No Diabetes Number of Patients	28	65	65
Median Percent Change in TG (Q1, Q3)	-13.0 (-25.8, -9.9)	-28.4 (-46.5, -9.5)	-26.0 (-39.8, -11.2)
Median Difference Relative to Placebo		-17.3 (-31.6, -3.5) P=0.0133	-16.9 (-30.8, -2.7) P=0.0172
Diabetes with HbA1c <8.0% Number of Patients	11	24	26
Median Percent Change in TG (Q1, Q3)	-16.2 (-32.1, 52.9)	-11.3 (-38.8, 20.0)	-17.3 (-32.3, 14.8)
Median Difference Relative to Placebo		-11 (-50.4, 22.9) P=0.4449	-12.5 (-52.2, 16.1) P=0.3786
Diabetes with HbA1c ≥8.0% Number of Patients	4	14	13
Median Percent Change in TG (Q1, Q3)	-42.1 (-62.3, -24.5)	-46.7 (-58.5, -25.1)	-34.5 (-41.5, -20.8)

	Placebo N=43	**Lovaza N=103**	**AKR-963 N=104**
Median Difference Relative to Placebo		1.7 (-32.7, 41.4) P=0.9577	13.1 (18.9, 47.3) P=0.4617

Source: Study Report, TRGG-963-002, Post-text Table 14.2.18.

In patients without diabetes, the median percent change in TG from Baseline to Period A Endpoint was -13.0% for the placebo group, -28.4% for the Lovaza group, and -26.0% for the AKR-963 group. The difference in median percent change between placebo and Lovaza was -17.3%, p=0.0133. The difference in median percent change between placebo and AKR-963 was -16.9%, p=0.0172.

In diabetic patients with HbA1c <8.0%, the median percent change in TG from Baseline to Period A Endpoint was -16.2% for the placebo group, -11.3% for the Lovaza group, and -17.3% for the AKR-963 group. The difference in median percent change between placebo and Lovaza was -11.0%, p=0.4449. The difference in median percent change between placebo and AKR-963 was -12.5%, p=0.3786.

In diabetic patients with HbA1c ≥8.0%, from Baseline to Period A Endpoint, the median percent change was -42.1% for placebo, -46.7% for Lovaza, and -34.5% for AKR-963. The difference in median percent change between placebo and Lovaza was 1.7%, p=0.9577. The difference in median percent change between placebo and AKR-963 was 13.1%, p=0.4617.

The figure below shows the median percent change from Baseline to Period A Endpoint according to diabetes status ---the presence of diabetes or no diabetes.

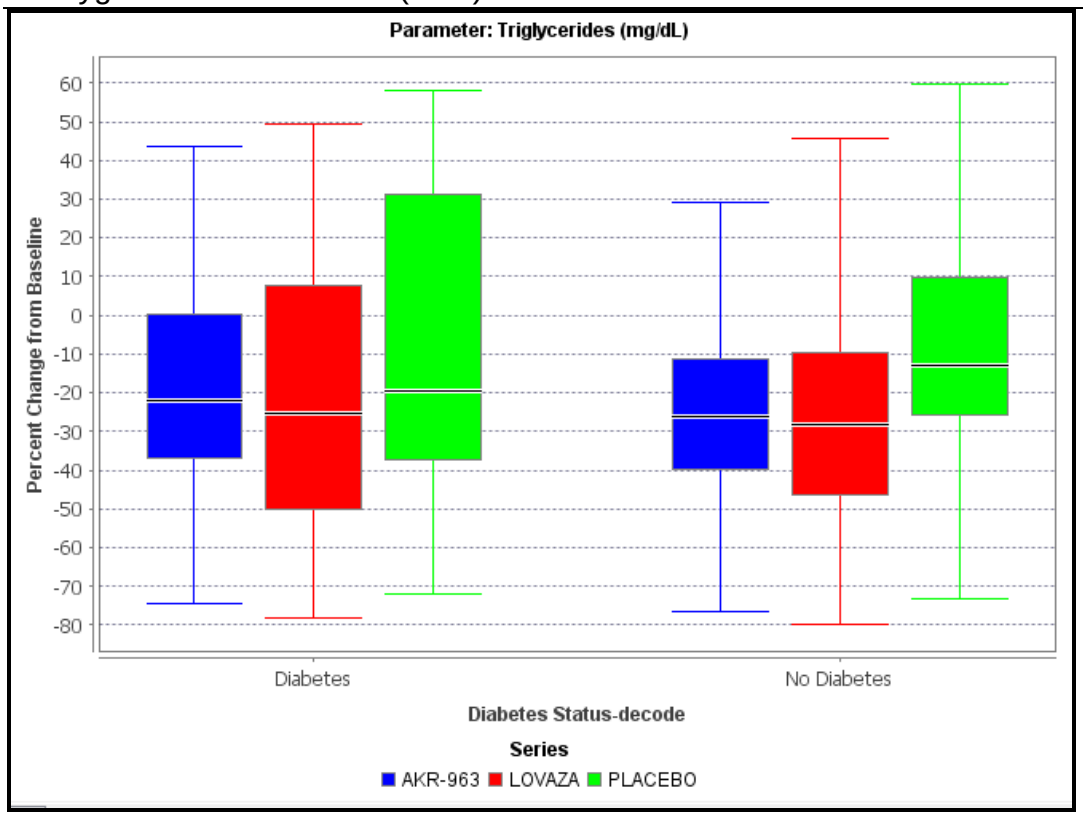


Figure 24: Median Percent Change in TG from Baseline to Period A Endpoint, by Diabetes Status, mITT population

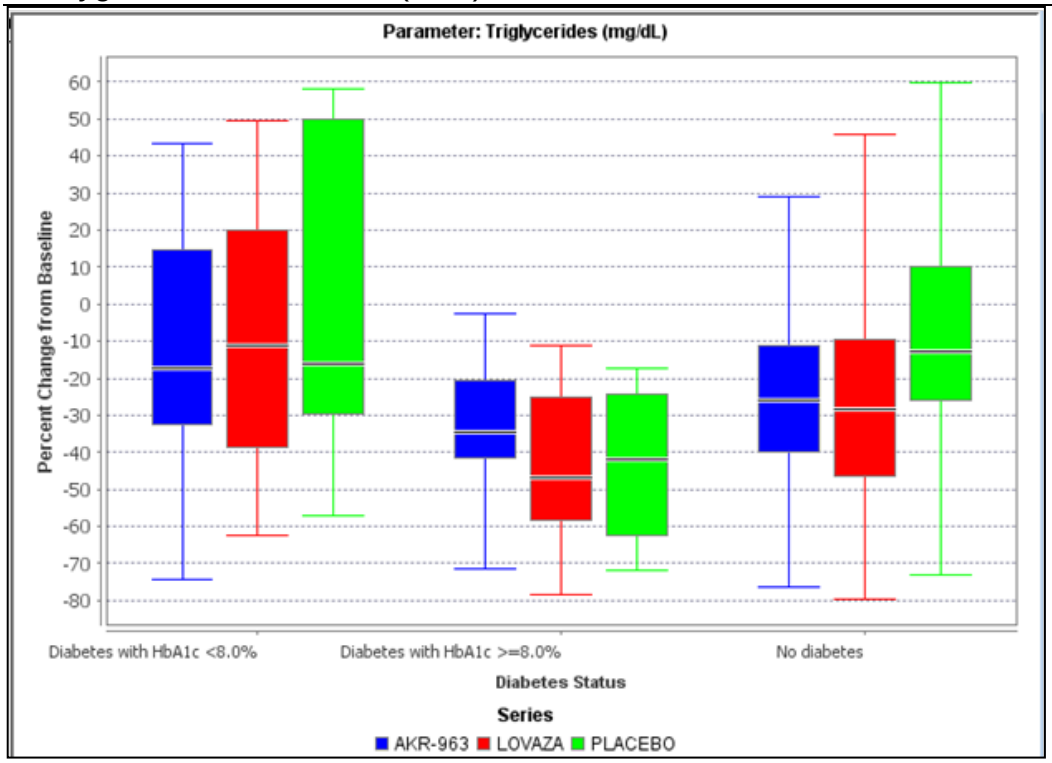


Figure 25: Median Percent Change from Baseline to Period A Endpoint, by HbA1c ≥8%, HbA1c<8%, or No Diabetes, mITT Population

Reviewer Comment: Greater reductions were seen with AKR-963 and Lovaza in non-diabetic patients than in diabetic patients. However, the population was small, and it is difficult to generalize the results to the larger population.

7.5.4 Drug-Disease Interactions

Study TRGG-963-002 excluded subjects with any recent history or current hepatic or biliary disease and required liver function tests (with the exception of ALT or AST≤ 3XULN) to be within the normal range. Thus, patients with hepatic impairment were not clearly represented in Study TRGG-963-002 and, therefore, no conclusions on this aspect can be made.

In Study TRGG-963-002, potential subjects were excluded if they had serum creatine levels > 2 mg/dL or clinically significant abnormal elevations in blood urea nitrogen (BUN). Thus, subjects enrolled into this study would generally be considered to have renal function in the normal range.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not specifically evaluated in Study TRGG-963-002. However, a review of the SAEs, severe AEs, and discontinuations due to AEs reported

in any treatment group did not reveal any disproportionate patterns associated with specific categories of concomitant medications.

Lovaza labeling contains a statement regarding the potential drug-drug interaction with anticoagulants and other drugs affecting coagulation:

"Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of LOVAZA and concomitant anticoagulants. Patients receiving treatment with LOVAZA and an anticoagulant or other drug affecting coagulation (e.g., anti-platelet agents) should be monitored periodically."

Reviewer Comment: It is recommended that AKR-963 have similar statements regarding anticoagulants or other drugs affecting coagulation as Lovaza.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to the pharmacology/toxicology report by Dr. Indra Antonipillai for carcinogenicity data in animals.

The Phase 3 clinical trial was searched by terms which could potentially represent neoplastic events such as polyps, cancer, metaplasia, nodule, cyst, carcinoma, neoplasm and mass. Some of these terms are not specific and may represent non-neoplastic events. The following tables summarize the incidence of these treatment-emergent terms by period.

Table 43: Treatment-Emergent Neoplasms, Malignant and Unspecified, Polyps and Cysts with Onset in Period A, Safety Population

System Organ Class	Preferred Term	Placebo N=43 n (%)	Lovaza N=105 n (%)	AKR-963 N=106 n (%)	Total N=254 n (%)
Infections and infestations	Any TEAE	8 (18.6)	16 (15.2)	21 (19.8)	45 (17.7)
	Infected cyst	0	0	1 (0.9)	1 (0.4)

Source: Study Report, TRGG-963-003, Table 14.3.1.4, pg. 459.

Table 44: Treatment-Emergent Neoplasms, Malignant and Unspecified, Polyps and Cysts with Onset in Period B/C, Safety Population

System Organ Class	Preferred Term	Lovaza N=112 n (%)	AKR-963 N=115 n (%)	Total N=227 n (%)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	Any TEAE	2 (1.8)	3 (2.6)	5 (2.2)
	Benign salivary gland neoplasm	0	1 (0.9)	1 (0.4)
	Chondroblastoma	0	1 (0.9)	1 (0.4)
	Fibrous histiocytoma	1 (0.9)	0	1 (0.4)
	Lipoma	1 (0.9)	0	1 (0.4)
	Neurofibroma	1 (0.9)	0	1 (0.4)
	Oesophageal carcinoma	0	1 (0.9)	1 (0.4)
Reproductive system and breast disorders	Any TEAE	3 (2.7)	0	3 (1.3)
	Uterine polyp	1 (0.9)	0	1 (0.4)
Musculoskeletal and Connective tissue disorders	Any TEAE	17 (15.2)	15 (13.0)	32 (14.1)
	Synovial cyst	1 (0.9)	0	1 (0.4)
Gastrointestinal disorders	Any TEAE	13 (11.6)	15 (13.0)	28 (12.3)
	Abdominal wall cyst	1 (0.9)	0	1 (0.4)

Source: Study Report, TRGG-963-003, Table 14.3.1.4, pg. 459.

There were sporadic reports of a uterine polyp, synovial cyst and an abdominal wall cyst reported in the Lovaza treatment arm during Period B/C.

Reviewer Comment: The incidence of TEAE reported under the SOC Neoplasm benign, malignant and unspecified (including cysts and polyps) was similar in both treatment arms in Period B/C (1.8% with Lovaza and 2.6% with AKR-963).

One patient, #111-019(b) (6), was diagnosed with esophageal carcinoma. The following is the patient narrative:

Patient #111-019/(b) (6) was randomized to AKR-963 on 12-April-2011. On Study Day 281 (17-Jan-2012), the subject began experiencing mid-back and mid-chest pain (reported as non-serious adverse events). On an unknown date, a computed tomography (CT) scan, endoscopy, and positron emission tomography (PET) scan revealed poorly differentiated epithelioid neoplasm obstructing the lower end of the esophagus with multiple diffuse hepatic metastases.

On Study Day (b) (6) the subject was diagnosed with stage 4 esophageal cancer with liver metastasis. Treatment of the event included epirubicin, oxaliplatin, carbotaxol, radiation, and insertion of a percutaneous endoscopic gastrostomy (PEG) tube for enteral nutrition.

The subject experienced increasing pain, nausea, vomiting, and an intolerance to tube feeding, and on Study Day (b) (6) the subject was admitted to the hospital for evaluation and treatment of dehydration, generalized abdominal pain, and intractable nausea and vomiting secondary to esophageal cancer.

A CT scan of the abdomen and pelvis revealed interval progression of extensive diffuse hepatic metastases with new small-to-moderate quantity of ascitic fluid identified about the liver and spleen and pooled in the pelvis, consistent with significant interval progression and metastatic disease, and a thickened distended galbladder. Additional treatment included granisetron, ondansetron, promethazine, lorazepam, fentanyl, unspecified intravenous fluids, hydromorphone, acetaminophen, diphenhydramine, discontinuation of tube feeding, naso-gastric (NG) tube to low continuous wall suction, and a referral for palliative care.

The subject's medical history included myopia; presbyopia; tonsillitis; tonsillectomy; hypertension; dyslipidemia; knee pain; right foot ruptured achilles tendon with repair; flat feet; arch build up bilateral feet; dislocated right shoulder; right shoulder repair; seasonal allergies; and fractured right index finger, hand, and wrist. Concomitant medications included lisinopril. Per subject report in March of 2012, the study medication was discontinued on an unknown date.

On Study Day (b) (6) after discussion with the family, the subject was transitioned to comfort care only and was discharged from the hospital to inpatient hospice. On Study Day (b) (6) the subject expired. An autopsy was not performed. The Investigator considered the event of esophageal cancer as severe and not related to the study medication.

Reviewer Comment: A literature search was conducted for an association with omega-3 fatty acids and esophageal carcinoma and none was found. There were reports of the benefits of omega-3 fatty acids in enteral nutrition post-esophageal cancer surgery.[10] There were also reports of Phase I trials of DHA-paclitaxel in solid tumor malignancies.[11]

10 Aiko S, Yoshizumi Y et al. The Effects of Immediate Enteral Feeding with a Formula Containing High Levels of omega-3 fatty acids in patients after surgery for esophageal cancer. 2005 Journal of Parenteral and Enteral Nutrition 29:141-147.
11 Fracasso P, Picus J et al. Phase 1 and pharmacokinetic study of weekly docosahexaenoic acid-paclitaxel, Taxoprexin, in resistant solid tumor malignancies. 2009 Cancer Chemother Pharmacol 63:451-458.

7.6.2 Human Reproduction and Pregnancy Data

The following is an excerpt from the sponsor's proposed labeling.

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether [redacted] (b) (4) can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. BRANDNAME should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Animal Data: Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 capsules/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day beginning 2 weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 capsules/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1,000, 3,000, and 6,000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 capsules/day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2,000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 capsules/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3,000 mg/kg/day (7 times human systemic exposure following an oral dose of 4 capsules/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, and 1,500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 capsules/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 capsules/day based on a body surface area comparison).

Reviewer Comment: The proposed language is similar to the reference listed drug Lovaza.

7.6.3 Pediatrics and Assessment of Effects on Growth

Trygg Pharma requested a full waiver of the requirement for pediatric studies for AKR-963 capsules in patients from birth to 16 years of age. The justification for this request is that due to the small number of pediatric patients with severe hypertriglyceridemia (TG>500 mg/dL), the necessary trials would be impossible or highly impracticable to conduct.

This justification is validated with data from the NHANES data (2001-2008) in which it is estimated that the US prevalence of severe hypertriglyceridemia (TG>500 mg/dL) consists of 53,946 children between 12 and 19 years of age or 0.2% of the US population.[12]

A recently approved fish oil product also approved for the treatment of severe hypertriglyceridemia, was also granted a waiver from pediatric studies because such studies are impossible or highly impracticable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

I conducted a literature search for publications on overdose or withdrawal effects with Lovaza, Omacor, Epadel, and Vascepa. The search terms used were abuse, recreation, and overdose, over-dose, high dose AND toxic, poison, and risk hazard. The following databases were searched: PubMED, Web of Science, ToxNet and EMBASE. No literature was found on this subject.
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7.7 Additional Submissions / Safety Issues

A 120-day safety update for AKR-963 was submitted in accordance with 21 CFR 314.50(d)(5)(vi)(b). No clinical trials were ongoing, and no new clinical trials have been initiated with AKR-963 since the submission of NDA 204977 on January 31, 2013. Because there have not been any new or ongoing AKR-963 clinical trials since the submission of NDA 204977, there is no new AKR-963-specific safety information on adverse events to update. Furthermore, the applicant has not become aware of any additional safety information from the public domain to report regarding omega-3-acid ethyl esters.

8 Postmarket Experience

Not applicable.

12 Christian, 2011.

9 Appendices

9.1 Literature Review/References

1. Banks PA, Freeman ML. Practice Guidelines in Acute Pancreatitis. Am J Gastroenterol 2006;101:2379-2400
2. Bays HE. Safety Considerations with Omega-3 Fatty Acid Therapy. Am J Cardiol 2007;99 [suppl] 35C-43C.
3. Bays HE, Tighe AP, Davidson MH. Prescription Omega-3 Fatty Acids and Their Lipid Effects: Physiologic Mechanisms of Action and Clinical Implications. Expert Rev Cardiovasc Ther 2008; 6(3):391-409.
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6. Davidson MH. Mechanisms for the Hypotriglyceridemic Effect of Marine Omega-3 Fatty Acids. Am J Cardiol 2006; 98[suppl]: 27i-33i.
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8. Hoy SH, Keating GM. Omega-3 Ethylester Concentrate. Drugs 2009;69(8): 1077-1105.
9. McClaskey EM, Michalets EL. High Dose Omega-3 Fatty Acids with Warfarin and Aspirin: Case Report and Review of the Literature. Pharmacotherapy 2007; 27(1):152-160.
10. Miller M, Stone NJ, Ballantyne C, Bittner V, et al. AHA Scientific Statement: Triglycerides and Cardiovascular Disease. Circulation 2011; 123” 2292-2333.
11. Munigoti S, Rees A. Hypertriglyceridemia, LPL deficiency and pancreatitis—pathogenesis and therapeutic options. Br J Diabetes Vasc Dis 2011; 11: 107-112.
12. Reiffel JA, McDonald A. Antiarrhythmic Effects of Omega-3 Fatty Acids. Am J Cardio 2006; 98[suppl]: 50i-60i.
13. Tanaka K, Yuichi I, et al. Reduction in the Recurrence of Stroke by Eicosapentaenoic Acid for Hypercholesterolemic Patients: Subanalysis of the JELIS trial. Stroke 2008; 39:2052-2058.
14. Yokoyama M, et al. Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolaemic Patients (JELIS): A Randomized Open-Label. Blinded Endpoint Analysis. Lancet 2007; 369:1090-98.

9.2 Labeling Recommendations

See final approved labeling.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not considered necessary given that there were no major safety issues identified with Vascepa.

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/s/

IFFAT N CHOWDHURY
11/26/2013

ERIC C COLMAN
11/26/2013

CLINICAL FILING CHECKLIST FOR NDA 204977

NDA 204977
AKR-963 (omega-3-acid-ethyl esters)
Applicant: Trygg Pharma, Inc.
Reviewer: Iffat N. Chowdhury, MD

Filing Meeting: March 21, 2013
Date Received: January 31, 2013
PDUFA date: November 30, 2013

The applicant, Trygg Pharma, Inc., has submitted NDA 204977 as a 505(b)(2) with Lovaza as the reference listed drug for the following indication:

AKR-963 (omega-3-acid ethyl esters) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Trygg Pharma acknowledges that AKR-963 capsules have a different overall formulation as that of Lovaza capsules, but that AKR-963 still delivers the [redacted] (b) (4) [redacted]" in the same dosage form and route as that of Lovaza.

The applicant has conducted nonclinical and clinical studies to establish that the differences in formulation of the drug product do not alter the nonclinical or clinical profile of AKR-963 relative to Lovaza. Trygg Pharma seeks to establish that AKR-963 is therapeutically equivalent (AB-rated) to Lovaza.

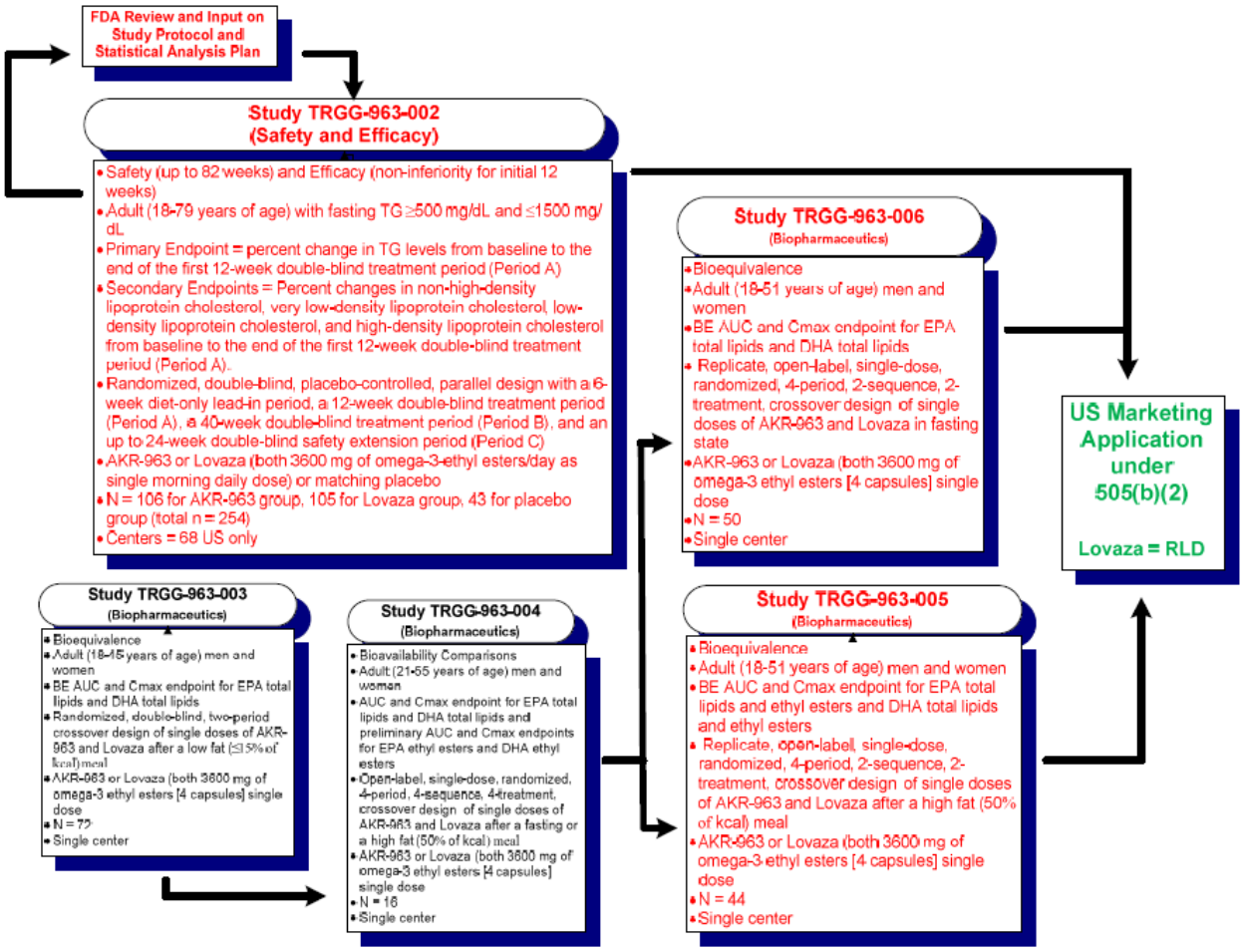
This NDA is comprised of a total of 5 clinical trials:

- one Phase 3 trial: Study TRGG-963-002 for patients with fasting TG levels between 500 mg/dL and 1500 mg/dL
- 4 bioequivalence studies in healthy subjects (Studies: TRGG-963-003, TRGG-963-004, TRGG-963-005; TRGG-963-006)

Comparative Bioavailabilty/ Bioequivalence Trials:
The applicant conducted a series of four trials under a variety of fed and fasted conditions to evaluate the comparative bioavailability of AKR-963 versus Lovaza. This series of studies used the same comparative dose of AKR-963 and Lovaza (3600 mg of omega-3-acid ethyl esters [4 capsules] as a single dose). Study designs evolved from testing total EPA and DHA lipid plasma concentrations after a moderate-fat [redacted] (b) (4) [redacted]% of total kcal) meal over a relatively short post-dose time interval (24 hours) to a replicate study design after either a high fat (50% of total kcal) meal or in the fasting state over a 72-hour post-dose sampling period for total EPA and DHA lipids, as well as EPA and DHA fatty acids and in the case of the post-dose with high-fat meal, the EPA and DHA ethyl esters.

According to the applicant, these trials indicate bioequivalence of AKR-963 to Lovaza on the following parameters following a high-fat breakfast or in the fasting state:

- Unadjusted and baseline-adjusted EPA and DHA from total lipids (AUC_{0-72} and C_{max})
- Unadjusted and baseline-adjusted EPA and DHA from free fatty acids (AUC_{0-72} and C_{max})

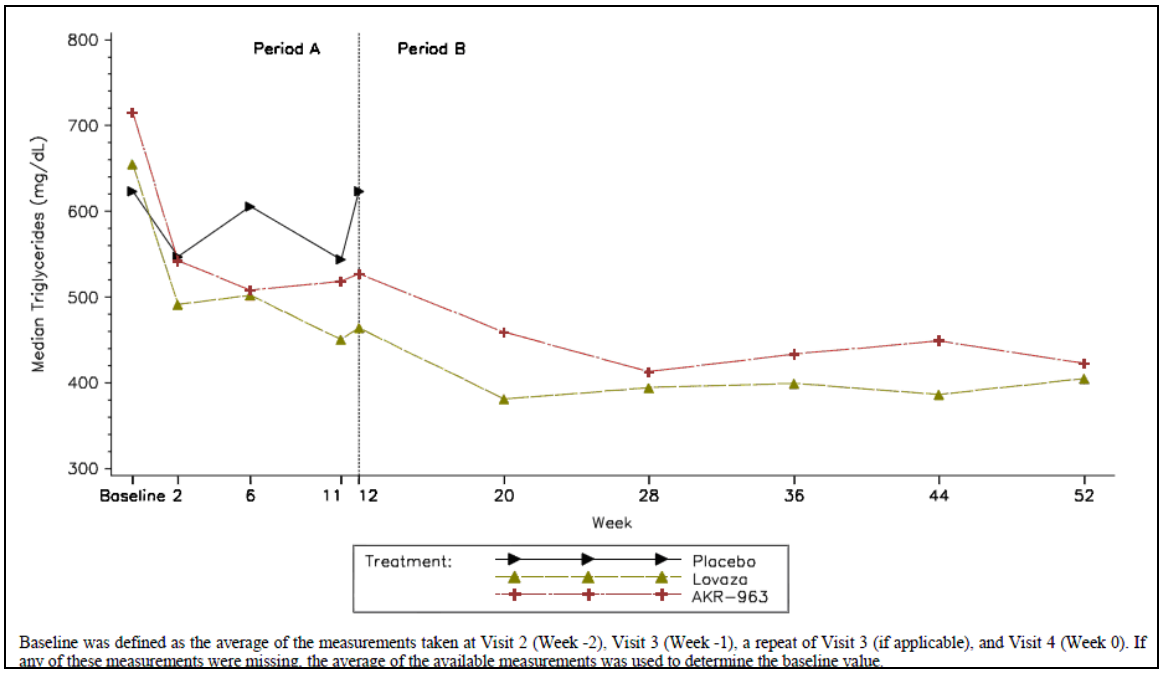


Phase 3 trial- TRGG-963-002:
This was an up to 82-week Phase III study, and consisted of a 6-week diet-only lead-in period, a 12-week double-blind treatment period (Period A), a 40-week double-blind treatment period (Period B), and an up to 24-week double-blind safety extension period (Period C).

After the diet lead-in period, qualifying subjects were randomly assigned to 1 of 3 double-blind treatment groups for Period A: AKR-963 (3600 mg/day), Lovaza® (3600 mg/day), or matching placebo. At the end of the first double-blind treatment period, subjects assigned to AKR-963 or Lovaza remained on their treatment during Period B; subjects assigned to placebo were re-assigned equally to double-blind treatment with either Lovaza or AKR-963.

Subjects who completed the first 52 weeks of treatment (Periods A and B) were eligible to enter a double-blind safety extension period (Period C). Subjects remained on the treatment they received during Period B for up to an additional 24 weeks.

Randomization was stratified based upon baseline triglycerides (TG) (<750 mg/dL or ≥750 mg/dL), presence of diabetes (no diabetes, diabetes with hemoglobin A1c <8.0%, or diabetes with HbA1c ≥8.0%), and concurrent statin use (yes or no).



Baseline was defined as the average of the measurements taken at Visit 2 (Week -2), Visit 3 (Week -1), a repeat of Visit 3 (if applicable), and Visit 4 (Week 0). If any of these measurements were missing, the average of the available measurements was used to determine the baseline value.

Table 1: Percent Change in TG (mg/dL) From Baseline to Period A Endpoint

Analysis Variable	Placebo (N = 43)	Lovaza (N = 103)	AKR-963 (N = 104)
n [1]	43	103	104
Baseline [2] median (Q1, Q3)	624.0 (555.0, 947.7)	655.3 (546.3, 878.7)	701.5 (576.7, 949.4)
Endpoint [3] median (Q1, Q3)	611.0 (458.5, 778.5)	495.0 (338.0, 693.0)	513.5 (397.5, 765.5)
Median (Q1, Q3) percent change	-17.4 (-32.1, 16.0)	-26.8 (-46.5, -7.2)	-24.7 (-39.2, -5.8)
Median of differences relative to placebo			
Estimate		-14.0	-12.2
95% CI		(-26.9, -1.1)	(-23.9, -0.4)
p-value		0.0234	0.0412
Adjusted p-value		0.0412	0.0412
Median of differences relative to Lovaza			
Estimate			2.3
95% CI			(-6.0, 10.5)
p-value			0.5768

95% CIs were estimated with the Hodges-Lehmann method. P-values were from the Wilcoxon rank-sum test. Adjusted p-values were calculated using Hommel's procedure.

1. Includes subjects with non-missing values at baseline and Period A endpoint.
2. Baseline was defined as the average of the measurements taken at Visit 2 (Week -2), Visit 3 (Week -1), a repeat of Visit 3 (if applicable), and Visit 4 (Week 0). If any of these measurements were missing, the average of the available measurements was used to determine the baseline TG value.
3. Endpoint was defined as the average of the measurements taken at Visit 7 (Week 11) and Visit 8 (Week 12). If either of these measurements were missing, the other measurement was used as the endpoint TG value. If both of these measurements were missing, the last measurement taken during Period A (last observation carried forward) was used as the endpoint TG value.

CI = confidence interval; Q1 = first quartile; Q3 = third quartile; TG = triglycerides.
Source: Post-text Table 14.2.1

Table 2: Percent Change in LDL-C (mg/dL) From Baseline to Period A

Analysis Variable	Placebo (N = 43)	Lovaza (N = 103)	AKR-963 (N = 104)
n [1]	43	103	104
Baseline [2] median (Q1, Q3)	94.0 (59.0, 123.0)	85.0 (58.0, 117.0)	78.0 (58.5, 104.0)
Endpoint [3] median (Q1, Q3)	88.0 (54.0, 118.0)	97.0 (76.0, 123.0)	93.0 (70.5, 119.5)
Median (Q1, Q3) percent change	-5.9 (-25.2, 17.8)	12.8 (-5.9, 36.6)	20.3 (2.4, 38.3)
Median of differences relative to placebo			
Estimate		18.9	24.7
95% CI		(7.2, 31.2)	(12.5, 36.8)
p-value		0.0025	0.0002
Adjusted p-value		0.0150	0.0015
Median of differences relative to Lovaza			
Estimate			6.0
95% CI			(-3.7, 14.8)
p-value			0.2101

95% CIs were estimated with the Hodges-Lehmann method. P-values were from the Wilcoxon rank-sum test. Adjusted p-values were calculated using Hommel's procedure to control the familywise type I error rate for testing multiple secondary endpoints.

1. Includes subjects with non-missing values at baseline and Period A endpoint.
2. Baseline was defined as the Visit 4 (Week 0) measurement. If this measurement was missing, the last measurement taken prior to randomization was used as the baseline value.
3. Endpoint was defined as the measurement taken at Visit 8 (Week 12). If this measurement was missing, the last available measurement taken during Period A (last observation carried forward) was used as the endpoint value.

CI = confidence interval; Q1 = first quartile; Q3 = third quartile.
Source: Post-text Table 14.2.6

Safety data:
There were two deaths in Study TRGG-963-002. One patient died of esophageal cancer (randomized to the AKR-963 group). A second patient died due to unknown cause after receiving both Lovaza and AKR-963. The death is still under active investigation.

Liver enzyme elevations were observed with both Lovaza and AKR-963. Otherwise no clearly evident patterns of SAEs and discontinuations due to AEs were observed. The clinical NDA review will be conducted by this reviewer.

Exclusivity
The applicant requested 3 year exclusivity for AKR-963 on the basis of a new clinical trial data.

Pediatric Use
The applicant has submitted a request for full waiver for pediatric studies for patients from birth to 16 years of age. The justification for this request is that due to the small number of pediatric patients with severe hypertriglyceridemia (TG>500 mg/dL), the necessary trials would be impossible or highly impracticable to conduct.

Assessment
From a clinical standpoint, the NDA is fileable.

CLINICAL FILING CHECKLIST FOR NDA 204977

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	One pivotal trial, so no need for ISS or ISE.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Submitted as a 505(b)(2) with RLD Lovaza
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?			X	Trygg is relying upon the Agency's previous findings for Lovaza with regard to information pertinent to relationships between efficacy, dose, and dosing regimen.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Study #1: TRGG-963-002 Indication: as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia	X			Efficacy data from one Phase 3 study with hypertriglyceridemic patients for 12 weeks, plus extension phase up to 52 weeks.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the	X			

	Content Parameter	Yes	No	NA	Comment
	extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Bioequivalence trials conducted in Canada.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 204977

	Content Parameter	Yes	No	NA	Comment
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Applicant submitted a waiver for pediatric population
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Studies 004, 005, 006 were conducted in Canada.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

74-Day Letter Request-

1. **Please submit a rationale for assuming the applicability of foreign data in the submission (bioequivalence trials) to the U.S. population.**
2. **Please submit data from your excluded site, #124 Dr. Michael Dao, in a similar format to the Site-Level Dataset submitted to the Agency on March 19th, 2013 for our review.**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IFFAT N CHOWDHURY
03/28/2013

ERIC C COLMAN
03/28/2013