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*APPLICATION NUMBER:*

**204977Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**



## Memorandum

**Date:** November 26, 2013

**From:** Martin Haber, Ph.D., Review Chemist

**Subject:** NDA 204977 Omtryg Capsules – Established Name, Strength and Inspection Status

**Background:**

Originally, the sponsor proposed the established name “(b) (4)” for this product. However, as discussed in the Chemistry review dated 10/17/2013 for this NDA there is another product with a USP drug substance monograph using that name and this product does not meet the monograph requirements. The sponsor has proposed the following new established names: first alternative option: “(b) (4)” or the second alternative option: “omega-3-acid ethyl esters A”. The new names are clearly distinguishable from the originally proposed name. The proposed new established name “omega-3-acid ethyl esters A” is acceptable from a chemistry viewpoint.

Regarding the drug product strength, the entire mixture of fish oils is designated by CDER decision as the active ingredient and/or the drug substance. Since the fill weight of drug substance is 1.16 g, the labeled strength should be 1200 mg. Regarding the manufacturing facilities inspection status, the overall Office of Compliance (OC) recommendation is Acceptable for NDA 204977, as reported by the EES system.

The recommendation and conclusion on approvability for this NDA from a chemistry viewpoint is approval. There are no pending chemistry issues.

R/D Init by: Dr. D. Christodoulou, Branch Chief

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/s/  
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MARTIN T HABER  
11/26/2013

DANAE D CHRISTODOULOU  
11/26/2013  
I concur

## CLINICAL PHARMACOLOGY REVIEW

<b>NDA: 204977</b>	Submission Date(s): 01/31/2013
<b>Brand Name</b>	OMTRYG™
<b>Generic Name</b>	<i>Pending</i>
<b>Reviewer</b>	Manoj Khurana, Ph.D.
<b>Team Leader</b>	Immo Zadezensky, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology -2
<b>OND division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	Trygg Pharma Inc.
<b>Submission Type; Code</b>	NDA 505(b)(2); Standard
<b>Formulation; Strength(s)</b>	Soft gelatin capsule (liquid filled) 1.16 g
<b>Proposed Indication</b>	As an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ( $\geq 500$ mg/dL) hypertriglyceridemia.

<b>LIST OF FIGURES.....</b>	<b>2</b>
<b>LIST OF TABLES.....</b>	<b>2</b>
<b>1 EXECUTIVE SUMMARY .....</b>	<b>3</b>
<b>1.1 RECOMMENDATION.....</b>	<b>3</b>
<b>1.2 PHASE IV COMMITMENTS .....</b>	<b>3</b>
<b>1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS.....</b>	<b>3</b>
<b>2 QUESTION-BASED REVIEW (QBR).....</b>	<b>5</b>
<b>2.1 GENERAL ATTRIBUTES .....</b>	<b>5</b>
<b>2.1.2 What are the features of the clinical pharmacology studies and the analyses used to support the current application?.....</b>	<b>5</b>
<b>2.1.2 What is the composition of to be marketed formulation of AKR-963 in relation to the reference product Lovaza? .....</b>	<b>6</b>
<b>2.2 KEY CLINICAL PHARMACOLOGY ISSUES .....</b>	<b>8</b>
<b>2.2.1 What is the relative bioavailability of EPA and DHA from the to-be-marketed formulation of AKR-963 in reference to Lovaza®? .....</b>	<b>8</b>
<b>2.2.2 What is the effect of food on the bioavailability of EPA and DHA components from AKR-963 in reference to Lovaza®?.....</b>	<b>17</b>
<b>2.2.3 How are the results of relative BA trials of AKR-963 related to the efficacy/safety evaluation of AKR-963?.....</b>	<b>21</b>
<b>2.3 ANALYTICAL.....</b>	<b>26</b>
<b>2.3.1 Are the analytical methods appropriately validated?.....</b>	<b>26</b>
<b>3 PRELIMINARY LABELING COMMENTS .....</b>	<b>30</b>
<b>4 APPENDIX .....</b>	<b>32</b>
<b>4.1 INDIVIDUAL STUDY SYNOPSES AS REPORTED .....</b>	<b>32</b>
<b>4.1.1 Relative BA Study - Food Effect (TRGG-963-004).....</b>	<b>32</b>

4.1.2	Definite BE Study Under Fed Condition (TRGG-963-005)	36
4.1.3	Definite BE Study Under Fasted Condition (TRGG-963-006)	46
4.2	OCF FILING MEMO	56

## List of Figures

---

Figure 1	Mean baseline-adjusted plasma Total EPA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given with high fat, high calorie breakfast (TRGG-963-005)	8
Figure 2	Mean baseline-adjusted plasma Total DHA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given with high fat, high calorie breakfast (TRGG-963-005)	9
Figure 3	Mean baseline-adjusted plasma Total EPA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given under fasted condition (TRGG-963-006)	13
Figure 4	Mean baseline-adjusted plasma Total DHA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given under fasted condition (TRGG-963-006)	13
Figure 5	Mean baseline-adjusted plasma Total EPA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given with or without meal	18
Figure 6	Mean baseline-adjusted plasma Total DHA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given with or without meal	19
Figure 7	Median Triglycerides (mg/dL) Over Time – Modified Intent-to-Treat Population (TRGG-963-002)	22

## List of Tables

---

Table 1	Overview of statistical assessments used for BE evaluation of primary pharmacokinetic parameters in clinical pharmacology studies	6
Table 2	Quantitative Composition of AKR-963 Capsules	7
Table 3	Drug Product Lots Used in AKR-963 Development Program	7
Table 4	Statistical analysis results for Total EPA PK parameters	10
Table 5	Statistical analysis results for Total DHA PK parameters	10
Table 6	Statistical analysis results for EPA-EE PK parameters	11
Table 7	Statistical analysis results for DHA-EE PK parameters	12
Table 8	Statistical analysis results for Total EPA PK parameters	14
Table 9	Statistical analysis results for Total DHA PK parameters	15
Table 10	Statistical analysis results for Free EPA PK parameters	16
Table 11	Statistical analysis results for Free DHA PK parameters	16
Table 12	Summary of Study Results Based on Plasma Total EPA Levels	18
Table 13	Summary of Study Results Based on Plasma Total DHA Levels	19
Table 14	Summary of Study Results Based on Measured Plasma Total EPA Levels	20
Table 15	Summary of Study Results Based on Measured Plasma Total EPA Levels	20
Table 16	Summary of Treatments Administered	22
Table 17	Summary of the Performance Characteristics of an LC/MS/MS Bioanalytical Method for Determination of Total EPA and Total DHA	27
Table 18	Summary of the Performance Characteristics of an LC/MS/MS Bioanalytical Method for Determination of Free EPA and Free DHA	28
Table 19	Summary of the Performance Characteristics of an LC/MS/MS Bioanalytical Method for Determination of EPA-EE and DHA-EE	29

## **1 Executive Summary**

Trygg Pharma Inc. (the sponsor) is seeking approval of OMTRYG™ (AKR-963 capsule) under the provisions of Section 505(b)(2) for the following proposed indication:

*“As an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia”*

The sponsor is relying upon the Agency’s previous findings of safety and effectiveness for the reference listed drug (RLD), Lovaza® (omega-3-acid ethyl esters) Capsules, oral (NDA 21-654, GlaxoSmithKline). AKR-963 is manufactured as a soft-gelatin liquid filled capsule formulation, intended for oral use. Each 1.16 g AKR-963 capsule contains at least 900 mg of total omega-3-acid ethyl esters sourced from fish oil. The major components are: approximately 465 mg of eicosapentaenoic acid ethyl ester (EPAee) and 375 mg of docosahexaenoic acid ethyl ester (DHAee).

Clinical pharmacology of AKR-963 under this 505(b)(2) submission was supported by 3 studies including one definitive bioequivalence (BE) trial conducted under fed condition, one BE trial conducted under fasted condition, and one pilot relative bioavailability study. Concentrations of eicosapentaenoic acid and docosahexaenoic acid from Total Lipids (Total EPA and DHA), EPA ethyl ester (EPA-EE) and DHA ethyl ester (DHA-EE), and EPA and DHA from Free Fatty Acids (Free EPA and DHA) were measured. The sponsor conducted a randomized, double-blind, placebo-controlled, parallel-group, non-inferiority phase 3 study in the target patient population to assess the relative safety and efficacy of AKR-963 compared to Lovaza. This pivotal efficacy trial used the to-be-marketed commercial AKR-963 formulation, and therefore, the BE trials were not deemed pivotal for approval.

### **1.1 Recommendation**

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted to NDA 204977 for approval of OMTRYG™ [AKR-963 Capsules]. The clinical pharmacology information is acceptable for AKR-963. The NDA can be approved with regards to the clinical pharmacology information.

### **1.2 Phase IV Commitments**

None

### **1.3 Summary of Important Clinical Pharmacology Findings**

The bioequivalence was appropriately demonstrated between the to-be-marketed OMTRYG 1.16 g formulation and the RLD (Lovaza® formulation) under high-fat diet fed conditions, for C<sub>max</sub> and AUC<sub>0-72h</sub> of total plasma EPA and DHA (with and

without baseline adjustment). In addition, the data demonstrated the bioequivalence between to-be-marketed OMTRYG 1.16 g formulation and the Lovaza® formulation under fasted condition for C<sub>max</sub> and AUC<sub>0-72h</sub> of total plasma EPA and DHA (with and without baseline adjustment). In conclusion, the clinical pharmacology aspects of OMTRYG were appropriately characterized and support the approvability of this NDA.

Significant food effect on the bioavailability of Total EPA and Total DHA in plasma was observed for both OMTRYG and reference Lovaza formulations. To this reviewer's knowledge such an effect has not been reported before for any approved omega-3 fatty acid/ester based drug product. However, based on the references provided by the sponsor, there are a number of publications that seem to substantiate the food effect.

The efficacy results from pivotal TRGG-963-002 trial showed median percent change in TG from baseline to Period A endpoint (Week 12) was -17.4% (Median baseline TG of 624.0 mg/dL) for the placebo group, -26.8% for the Lovaza group (Median baseline TG of 655.3 mg/dL), and -24.7% for the AKR-963 group (Median baseline TG of 701.5 mg/dL). The median of the differences in percent change between placebo and Lovaza was -14.0%.

Although sponsor claimed non-inferiority of AKR-963 to Lovaza, the magnitude of efficacy was substantially lower for both test drug and comparator. During the review Agency identified statistical issues with the efficacy results, and sent an information request to the sponsor (see Letter in DAARTS dated 05/21/2013) to explain the observed lower than expected treatment effects of AKR-963 and Lovaza, and was also requested to clarify how treatments were administered with regards to meals. Sponsor submitted their response on 07/03/2013 including the results of a revised statistical analysis defending their results. While readers are referred to the Clinical and Statistical Review for more details on this issue, the sponsor's conclusions from the revised statistical analysis are captured below:

- The estimated placebo-adjusted difference for Lovaza is -16.9%; 1-sided p = 0.002; 95% CI (-31.8%, -5.0%).
- The estimated placebo-adjusted difference for AKR-963 is -16.8%; 1-sided p = 0.005; 95% CI (-30.5%, -3.4%).
- The lower bound of the 95% confidence interval comparing AKR-963 to Lovaza is 8.7%.
- The p-value for the noninferiority test of AKR-963 to Lovaza under a hypothesized noninferiority margin of 10 is 0.013.

If the main question is framed as “How do the results of these relative BA studies relate to the observed clinical efficacy results for this application?” there are some important things to highlight with regards to the clinical relevance of the bridging data on EPA/DHA pharmacokinetics between AKR-963 and Lovaza:

- The two formulations are bioequivalent for total plasma EPA and DHA as well as EPA-EE and DHA-EE components both under high-fat diet and fasted condition. This means that both AKR-963 and Lovaza are expected to behave identically based on the conditions under which they will be administered. Considering the nature of treatment administration used in trial TRGG-963-002 where, as per the sponsor, no dosing recommendation with regards to meal has been given and

potentially, treatment was administered under fasted or occasionally fed condition), the food effect on efficacy cannot be ruled out. This might explain observed lower mean response for both AKR-963 and Lovaza treatments, in comparison to the historical data from Lovaza clinical studies. In Lovaza's Phase 3 trials, the treatments were administered under fed conditions. However, no food effect study was conducted by the sponsor. In that sense, the Clinical Pharmacology results fully corroborate with the observed clinical results and are supportive of an approval decision for AKR-963.

- The relevance of food effect cannot be neglected for omega 3 fatty acid ester based drugs. Therefore, AKR-963 should preferably be administered under fed condition to maximize the benefit.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes

#### 2.1.2 What are the features of the clinical pharmacology studies and the analyses used to support the current application?

Omtryg™ (AKR-963) belongs to the pharmacological class of omega-3-acid ethyl esters. Omega-3 ethyl esters have been shown to decrease TG levels in patients with TG levels > 500 mg/dL by up to 45% (Lovaza® Label, 2012). 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  $\beta$ -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.

Clinical pharmacology of AKR-963 under this 505(b)(2) submission was supported by 3 studies including one definitive bioequivalence (BE) trial conducted under fed state, one BE trial conducted under fasted state, and one pilot relative bioavailability study. Concentrations of EPA and DHA from Total Lipids (Total EPA and DHA), EPA ethyl ester (EPA-EE) and DHA ethyl ester (DHA-EE), and EPA and DHA from Free Fatty Acids (Free EPA and DHA) were measured. The definitive BE studies were conducted in a replicate cross-over design and the sponsor pre-specified the following for statistical analysis approach (as described in detail in agency's Guidance on Progesterone<sup>1</sup>):

In short, using PROC MIXED in SAS®, based on the log-transformed individual values obtained for the AUC(0-72h) and C<sub>max</sub> parameters between-treatments and within-reference treatment differences were calculated for each subject included in the final dataset. The within-reference differences were analyzed using PROC Mixed in SAS® with sequence as the only factor to estimate the sequence-pooled within-reference variance. The intra-subject-within-reference standard deviation was estimated from the residual variance (S<sub>WR</sub>):

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<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>

$$S_{WR} = \sqrt{\frac{\text{residual}}{2}}$$

The method used to test bioequivalence between the test and reference products was decided by the value of the intra-subject-within-reference standard deviation ( $S_{WR}$ ):

- If  $S_{WR} < 0.294$ : the regular un-scaled average bioequivalence approach (ABE) was used.
- If  $S_{WR} \geq 0.294$ : the reference-scaled average bioequivalence approach (RSABE) was used.

The Table 1 below summarizes statistical assessments used for BE evaluation of primary pharmacokinetic parameters in clinical pharmacology studies.

**Table 1 Overview of statistical assessments used for BE evaluation of primary pharmacokinetic parameters in clinical pharmacology studies**

Study	Analyte	Parameter	Type	Method
<b>TRGG-963-005 (Fed BE)</b>	Total EPA and Total DHA (Primary)	Cmax and AUC <sub>0-72h</sub>	Adjusted and Measured:	ABE
	EPA-EE and DHA-EE (Primary)	Cmax, AUC <sub>0-t</sub> , and AUC <sub>0-inf</sub> *	Adjusted and Measured	RSABE
	Free-EPA and Free-DHA (Secondary)	Cmax★ and AUC <sub>0-72h</sub>	Adjusted: Measured:	RSABE ABE
<b>TRGG-963-006 (Fasted BE)</b>	Total EPA and Total DHA (Primary)	Cmax and AUC <sub>0-72h</sub>	Adjusted: Measured:	RSABE ABE
	Free-EPA and Free-DHA (Secondary)	Cmax** and AUC <sub>0-72h</sub>	Adjusted: Measured:	RSABE ABE
*For DHA-EE AUC <sub>0-inf</sub> the ABE method was used.**Baseline adjusted Cmax for Free-EPA and Free-DHA, ABE method was used. ★For Baseline adjusted Free-EPA and Free-DHA Cmax, RSABE method was used.				

Total plasma EPA and total plasma DHA pharmacokinetic parameters were common primary evaluation in all clinical pharmacology studies.

### 2.1.2 What is the composition of to be marketed formulation of AKR-963 in relation to the reference product Lovaza?

AKR-963 capsule formulation intended for oral use has been manufactured as a soft-gelatin liquid filled capsule. The strength of AKR-963 is expressed as 0.9 g to reflect that each capsule contains at least 900 mg of total omega-3-acid ethyl esters [Approximately

465 mg eicosapentaenoic acid ethyl ester (EPA-EE) and 375 mg docosahexaenoic acid ethyl ester (DHA-EE)] sourced from fish oil.

The quantitative composition of the to-be-marketed AKR-963 formulations is presented in Table 2 below. The concentration of the omega-3-acid ethyl esters in the drug substance for the proposed drug product is lower than that of Lovaza. (b) (4)

**Table 2 Quantitative Composition of AKR-963 Capsules**

	Lovaza	AKR-963 Capsules
Route of administration	Oral	
Active Ingredient	Omega-3-acid ethyl esters	
Product source	Fish oil	
Expressed Strength (g)	1 <sup>b</sup>	0.9
Total omega-3-acid ethyl esters (mg/capsule) <sup>e</sup>	At least 900	
EPA <sub>ee</sub> (mg/capsule)	Approximately 465	
DHA <sub>ee</sub> (mg/capsule)	Approximately 375	
Minor omega-3-acid ethyl esters	Not specified in RLD label	(b) (4)
Dosage form	Capsule	
Inactive ingredients	Gelatin, glycerol, water, α-tocopherol (in a carrier of soybean oil)	Gelatin, glycerol, water, α-tocopherol (in a carrier of sunflower oil)
Capsule fill weight (g)	1	1.16

**Table 3 Drug Product Lots Used in AKR-963 Development Program**

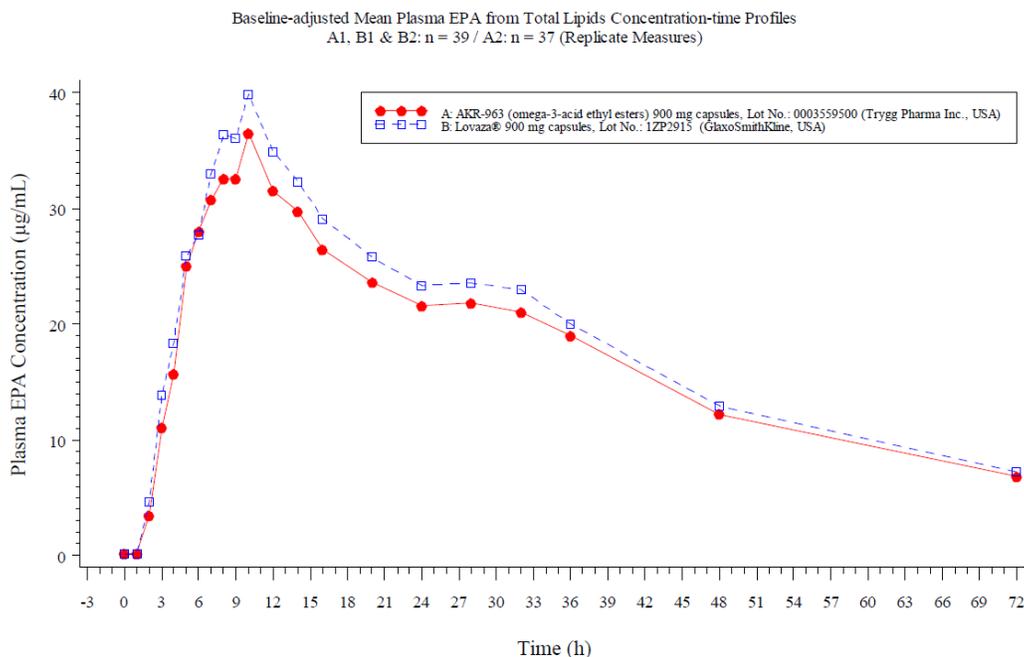
Lot	Manufacture Date	Batch Size (kg)	Target Fill Weight (g)	Initial Fill Weight (g)	Usage	Drug Substance Lot
0003172900	Feb 24, 2010	(b) (4)			Stability	M100002
0003170601	May 3, 2010				Clinical TRGG-963-002	M100021
0003170602	May 3, 2010				Clinical TRGG-963-002	M100022
0003550700	Jan 17, 2011				Clinical TRGG-963-002	M100086/S
					TRGG-963-003	
					Nonclinical 241342 241656 241657	
0003559500	May 2, 2011				Clinical TRGG-963-002 TRGG-963-004 TRGG-963-005 TRGG-963-006	M110013
0003910400	Jul 4, 2011				Primary stability	M110015
0003910500	Jul 4, 2011				Primary stability	M110017
0003910600	Jul 4, 2011				Primary stability	M100018

## 2.2 Key Clinical Pharmacology Issues

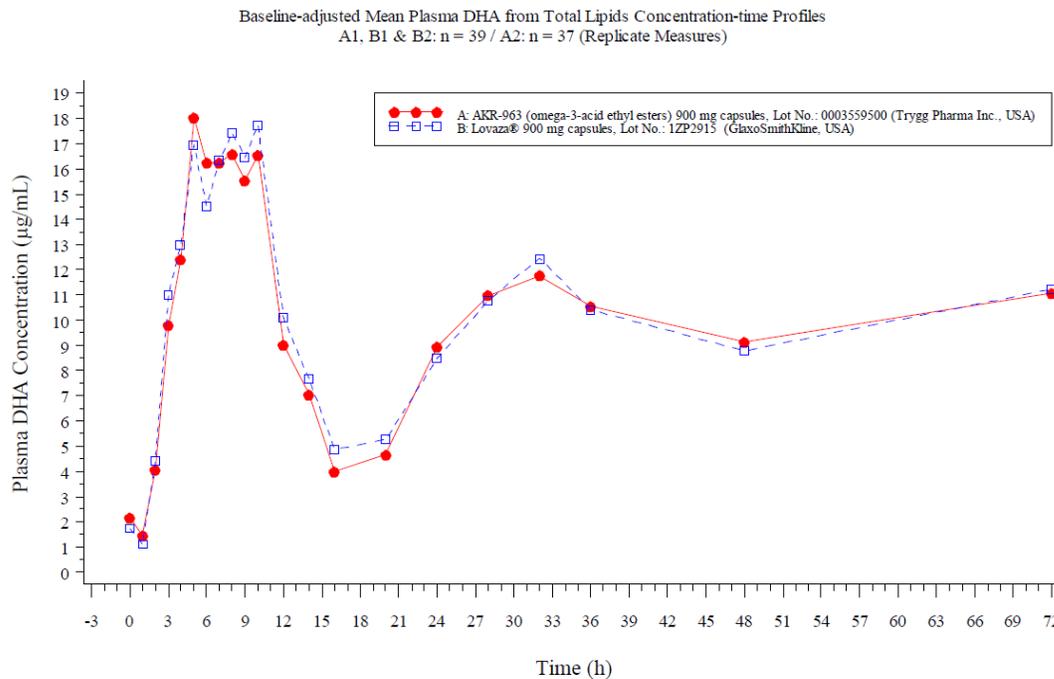
### 2.2.1 What is the relative bioavailability of EPA and DHA from the to-be-marketed formulation of AKR-963 in reference to Lovaza®?

**Under Fed Condition:** The relative bioavailability of measured and baseline adjusted EPA and DHA components from the to-be-marketed AKR-963 formulation in comparison to the Lovaza formulation (reference) was evaluated in study TRGG-963-005, conducted under fed conditions. This was an open-label, single-dose, randomized, 4-period, 2-sequence, 2-treatment, replicate, crossover study, designed to evaluate the comparative bioavailability of two formulations of omega-3 fatty acid ethyl esters, 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 fasting conditions. Concentrations of EPA and DHA from Total Lipids (Total EPA and Total DHA) and EPA and DHA from Free Fatty Acids (Free EPA and DHA), and as EPA-EE and DHA-EE were measured from samples collected over a 72-hour interval after dosing in each period. The primary bioequivalence assessment was based on the AUC<sub>0-72</sub> and C<sub>max</sub> of plasma total EPA and total DHA levels (both observed and baseline adjusted), and AUC<sub>t</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> of EPA-EE and DHA-EE plasma levels.

Mean baseline-adjusted plasma Total EPA and DHA concentration-time profiles from single oral dose of AKR-963 or Lovaza® formulations given with high fat, high calorie breakfast are presented below in Figure 1 and Figure 2, respectively.



**Figure 1 Mean baseline-adjusted plasma Total EPA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given with high fat, high calorie breakfast (TRGG-963-005)**



**Figure 2 Mean baseline-adjusted plasma Total DHA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given with high fat, high calorie breakfast (TRGG-963-005)**

The summary of bioequivalence assessment using pharmacokinetic parameters of Total EPA, Total DHA, EPA-EE, and DHA-EE are presented in Tables 4, 5, 6, and 7, respectively.

*Total Plasma EPA:* The un-scaled, average bioequivalence approach was used for assessment of bioequivalence (sWR for Total EPA < 0.294 for both C<sub>max</sub> and AUC<sub>0-72</sub>). The 90% confidence intervals of the test to reference ratio were entirely contained within the pre-specified 80.00-125.00% bioequivalence range for both C<sub>max</sub> and AUC<sub>0-72</sub>. However, a significant treatment effect was detected by ANOVA for the baseline-adjusted C<sub>max</sub> (p=0.0006) and AUC<sub>0-72</sub> (p=0.0495) parameters. As indicated by the geometric mean ratio, for AKR-963 formulation the mean baseline-adjusted C<sub>max</sub> was ~10% lower and the baseline-adjusted AUC<sub>0-72</sub> was ~9% lower than Lovaza (Table 4).

*Total Plasma DHA:* The estimated sWR for Total DHA is less than 0.294 for C<sub>max</sub> and AUC<sub>0-72</sub> obtained based on both baseline-adjusted and measured concentrations. Therefore, the un-scaled, average bioequivalence approach was used for assessment of bioequivalence. The 90% confidence intervals of the test to reference ratio were entirely contained within the 80.00-125.00% bioequivalence range for both C<sub>max</sub> and AUC<sub>0-72</sub> (Table 5).

**Table 4 Statistical analysis results for Total EPA PK parameters**

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Total EPA Data</i>											
AUC <sub>0-72</sub> (µg*h/mL)	A <sub>1</sub>	1218.16	41	1144.40	A vs. B	91.22	84.48 - 98.49	A: 36	N/A	N/A	
	A <sub>2</sub>	1259.32	31								
	B <sub>1</sub>	1345.60	33	B: 19				0.191			
	B <sub>2</sub>	1325.03	34	1254.56							
Cmax (µg/mL)	A <sub>1</sub>	44.79	33	44.97	A vs. B	89.78	85.35 - 94.43	A: 21	N/A	N/A	
	A <sub>2</sub>	49.50	36								
	B <sub>1</sub>	53.37	34	B: 17				0.167			
	B <sub>2</sub>	51.41	30	50.09							
<i>Based on Measured Total EPA Data</i>											
AUC <sub>0-72</sub> (µg*h/mL)	A <sub>1</sub>	2223.60	33	2161.23	A vs. B	96.68	93.96 - 99.48	A: 8	N/A	N/A	
	A <sub>2</sub>	2264.66	32								
	B <sub>1</sub>	2316.12	30	B: 10				0.101			
	B <sub>2</sub>	2335.85	31	2235.40							
Cmax (µg/mL)	A <sub>1</sub>	59.31	31	59.13	A vs. B	92.92	89.34 - 96.64	A: 15	N/A	N/A	
	A <sub>2</sub>	63.79	33								
	B <sub>1</sub>	66.94	31	B: 14				0.145			
	B <sub>2</sub>	65.65	30	63.64							

[Treatment A1, A2: AKR-963 Fed; B1, B2: Lovaza Fed]

**Table 5 Statistical analysis results for Total DHA PK parameters**

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Total DHA Data</i>											
AUC <sub>0-72</sub> (µg*h/mL)	A <sub>1</sub>	664.62	34	667.74	A vs. B	103.88	94.40 - 114.32	A: 24	N/A	N/A	
	A <sub>2</sub>	754.79	35								
	B <sub>1</sub>	696.49	39	B: 24				0.228			
	B <sub>2</sub>	728.11	41	642.79							
Cmax (µg/mL)	A <sub>1</sub>	25.95	43	26.40	A vs. B	91.01	84.58 - 97.94	A: 29	N/A	N/A	
	A <sub>2</sub>	32.49	49								
	B <sub>1</sub>	31.06	47	B: 27				0.261			
	B <sub>2</sub>	31.97	36	29.01							
<i>Based on Measured Total DHA Data</i>											
AUC <sub>0-72</sub> (µg*h/mL)	A <sub>1</sub>	4142.03	26	4138.54	A vs. B	99.16	97.66 - 100.68	A: 6	N/A	N/A	
	A <sub>2</sub>	4362.48	28								
	B <sub>1</sub>	4189.26	25	B: 5				0.056			
	B <sub>2</sub>	4409.73	26	4173.73							
Cmax (µg/mL)	A <sub>1</sub>	74.33	27	75.95	A vs. B	96.10	93.29 - 98.99	A: 13	N/A	N/A	
	A <sub>2</sub>	82.68	30								
	B <sub>1</sub>	79.72	26	B: 9				0.084			
	B <sub>2</sub>	83.19	27	79.03							

[Treatment A1, A2: AKR-963 Fed; B1, B2: Lovaza Fed]

*EPA-EE*: The estimated sWR for EPA Ethyl-ester was greater than 0.294 for Cmax, AUCt and AUC0-inf. The reference-scaled bioequivalence approach was used for assessment of bioequivalence. As shown in Table 6 below, the results satisfied the two criteria for demonstrating bioequivalence based on this method:

- test/reference ratio was contained within the 80.00-125.00% range, and
- the upper 95% bound of the confidence interval of the reference-scaled criterion was negative.

*DHA-EE*: The estimated sWR for DHA Ethyl-ester was greater than 0.294 for Cmax and AUCt. The reference-scaled bioequivalence approach was used for assessment of bioequivalence for these parameters.

As shown in Table 7, the results satisfied the two criteria for demonstrating bioequivalence based on the reference-scaled BE method:

- test/reference ratio was contained within the 80.00-125.00% range, and
- the upper 95% bound of the confidence interval of the reference-scaled criterion was negative.

**Table 6 Statistical analysis results for EPA-EE PK parameters**

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Measured/Baseline-Adjusted EPA Ethyl-ester Data</i>											
<b>AUC<sub>0-t</sub></b> (ng*h/mL)	A <sub>1</sub>	381.378	46	N/A	<b>A vs. B</b>	88.73	N/A	-	N/A	N/A	N/A
	A <sub>2</sub>	421.040	52	N/A							
	B <sub>1</sub>	482.751	49	N/A							
	B <sub>2</sub>	429.334	49	N/A							
<b>AUC<sub>0-inf</sub></b> (ng*h/mL)	A <sub>1</sub>	427.012	39	N/A	<b>A vs. B</b>	96.24	N/A	-	N/A	N/A	N/A
	A <sub>2</sub>	414.545	51	N/A							
	B <sub>1</sub>	502.955	50	N/A							
	B <sub>2</sub>	453.773	48	N/A							
<b>Cmax</b> (ng/mL)	A <sub>1</sub>	183.500	64	N/A	<b>A vs. B</b>	83.42	N/A	-	N/A	N/A	N/A
	A <sub>2</sub>	192.450	68	N/A							
	B <sub>1</sub>	237.067	67	N/A							
	B <sub>2</sub>	201.410	58	N/A							

[Treatment A1, A2: AKR-963 Fed; B1, B2: Lovaza Fed]

**Table 7 Statistical analysis results for DHA-EE PK parameters**

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Measured/Baseline-Adjusted DHA Ethyl-ester Data</i>											
<b>AUC<sub>0-t</sub></b> (ng*h/mL)	A <sub>1</sub>	1699.232	43	N/A	A vs. B	92.20	N/A - N/A	N/A	N/A	N/A	
	A <sub>2</sub>	1868.335	48								
	B <sub>1</sub>	2026.347	40								
	B <sub>2</sub>	1866.066	46								
<b>AUC<sub>0-inf</sub></b> (ng*h/mL)	A <sub>1</sub>	1762.930	39	1733.262	A vs. B	92.04	83.70 - 101.21	A: 25 B: 26	N/A	N/A	
	A <sub>2</sub>	2096.299	45								
	B <sub>1</sub>	2052.842	43	1883.138							
	B <sub>2</sub>	2106.363	39								
<b>Cmax</b> (ng/mL)	A <sub>1</sub>	683.003	56	N/A	A vs. B	86.47	N/A - N/A	N/A	N/A	N/A	
	A <sub>2</sub>	769.526	62								
	B <sub>1</sub>	859.846	56								
	B <sub>2</sub>	767.172	54	N/A							

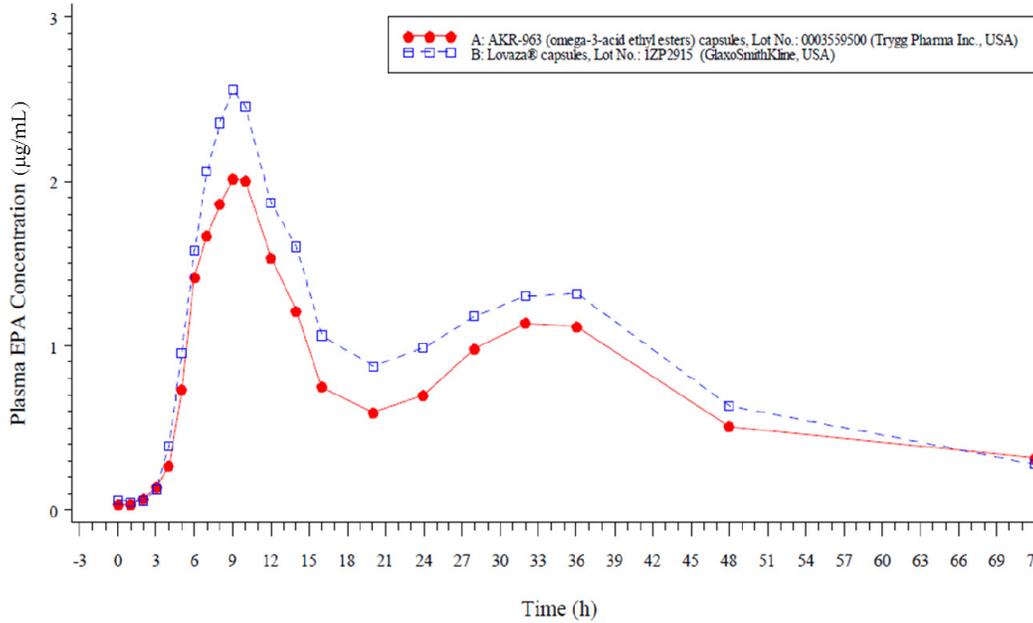
[Treatment A1, A2: AKR-963 Fed; B1, B2: Lovaza Fed]

Therefore, based on the statistical analysis results, when both AKR-963 and Lovaza treatments were administered under fed condition (high fat, high calorie diet):

- The AKR-963 formulation was bioequivalent to the Lovaza formulation with regards to the AUC<sub>0-72</sub> and Cmax of Total Plasma EPA and Total Plasma DHA.
- The AKR-963 formulation was also bioequivalent to the Lovaza formulation with regards to the AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and Cmax of plasma EPA-EE and DHA-EE.

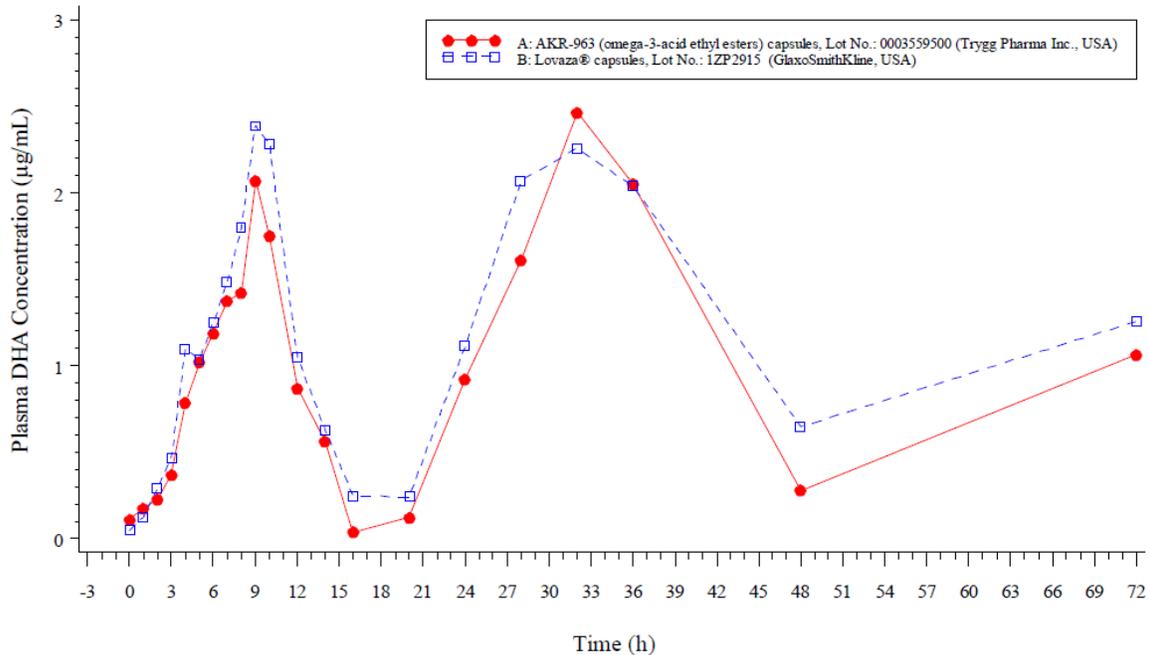
**Under Fasted Condition:** The relative bioavailability of measured and baseline adjusted EPA and DHA components from the to-be-marketed AKR-963 formulation in comparison to the Lovaza formulation (reference) was evaluated in study TRGG-963-006, conducted under fasted conditions. This was an open-label, single-dose, randomized, 4-period, 2-sequence, 2-treatment, replicate, crossover study, designed to evaluate the comparative bioavailability of two formulations of omega-3 fatty acid ethyl esters, administered to healthy male and female subjects under fasted conditions. Subjects 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 Total 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. The primary bioequivalence assessment was based on the AUC<sub>0-72</sub> and Cmax of plasma total EPA and total DHA levels as well as for EPA and DHA from Free Fatty Acids (both observed and baseline adjusted).

Mean baseline-adjusted plasma Total EPA and DHA concentration-time profiles from single oral dose of AKR-963 or Lovaza® formulations given with high fat, high calorie breakfast are presented below in Figures 3 and 4, respectively.



**Figure 3 Mean baseline-adjusted plasma Total EPA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given under fasted condition (TRGG-963-006)**

[Note For figure above, the concentration units were reported incorrectly as ng/mL in the study report]



**Figure 4 Mean baseline-adjusted plasma Total DHA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given under fasted condition (TRGG-963-006)**

The summary of bioequivalence assessment using pharmacokinetic parameters of Total EPA, Total DHA, Free EPA, and Free DHA are presented in Tables 8, 9, 10, and 11, respectively.

*Total Plasma EPA:* The reference-scaled bioequivalence approach was used for assessment of bioequivalence (sWR for Total EPA > 0.294) for both Cmax and AUC0-72 using baseline-adjusted data. The test/reference ratio was contained within the 80.00-125.00% range, though indicating ~12% lower peak and total exposure, and the upper 95% bound of the confidence interval of the reference-scaled criterion was negative.

The un-scaled, average bioequivalence approach was used for assessment of bioequivalence (sWR for Total EPA < 0.294) for both Cmax and AUC0-72 based on measured data. The 90% confidence intervals of the test to reference ratio were entirely contained within the pre-specified 80.00-125.00% bioequivalence range for both Cmax and AUC0-72 (Table 8).

**Table 8 Statistical analysis results for Total EPA PK parameters**

<i>Total Lipids of Plasma</i>											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Total EPA Data</i>											
AUC <sub>0-72</sub> ( $\mu\text{g}^*\text{h/mL}$ )	A <sub>1</sub>	81.29	205	N/A	A vs. B	87.78	N/A -	N/A	N/A	N/A	
	A <sub>2</sub>	52.44	83								
	B <sub>1</sub>	90.21	157	N/A							
	B <sub>2</sub>	65.58	84								
Cmax ( $\mu\text{g/mL}$ )	A <sub>1</sub>	4.37	164	N/A	A vs. B	81.94	N/A -	N/A	N/A	N/A	
	A <sub>2</sub>	3.09	56								
	B <sub>1</sub>	4.14	102	N/A							
	B <sub>2</sub>	4.16	60								
<i>Based on Measured Total EPA Data</i>											
AUC <sub>0-72</sub> ( $\mu\text{g}^*\text{h/mL}$ )	A <sub>1</sub>	1027.17	43	929.54	A vs. B	95.43	92.74 -	98.19	A: 11	N/A	
	A <sub>2</sub>	979.26	47								
	B <sub>1</sub>	1097.59	44	974.06							
	B <sub>2</sub>	1009.58	45								
Cmax ( $\mu\text{g/mL}$ )	A <sub>1</sub>	17.88	54	15.76	A vs. B	92.98	89.12 -	97.01	A: 17	N/A	
	A <sub>2</sub>	16.79	50								
	B <sub>1</sub>	19.15	48	16.95							
	B <sub>2</sub>	17.83	44								

[Treatment A1, A2: AKR-963 Fasted; B1, B2: Lovaza Fasted]

*Total Plasma DHA:* The estimated sWR for Total DHA is greater than 0.294 for the Cmax and AUC72 parameters based on baseline-adjusted concentrations. Therefore, the reference-scaled bioequivalence approach was used for the assessment of bioequivalence. The test/reference ratio was contained within the 80.00-125.00% range, and the upper 95% bound of the confidence interval of the reference-scaled criterion was negative. The estimated sWR for Total DHA is less than 0.294 for Cmax and AUC0-72 obtained based on both baseline-adjusted and measured concentrations. Therefore, the un-scaled, average

bioequivalence approach was used for assessment of bioequivalence. The 90% confidence intervals of the test to reference ratio were entirely contained within the 80.00-125.00% bioequivalence range for both Cmax and AUC0-72 (Table 9).

*Free EPA:* The reference-scaled bioequivalence approach was used for the assessment of bioequivalence for the AUC0-72 (estimated sWR > 0.294). The average bioequivalence approach was used for the assessment of bioequivalence for Cmax (estimated sWR < 0.294). As shown in Table 10 below, using the baseline corrected data: for AUC0-72, the results satisfied the two criteria for demonstrating bioequivalence based on this method, the test/reference ratio was contained within the 80.00-125.00% range, and the upper 95% bound of the confidence interval of the reference-scaled criterion was negative.

For measured Free EPA data, the average bioequivalence approach was used for the assessment of bioequivalence for Cmax and AUC0-72 (estimated sWR < 0.294). ANOVA did not detect any significant treatment difference.

**Table 9 Statistical analysis results for Total DHA PK parameters**

<i>Total Lipids of Plasma</i>											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Total DHA Data</i>											
<b>AUC<sub>0-72</sub></b> ( $\mu\text{g}^*\text{h/mL}$ )	A <sub>1</sub>	83.85	66	N/A	A vs. B	101.08	N/A -	N/A	N/A	N/A	
	A <sub>2</sub>	73.46	85	N/A							
	B <sub>1</sub>	90.92	71	N/A							
	B <sub>2</sub>	98.15	72	N/A							
<b>Cmax</b> ( $\mu\text{g/mL}$ )	A <sub>1</sub>	6.09	83	N/A	A vs. B	103.51	N/A -	N/A	N/A	-0.310813	
	A <sub>2</sub>	5.20	49	N/A							
	B <sub>1</sub>	5.48	50	N/A							
	B <sub>2</sub>	5.65	32	N/A							
<i>Based on Measured Total DHA Data</i>											
<b>AUC<sub>0-72</sub></b> ( $\mu\text{g}^*\text{h/mL}$ )	A <sub>1</sub>	3452.06	31	3321.34	A vs. B	100.89	99.24 -	102.57	A: 7	N/A	
	A <sub>2</sub>	3472.59	33								
	B <sub>1</sub>	3441.36	31	3292.02					B: 7	0.076	
	B <sub>2</sub>	3430.52	32								
<b>Cmax</b> ( $\mu\text{g/mL}$ )	A <sub>1</sub>	54.04	34	51.63	A vs. B	101.57	99.59 -	103.58	A: 8	N/A	
	A <sub>2</sub>	53.92	33								
	B <sub>1</sub>	53.05	31	50.83					B: 8	0.089	
	B <sub>2</sub>	53.08	31								

[Treatment A1, A2: AKR-963 Fasted; B1, B2: Lovaza Fasted]

**Table 10 Statistical analysis results for Free EPA PK parameters**

<i>Free Fatty Acids of Plasma</i>													
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion		
		Arithmetic	CV%	Geometric			Lower	Upper					
<i>Based on Baseline-Adjusted Free EPA Data</i>													
AUC <sub>0-72</sub> (ng*h/mL)	A <sub>1</sub>	2332.5	85	N/A	A vs. B	94.86	N/A -	N/A	N/A	N/A	-0.113530		
	A <sub>2</sub>	2483.1	87										
	B <sub>1</sub>	2211.6	64	N/A								N/A	0.457
	B <sub>2</sub>	2527.2	55										
C <sub>max</sub> (ng/mL)	A <sub>1</sub>	134.9	59	114.0	A vs. B	101.63	95.29 -	108.40	A: 23	N/A	N/A		
	A <sub>2</sub>	131.2	73										
	B <sub>1</sub>	126.7	61									B: 23	0.229
	B <sub>2</sub>	133.0	51	112.2									
<i>Based on Measured Free EPA Data</i>													
AUC <sub>0-72</sub> (ng*h/mL)	A <sub>1</sub>	7601.6	63	6680.3	A vs. B	96.96	93.47 -	100.57	A: 15	N/A	N/A		
	A <sub>2</sub>	7538.7	65										
	B <sub>1</sub>	7616.7	50	6890.0								B: 15	0.153
	B <sub>2</sub>	7660.5	53										
C <sub>max</sub> (ng/mL)	A <sub>1</sub>	223.0	59	191.3	A vs. B	99.74	95.83 -	103.82	A: 16	N/A	N/A		
	A <sub>2</sub>	213.3	66										
	B <sub>1</sub>	217.2	56									B: 17	0.172
	B <sub>2</sub>	216.0	54	191.8									

[Treatment A1, A2: AKR-963 Fasted; B1, B2: Lovaza Fasted]

**Table 11 Statistical analysis results for Free DHA PK parameters**

<i>Free Fatty Acids of Plasma</i>													
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion		
		Arithmetic	CV%	Geometric			Lower	Upper					
<i>Based on Baseline-Adjusted Free DHA Data</i>													
AUC <sub>0-72</sub> (ng*h/mL)	A <sub>1</sub>	11716.7	62	N/A	A vs. B	93.82	N/A -	N/A	N/A	N/A	-0.111234		
	A <sub>2</sub>	12842.5	65										
	B <sub>1</sub>	12443.9	61	N/A								N/A	0.455
	B <sub>2</sub>	13958.6	54										
C <sub>max</sub> (ng/mL)	A <sub>1</sub>	611.7	45	562.1	A vs. B	100.10	94.90 -	105.59	A: 23	N/A	N/A		
	A <sub>2</sub>	622.5	52										
	B <sub>1</sub>	611.6	52									B: 22	0.224
	B <sub>2</sub>	638.7	45	561.5									
<i>Based on Measured Free DHA Data</i>													
AUC <sub>0-72</sub> (ng*h/mL)	A <sub>1</sub>	42385.4	47	39512.1	A vs. B	98.69	95.70 -	101.77	A: 12	N/A	N/A		
	A <sub>2</sub>	43912.4	46										
	B <sub>1</sub>	42796.6	43	40038.2								B: 13	0.144
	B <sub>2</sub>	44222.3	44										
C <sub>max</sub> (ng/mL)	A <sub>1</sub>	1127.3	45	1043.3	A vs. B	100.43	97.31 -	103.65	A: 13	N/A	N/A		
	A <sub>2</sub>	1138.0	47										
	B <sub>1</sub>	1130.4	46									B: 14	0.143
	B <sub>2</sub>	1127.3	45	1038.8									

[Treatment A1, A2: AKR-963 Fed; B1, B2: Lovaza Fed]

[Note: The units for C<sub>max</sub> and AUC for Free EPA (Table 10) and Free DHA (Table 11) are incorrectly reported as µg/mL and µg\*h/mL, respectively in the sponsor's tables in the study report, the table above reflects the corrected units]

*Free DHA*: The reference-scaled bioequivalence approach was used for the assessment of bioequivalence for the AUC<sub>0-72</sub> (estimated sWR > 0.294). The average bioequivalence approach was used for the assessment of bioequivalence for C<sub>max</sub> (estimated sWR < 0.294). As shown in Table 9 below, using the baseline corrected data: for AUC<sub>0-72</sub>, the results satisfied the two criteria for demonstrating bioequivalence based on this method, the test/reference ratio was contained within the 80.00-125.00% range, and the upper 95% bound of the confidence interval of the reference-scaled criterion was negative.

For measured Free DHA data, the average bioequivalence approach was used for the assessment of bioequivalence for C<sub>max</sub> and AUC<sub>0-72</sub> (estimated sWR < 0.294). ANOVA did not detect any significant treatment difference.

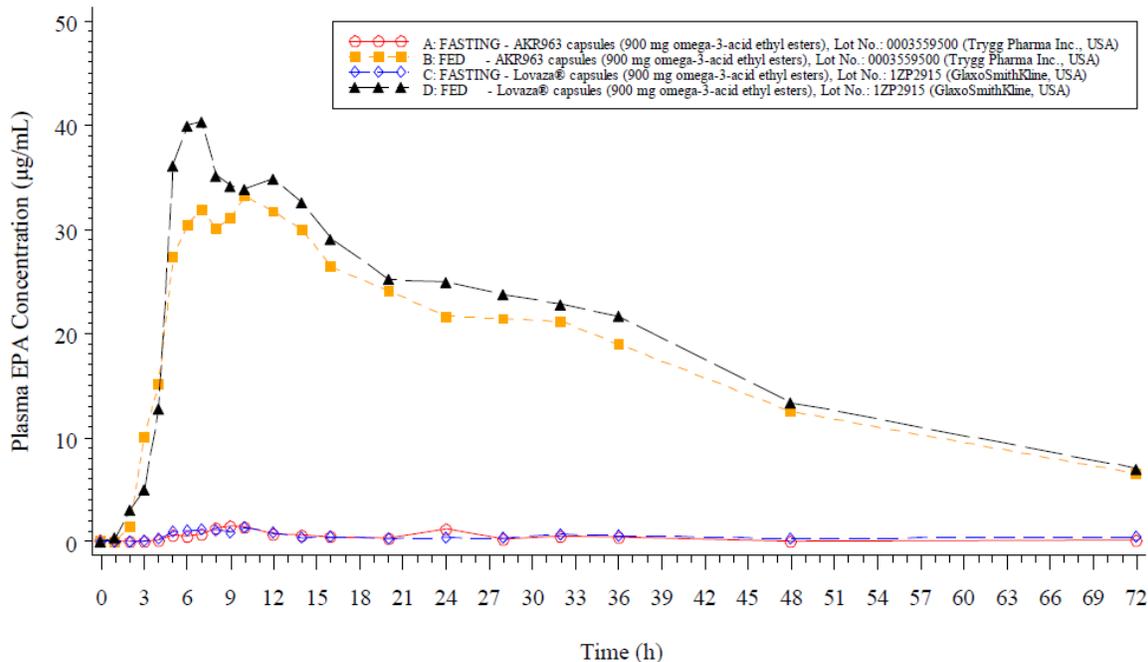
Therefore, based on the statistical analysis results, when both AKR-963 and Lovaza treatments were administered under fasted condition:

- The AKR-963 formulation was bioequivalent to the Lovaza formulation with regards to the AUC<sub>0-72</sub> and C<sub>max</sub> of Total Plasma EPA and Total Plasma DHA.
- The AKR-963 formulation was also bioequivalent to the Lovaza formulation with regards to the AUC<sub>0-72</sub> and C<sub>max</sub> of plasma Free EPA and Free DHA.

### **2.2.2 What is the effect of food on the bioavailability of EPA and DHA components from AKR-963 in reference to Lovaza®?**

A significant food effect on the bioavailability of baseline adjusted total plasma EPA and total plasma DHA was observed, perhaps for the first time, for both AKR-963 and Lovaza® formulations. Results from study TRGG-963-004 are discussed here, which was conducted to evaluate the comparative bioavailability between AKR-963 capsules and Lovaza® after a single-dose in healthy subjects under fasting and fed conditions. The secondary objective of this study was to evaluate the effect of food on the study medications. The mean plasma total EPA concentrations and pharmacokinetic parameters after administration of each of the four treatments are presented below in Figure 5 and Table 12, respectively.

Baseline-adjusted Mean Plasma Total EPA Concentration-time Profiles  
A, B & D: n = 15 / C: n = 14



**Figure 5 Mean baseline-adjusted plasma Total EPA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given with or without meal**

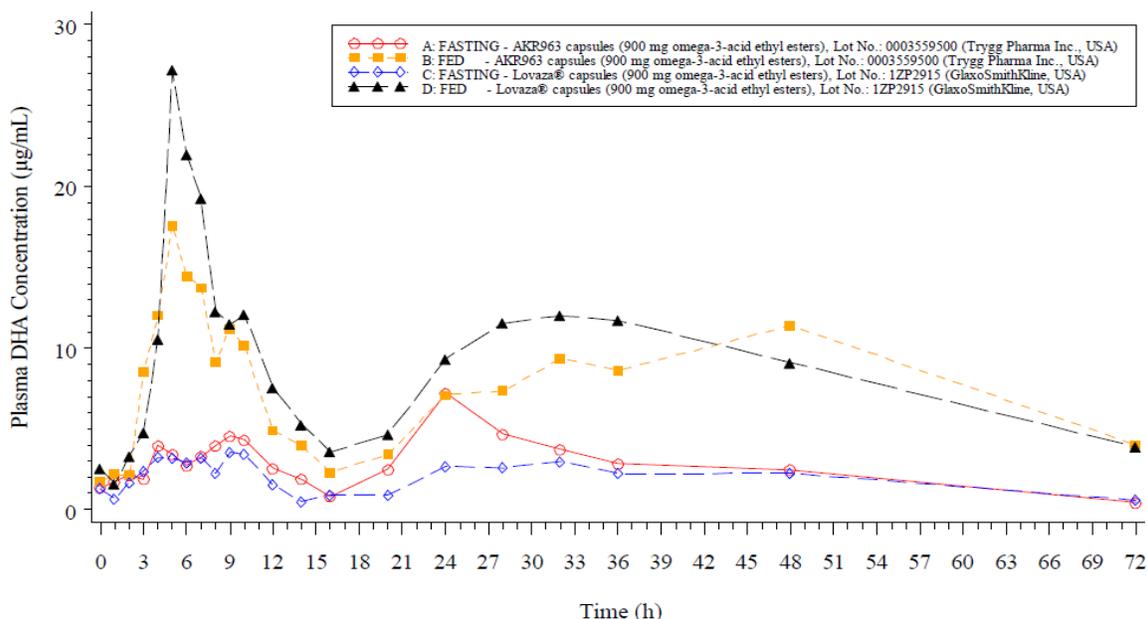
**Table 12 Summary of Study Results Based on Plasma Total EPA Levels.**

<i>Based on Baseline-adjusted Plasma Total EPA Concentrations</i>								
<i>Parameter</i>	<i>Trt</i>	<i>n</i>	<i>Arithmetic Mean (CV%)</i>	<i>Geometric Mean</i>	<i>Contrast</i>	<i>Ratio (%)</i>	<i>90% Confidence Interval</i>	<i>Intra-Sbj CV(%)</i>
<b>C<sub>max</sub></b> (µg/mL)	<b>A</b>	14	2.99 (152)	1.95	<b>A vs C</b>	92.46	57.44 - 148.83	77
	<b>B</b>	14	44.32 ( 44)	41.55	<b>B vs D</b>	84.05	54.22 - 130.28	77
	<b>C</b>	14	2.37 ( 67)	2.11	<b>B vs A</b>	2129.47	1341.00 - 3381.54	77
	<b>D</b>	14	50.89 ( 32)	49.44	<b>D vs C</b>	2342.64	1494.95 - 3670.98	77
<b>AUC<sub>72</sub></b> (µg.h/mL)	<b>A</b>	10	33.66 (127)	12.85	<b>A vs C</b>	60.90	29.01 - 127.83	117
	<b>B</b>	14	1217.03 ( 54)	1023.38	<b>B vs D</b>	78.30	43.04 - 142.46	117
	<b>C</b>	11	39.95 (105)	21.10	<b>B vs A</b>	7962.97	4022.87 - 15762.12	117
	<b>D</b>	14	1380.04 ( 45)	1306.91	<b>D vs C</b>	6192.99	3237.63 - 11846.08	117

[Treatment A: AKR-963 Fasted; B: AKR-963 Fed; C: Lovaza Fasted; D: Lovaza Fed]

The mean plasma total DHA concentrations and pharmacokinetic parameters after administration of each of the four treatments are presented below in Figure 6 and Table 13, respectively.

Baseline-adjusted Mean Plasma Total DHA Concentration-time Profiles  
A, B & D: n = 15 / C: n = 14



**Figure 6** Mean baseline-adjusted plasma Total DHA concentration-time profiles from single oral dose of AKR-963 or Lovaza formulations given with or without meal

**Table 13** Summary of Study Results Based on Plasma Total DHA Levels

<i>Based on Baseline-adjusted Plasma Total DHA Concentrations</i>								
<i>Parameter</i>	<i>Trt</i>	<i>n</i>	<i>Arithmetic Mean (CV%)</i>	<i>Geometric Mean</i>	<i>Contrast</i>	<i>Ratio (%)</i>	<i>90% Confidence Interval</i>	<i>Intra-Sbj CV(%)</i>
<b>C<sub>max</sub></b> (µg/mL)	<b>A</b>	14	12.81 (112)	9.54	<b>A vs C</b>	171.74	110.83 - 266.10	77
	<b>B</b>	14	25.38 (52)	23.05	<b>B vs D</b>	78.91	50.93 - 122.27	77
	<b>C</b>	14	7.01 (62)	5.55	<b>B vs A</b>	241.72	156.17 - 374.13	77
	<b>D</b>	14	31.22 (43)	29.21	<b>D vs C</b>	526.07	339.89 - 814.24	77
<b>AUC<sub>72</sub></b> (µg.h/mL)	<b>A</b>	14	167.50 (92)	107.72	<b>A vs C</b>	122.25	74.84 - 199.69	86
	<b>B</b>	14	510.38 (58)	436.14	<b>B vs D</b>	78.84	48.82 - 127.35	86
	<b>C</b>	13	119.53 (71)	88.12	<b>B vs A</b>	404.88	251.00 - 653.10	86
	<b>D</b>	14	586.35 (33)	553.16	<b>D vs C</b>	627.76	384.12 - 1025.94	86

[Treatment A: AKR-963 Fasted; B: AKR-963 Fed; C: Lovaza Fasted; D: Lovaza Fed]

**Table 14 Summary of Study Results Based on Measured Plasma Total EPA Levels.**

<i>Based on Measured Plasma Total EPA Concentrations</i>								
<i>Parameter</i>	<i>Trt</i>	<i>n</i>	<i>Arithmetic Mean (CV%)</i>	<i>Geometric Mean</i>	<i>Contrast</i>	<i>Ratio (%)</i>	<i>90% Confidence Interval</i>	<i>Intra-Sbj CV(%)</i>
<b>C<sub>max</sub></b> ( <i>µg/mL</i> )	<b>A</b>	14	21.23 ( 55)	18.97	<b>A vs C</b>	109.48	92.44 - 129.67	27
	<b>B</b>	14	60.92 ( 31)	58.48	<b>B vs D</b>	89.64	75.69 - 106.17	27
	<b>C</b>	14	18.70 ( 43)	17.32	<b>B vs A</b>	308.31	260.42 - 365.00	27
	<b>D</b>	14	67.40 ( 27)	65.23	<b>D vs C</b>	376.53	318.05 - 445.77	27
<b>AUC<sub>72</sub></b> ( <i>µg.h/mL</i> )	<b>A</b>	12	1221.60 ( 48)	1062.19	<b>A vs C</b>	109.77	96.74 - 124.57	18
	<b>B</b>	14	2386.24 ( 32)	2270.19	<b>B vs D</b>	92.22	82.32 - 103.32	18
	<b>C</b>	12	1119.15 ( 46)	967.61	<b>B vs A</b>	213.73	189.51 - 241.04	18
	<b>D</b>	14	2567.86 ( 28)	2461.68	<b>D vs C</b>	254.41	225.78 - 286.66	18

[Treatment A: AKR-963 Fasted; B: AKR-963 Fed; C: Lovaza Fasted; D: Lovaza Fed]

**Table 15 Summary of Study Results Based on Measured Plasma Total EPA Levels.**

<i>Based on Measured Plasma Total DHA Concentrations</i>								
<i>Parameter</i>	<i>Trt</i>	<i>n</i>	<i>Arithmetic Mean (CV%)</i>	<i>Geometric Mean</i>	<i>Contrast</i>	<i>Ratio (%)</i>	<i>90% Confidence Interval</i>	<i>Intra-Sbj CV(%)</i>
<b>C<sub>max</sub></b> ( <i>µg/mL</i> )	<b>A</b>	14	71.71 ( 39)	67.68	<b>A vs C</b>	106.38	96.20 - 117.64	16
	<b>B</b>	14	81.28 ( 28)	78.53	<b>B vs D</b>	94.77	85.70 - 104.79	16
	<b>C</b>	14	66.69 ( 36)	63.62	<b>B vs A</b>	116.03	104.95 - 128.27	16
	<b>D</b>	14	85.94 ( 30)	82.86	<b>D vs C</b>	130.25	117.81 - 143.99	16
<b>AUC<sub>72</sub></b> ( <i>µg.h/mL</i> )	<b>A</b>	14	4229.53 ( 32)	4053.25	<b>A vs C</b>	101.02	96.31 - 105.96	7
	<b>B</b>	14	4482.88 ( 27)	4334.62	<b>B vs D</b>	98.97	94.46 - 103.70	7
	<b>C</b>	13	4015.75 ( 30)	4012.32	<b>B vs A</b>	106.94	102.08 - 112.04	7
	<b>D</b>	14	4509.55 ( 26)	4379.69	<b>D vs C</b>	109.16	104.06 - 114.50	7

[Treatment A: AKR-963 Fasted; B: AKR-963 Fed; C: Lovaza Fasted; D: Lovaza Fed]

The overall conclusions of this study are as follows:

- Blood concentrations of baseline-adjusted Total EPA fatty acids indicate that significant bioavailability was only attained for both the reference drug (Lovaza) or AKR-963 when taken after a high fat meal. This is similar but not as pronounced for baseline-adjusted Total DHA fatty acids.
- Peak (C<sub>max</sub>) and total (AUC<sub>0-72h</sub>) exposure of baseline adjusted Total Plasma EPA was up to ~20-fold and ~60 to 80 fold higher, respectively for both AKR-

963 and Lovaza treatments when administered with high-fat meal in comparison to the fasted condition.

- Peak (C<sub>max</sub>) and total (AUC<sub>0-72h</sub>) exposure of baseline adjusted Total Plasma DHA was up to ~2 to 5 fold and ~4 to 6 fold higher, respectively for both AKR-963 and Lovaza treatments when administered with high-fat meal in comparison to the fasted condition.
- The absorption of EPA Ethyl-ester and DHA Ethyl-ester was negligible under fasting conditions.
- The maximum concentrations obtained for the Ethyl-ester compounds are substantially lower (EPA approximately 235 times and DHA approximately 35 times) when compared to the concentrations from the Total EPA and Total DHA fatty acids.

Although this was a pilot study with limited number of subjects (N~14) resulting in wide 90% confidence intervals for the geometric mean ratios, the results are highly relevant as discussed in section 2.2.3.

### **2.2.3 How are the results of relative BA trials of AKR-963 related to the efficacy/safety evaluation of AKR-963?**

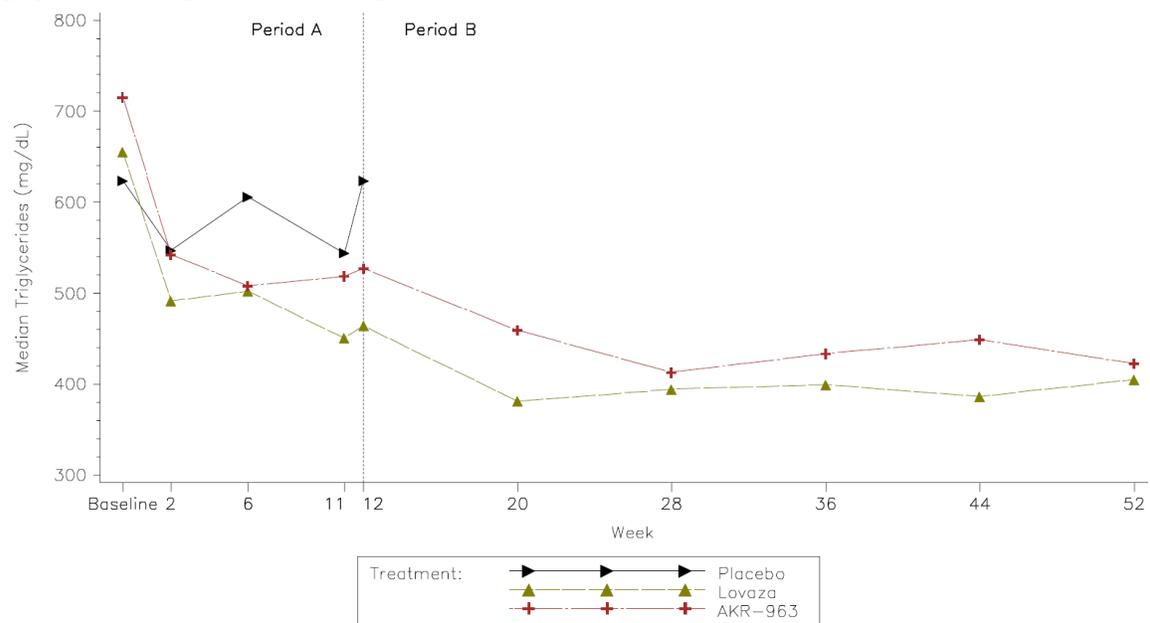
Efficacy and safety of AKR-963 was compared head to head against Lovaza and placebo in Phase 3 trial TRGG-963-002. This trial was a randomized, double-blind, placebo-controlled, parallel-group study to assess efficacy and safety of AKR-963 therapy in subjects with severe hypertriglyceridemia. The trial 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). During the diet lead-in period, subjects were to follow the National Cholesterol Education Program Therapeutic Lifestyle Changes diet. 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® (4 g/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. Randomization was stratified based upon baseline triglycerides (TG) (<750 mg/dL or ≥750 mg/dL), presence of diabetes (no diabetes, diabetes with hemoglobin A1c [HbA1c] <8.0%, or diabetes with HbA1c ≥8.0%), and concurrent statin use (yes or no). The summary of treatments administered is presented below in Table 16.

**Table 16 Summary of Treatments Administered**

Study Medication	Dose and Mode of Administration
AKR-963	3600 mg given as 4 capsules/day taken orally
Lovaza	3600 mg given as 4 capsules/day taken orally
Placebo	0 mg (vegetable oil) given as 4 capsules/day taken orally

(Note: Per Lovaza label this dose correspond to 4 g/day)

The primary outcome variable was the percent change in TG levels from baseline to the end of the first 12-week double-blind treatment period (Period A). The median triglyceride (mg/dL) over time profile by treatment, in modified intent-to-treat population, is presented in Figure 7 below:



**Figure 7 Median Triglycerides (mg/dL) Over Time – Modified Intent-to-Treat Population (TRGG-963-002)**

The reported key efficacy results from this trial were:

- Median baseline TG levels were 624.0 mg/dL for the placebo group, 655.3 mg/dL for the Lovaza group, and 701.5 mg/dL for the AKR-963 group.
- The median percent change in TG from baseline to Period A endpoint (Week 12) 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 Lovaza was -14.0%.

According to the approved Lovaza label<sup>2</sup>, in patients with Severe Hypertriglyceridemia ( $\geq 500$  mg/dL) the absolute median % change in TG was -44.9% (Baseline median TG of 816 mg/dL) for Lovaza and +6.7% for Placebo (Net difference from placebo of -51.6%). Although sponsor claimed non-inferiority of AKR-963 to Lovaza, the magnitude of efficacy was substantially lower for both test drug and comparator.

During the review Agency identified statistical issues with the efficacy results, and sent an information request to the sponsor (see Letter in DAARTS dated 05/21/2013) to explain “*why the treatment effects of AKR-963 and Lovaza were far less than expected when compared with placebo in this trial*”. Sponsor submitted their response on 07/03/2013 including the results of a revised statistical analysis defending their results.

While readers are referred to the Clinical and Statistical Review for more details on this issue, the sponsor’s conclusions from the revised statistical analysis and conclusive remarks are captured below:

- The estimated placebo-adjusted difference for Lovaza is -16.9%; 1-sided p = 0.002; 95% CI (-31.8%, -5.0%).
- The estimated placebo-adjusted difference for AKR-963 is -16.8%; 1-sided p = 0.005; 95% CI (-30.5%, -3.4%).
- The lower bound of the 95% confidence interval comparing AKR-963 to Lovaza is 8.7%.
- The p-value for the noninferiority test of AKR-963 to Lovaza under a hypothesized noninferiority margin of 10 is 0.013.

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<sup>2</sup> Lovaza® Label ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/021654s037lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021654s037lbl.pdf))

Based on the above analyses, as well as a comprehensive review of the data, Trygg believes the following conclusions can be reached in a valid fashion for consideration by DMEP in their review of the efficacy data in support of Trygg's 505(b)(2) NDA:

- The results of Study TRGG-963-002 need to be considered in the context of the bridging approach being used in the 505(b)(2) NDA.
- DMEP and Trygg agreed to the study design and statistical analysis plan that was the basis for the analysis and results of Study TRGG-963-002 that are described in NDA 204977. These results did, in fact, support the prespecified noninferiority margin of 15% (and, in fact, support a noninferiority margin of 10.5%) and demonstrated a statistically significant difference between active and placebo for both AKR-963 and Lovaza. The preplanned sensitivity analyses agreed to by DMEP support the robustness of these results.
- DMEP and Trygg agreed to the study design and statistical analysis plan that was the basis for the analysis and results of Study TRGG-963-002 that are described in NDA 204977. These results did, in fact, support the prespecified noninferiority margin of 15% (and, in fact, support a noninferiority margin of 10.5%) and demonstrated a statistically significant difference between active and placebo for both AKR-963 and Lovaza. The preplanned sensitivity analyses agreed to by DMEP support the robustness of these results. An additional sensitivity analysis was conducted by the sponsor to account for the complexities of the design of Study TRGG-963-002. The method makes no assumptions about the underlying distribution of the data. The calculations show mean placebo-adjusted differences of -16.9% (1-sided  $p = 0.002$ ) for Lovaza and -16.8% (1-sided  $p = 0.005$ ) for AKR-963. The lower bound of the 95% CI comparing AKR-963 to Lovaza is 8.7% with a 1-sided  $p$ -value of 0.013 when testing against a noninferiority margin of 10.0% (ie, continues to support a noninferiority at this level).
- The treatment responses for the primary end point in study TRGG-963 (percent change in triglycerides from baseline) were consistent with the results of contemporary controlled studies of omega-3 fatty acid products.
- The heterogeneity of the placebo response reported in the literature is a confounding factor in interpretation of double-blind omega-3 fatty acid studies in this therapeutic area.

In response to a separate information request (Dated 08/07/2013) the sponsor submitted (Dated 08/20/2013) the following explanations:

1. Please clarify the timing of daily treatment administration with respect to meals in your Phase 3 trial. Did subjects take the treatments at a consistent time relative to the time of breakfast (e.g. consistently with breakfast, prior to breakfast, or after breakfast)? If treatments were to be taken either before or after breakfast, how much time was there between the meal and treatment administration?

**Applicant's Response:** *“The overall goal of the AKR-963 clinical development program was to show therapeutic equivalence, and hence substitutability between AKR-963 and Lovaza.*

*The clinical non-inferiority study was designed to be reflective of “real life” and consistent with the dosing information on the Lovaza® label. The product label for Lovaza does not specify how the product has to be taken in relation to meals; therefore, this item was not specified in the study protocol. Other than*

*instructions to swallow 4 capsules in the morning every day, the protocol for study TRGG-963-002 was silent on when dosing should take place. The drug was taken when most convenient for the subject. It was also assumed that this would be a better way of ensuring compliance and again more reflective of a real life situation.”*

2. Specify the composition of diet recommended for the patients during the trial (for breakfast, lunch, and dinner)?

**Applicant’s Response:** *“There was no specified diet in the protocol for study TRGG-963-002 other than inclusion criteria of a willingness to follow a low-saturated fat diet throughout the study period. This was done intentionally to aid compliance and reduce drop-outs from the study. The subjects, however, received counseling on the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Change (TLC) diet (see protocol TRGG-963-002, appendix 1). This counseling and reinforcement occurred at every single visit except the last visit at week 52. In addition the subjects answered the MEDFICTS dietary questionnaire at week -6 (visit 1) and week 0 (visit 4) during the diet lead-in period and at week 12 and 52 (see protocol TRGG-963-002, appendix 2)”.*

If we put the question in another way as “How do the results of these relative BA studies relate to the observed clinical efficacy results for this application?” there are some relevant things to highlight:

- The two formulations are bioequivalent for total plasma EPA and DHA as well as EPA-EE and DHA-EE components both under high-fat diet and fasted conditions. This means that both the formulations could be expected to behave identically based on the conditions under which they will be administered. Considering the sponsor’s response to Question 1 above, these clinical pharmacology results may reasonably explain the observed results from trial TRGG-963-002 (treatment potentially under fasted, or occasionally fed?) in terms of lower mean response for both AKR-963 and Lovaza treatments, in comparison to the historical data from Lovaza clinical trials (conducted under fed condition). In fact, the Clinical Pharmacology results fully corroborate with the observed clinical results.
- In Phase 3 trials of Lovaza as well as Vascepa (NDA 202057), the treatments were administered with food. However, no food effect study was conducted by the respective sponsors. Sponsor acknowledged that reliable and measurable concentrations of EPA and DHA components were seen only under fed conditions for both AKR-963 and Lovaza. Presumably, this condition maximizes the hydrolysis and emulsification of the products, which in turn maximizes the post-dose increases in concentration as compared to the endogenous levels. However, this information came too late to become relevant for the Phase 3 design as the food effect study was conducted (Study initiation to completion: March 24, 2012 - May 08, 2012) towards

the end of the Phase 3 trial (Study initiation to completion: October 05, 2010 - July 20, 2012). Although from a simple exposure-response perspective, this would have been sufficient to specify the administration of treatments under fed condition in the Phase 3 trial. The exposure-response for plasma EPA and TG lowering has been observed for Vascepa (NDA202057). The food effect study TRGG-963-004 and the fed BE study TRGG-963-005 should have formed the guiding clinical pharmacology principals for the efficacy/safety evaluation.

- Nevertheless, the relevance of food effect cannot be neglected for omega 3 fatty acid ester based drugs. This reviewer recommends that AKR-963 should be administration under fed condition with the recommended diet in this population to maximize the efficacy.

## 2.3 Analytical

### 2.7.1 Are the analytical methods appropriately validated?

For Studies TRGG-963-004, 005, and 006, a sensitive LC/MS/MS method for the determination of total EPA and total DHA, Free EPA and Free DHA, and EPA-EE and DHA-EE in human plasma was developed and validated at [REDACTED] (b) (4), Bioanalytical Division. The method for Total EPA and Total DHA involved hydrolysis followed by protein precipitation. The standard calibration range was from 1.00 to 150 µg/mL for EPA and DHA, using plasma sample volume of 0.100 mL. Plasma samples were diluted, hydrolyzed and precipitated under acidic conditions with a mixture of organic solvents. Supernatant was diluted and 0.120 mL was transferred into polypropylene vials for LC-MS/MS analysis. The summary of the validation results are presented below in Tables 17, 18, and 19:

**Table 17 Summary of the Performance Characteristics of an LC/MS/MS Bioanalytical Method for Determination of Total EPA and Total DHA**

Validation Aspect	Method Parameter	Result/Specification	
Matrix	Type	Human plasma in K <sub>2</sub> EDTA	
	Volume	(b) (4) mL	
Concentrations for EPA	LLOQ	(b) (4) µg/mL	
	Concentration range	(b) (4) µg/mL	
Concentrations for DHA	LLOQ	(b) (4) µg/mL	
	Concentration range	(b) (4) µg/mL	
EPA accuracy and precision	LLOQ intraday	Precision	≤ 6.1%
		Accuracy	93.0%-105.0%
	LLOQ interday	Precision	5.7%
		Accuracy	100.0%
DHA accuracy and precision	LLOQ intraday	Precision	≤ 5.4%
		Accuracy	94.8%-107.0%
	LLOQ interday	Precision	5.3%
		Accuracy	102.0%
Stability in human plasma	Freeze-thaw	3 cycles at -80°C ± 15°C	
Stability in human plasma and in dilution solvent and buffer	Bench top	20.50 h at room temperature	
	Refrigerated	19.75 h at 5°C ± 3°C	
Stability of processed samples	Autosampler	159.50 h at approximately 5°C	
	Storage stability	120.25 h at approximately 5°C	
Stability in stock solutions (short-term)	EPA and DHA	6 h at room temperature	
	Internal standard	6 h at room temperature	
Recovery	EPA	91.1%-103.9%	
	DHA	95.6%-104.2%	
	Internal standard	99.2%	
Selectivity	Not applicable		
Matrix effect	EPA	Precision	≤ 7.5%
		Accuracy	90.3%-98.2%
	DHA	Precision	≤ 3.5%
		Accuracy	95.7%-100.8%

LLOQ = Lower limit of quantitation.

The method for determination of Free EPA and Free DHA involved protein precipitation. The standard calibration range was from 10.0 to 2500 ng/mL and 10.0 to 5000 ng/mL for EPA and DHA respectively using a plasma sample volume of 0.100 mL. Plasma samples were precipitated under acidic conditions with a mixture of organic solvents. 0.150 mL of supernatant was transferred into polypropylene vials for LC-MS/MS analysis.

**Table 18 Summary of the Performance Characteristics of an LC/MS/MS Bioanalytical Method for Determination of Free EPA and Free DHA**

Validation Aspect	Method Parameter	Result/Specification	
Matrix	Type	Human plasma in K <sub>2</sub> EDTA	
	Volume	(b) (4) mL	
Concentrations for EPA	LLOQ	(b) (4) ng/mL	
	Concentration range	(b) (4) ng/mL	
Concentrations for DHA	LLOQ	ng/mL	
	Concentration range	(b) (4) ng/mL	
EPA accuracy and precision	LLOQ intraday	Precision	≤ 4.8%
		Accuracy	99.0%-114.0%
	LLOQ interday	Precision	6.6%
		Accuracy	107.0%
DHA accuracy and precision	LLOQ intraday	Precision	≤ 3.1%
		Accuracy	100.0%-104.0%
	LLOQ interday	Precision	3.3%
		Accuracy	101.0%
Stability in human plasma	Freeze-thaw	6 cycles at -80°C ± 15°C	
Stability in human plasma and in dilution solvent and buffer	Bench top	21.7 h on ice 4.25 h at room temperature	
	Refrigerated	21.5 h at 5°C ± 3°C	
Stability of processed samples	Autosampler	38.50 h at approximately 5°C	
	Extracted samples	172.75 h at approximately 5°C	
Working solution stability	Internal standard	20.25 h at room temperature	
		89.75 h at -25°C ± 10°C	
Recovery	EPA	115.8%-122.3%	
	DHA	108.5%-119.4%	
	Internal standard for EPA	117.1%	
	Internal standard for DHA	110.0%	
Selectivity	Not applicable		
Matrix effect	EPA	Precision	≤ 3.0%
		Accuracy	102.2%-114.0%
	DHA	Precision	≤ 2.9 %
		Accuracy	98.0%-100.9%
LLOQ = Lower limit of quantitation.			

The analytical method for EPA-EE and DHA-EE involved liquid-liquid extraction. The standard calibration range was from 0.250 to 500 ng/mL for EPA-EE and 0.500 to 1000 ng/mL for DHA-EE, respectively using a plasma sample volume of 0.200 mL. Plasma samples were extracted under basic conditions with an organic solvent, the organic phase was then dried. The remaining residue was then reconstituted in reconstitution solvent and 0.125 mL of the aqueous layer was transferred into polypropylene vials for LC-MS/MS analysis.

**Table 19 Summary of the Performance Characteristics of an LC/MS/MS Bioanalytical Method for Determination of EPA-EE and DHA-EE**

Validation Aspect	Method Parameter	Result/Specification	
Matrix	Type	Human plasma in K <sub>2</sub> EDTA	
	Volume	(b) (4) mL	
Concentrations for EPA-EE	LLOQ	ng/mL	
	Concentration range	(b) (4) g/mL	
Concentrations for DHA-EE	LLOQ	ng/mL	
	Concentration range	(b) (4) ng/mL	
EPA-EE accuracy and precision	LLOQ intraday	Precision	≤ 9.9%
		Accuracy	95.2%-96.8%
	LLOQ interday	Precision	7.0%
		Accuracy	95.6%
DHA-EE accuracy and precision	LLOQ intraday	Precision	≤ 6.5%
		Accuracy	98.4%-103.8%
	LLOQ interday	Precision	5.8%
		Accuracy	100.4%
Stability in human plasma	Freeze-thaw	4 cycles at -80°C ± 15°C	
	Bench top	3 h at room temperature	
	Refrigerated	19.00 h at 5°C ± 3°C	
Stability in human whole blood		1.00 h on ice	
Stability of processed samples	Autosampler	28.50 h at approximately 5°C	
	Storage stability of reconstituted samples	89.75 h at approximately 5°C	
	Storage stability of evaporated samples	17.75 h at 5°C ± 3°C	
Stability in stock solutions (short-term)	EPA-EE and DHA-EE	6 h at room temperature	
	Internal standards	6 h at room temperature	
Recovery	EPA-EE	65.2%-67.3%	
	DHA-EE	56.5%-59.9%	
	Internal standard for EPA-EE	75.4%	
	Internal standard for DHA-EE	63.2%	
Selectivity	Test met acceptance criteria		
Matrix effect	EPA-EE	Precision	≤ 5.5%
		Accuracy	105.9%-108.3%
	DHA-EE	Precision	≤ 4.1%
		Accuracy	101.3%-101.8%

LLOQ = Lower limit of quantitation.

The assay methods were adequately validated and covered the observed concentrations ranges of Total plasma EPA and DHA, free EPA and DHA, as well as EPA-EE and DHA-EE in the clinical pharmacology studies TRGG-963-004, -005, and -006.

### 3 Preliminary Labeling Comments

**Note:** Labeling Comments are provided for specific sections in the proposed label. The underlined **RED** text indicates added text and ~~strike through~~ text indicates recommended deletion.

#### 1. Under Highlights

##### -----DOSAGE AND ADMINISTRATION -----

The daily dose of OMTRYG is 4 capsules per day taken as a single 4-capsule dose or as two 2-capsule doses (two capsules given twice daily). **OMTRYG should be taken with meals. (2)**

#### 12.3 Pharmacokinetics

Systemic Bioavailability: [REDACTED] (b) (4)

**When OMTRYG was administered under fasted condition, on average the peak (C<sub>max</sub>) and total (AUC<sub>0-72h</sub>) exposure were lower by up to 20 to 80-fold, respectively for total plasma EPA, and lower by up to 2 to 4-fold, respectively for total plasma DHA in comparison to those observed under fed condition (high-fat high-calorie meal). Therefore, OMTRYG should be taken with food.**

In healthy volunteers and in patients with hypertriglyceridemia, EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters.

Specific Populations: *Age:* Uptake of EPA and DHA into serum phospholipids in subjects treated with omega-3-acid ethyl esters was independent of age (<49 years versus ≥49 years).

*Gender:* Females tended to have more uptake of EPA into serum phospholipids than males. The clinical significance of this is unknown.

*Pediatric:* Pharmacokinetics of [REDACTED] (b) (4)

*Renal or Hepatic Impairment:* [REDACTED] (b) (4) has not been studied in patients with renal or hepatic impairment.

Drug-Drug Interactions: *Simvastatin:* In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg with omega-3-acid ethyl esters [REDACTED] (b) (4) did not affect the extent (AUC) or rate (C<sub>max</sub>) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.

*Atorvastatin:* in a 14-day study of 50 healthy adult subjects, daily co-administration of atorvastatin 80 mg with omega-3-acid ethyl esters (b)(4) did not affect AUC or C<sub>max</sub> of exposure to atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin at steady state.

*Rosuvastatin:* In a 14-day study of 48 healthy adult subjects, daily co-administration of rosuvastatin 40 mg with omega-3-acid ethyl esters (b)(4) did not affect AUC or C<sub>max</sub> of exposure to rosuvastatin at steady state.

*In vitro* studies using human liver microsomes indicated that clinically significant cytochrome P450 mediated inhibition by EPA/DHA combinations are not expected in humans.

## 4 Appendix

### 4.1 Individual Study Synopses as Reported

#### 4.1.1 Relative BA Study - Food Effect (TRGG-963-004)

<b>Name of Sponsor:</b> <i>Trygg Pharma Inc.</i>	
<b>Name of Finished Product:</b> <i>AKR-963 (omega-3-acid ethyl esters) capsules</i>	
<b>Name of Active Ingredient:</b> <i>omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>	
<b>Title of Study:</b> A Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters Capsules under Fasting and Fed Conditions	
<b>Investigators:</b> Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C) Tomislav Buconjic, M.D., M.Sc., CCFP Andrea S. Gershon, M.D., FRCP(C), M.Sc. Carol Townsley, M.D., M.Sc., CCFP	
<b>Study Centre(s):</b>	
<b>Clinical Facility:</b>	Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6
<b>Clinical Laboratory:</b>	Alpha Laboratories Incorporated 1262 Don Mills Road North York, Ontario, Canada, M3B 2W7
<b>Analytical, Pharmacokinetic, Statistical and Report Issuing Facility:</b>	(b) (4)
<b>Study Periods:</b> <ul style="list-style-type: none"><li>• Period 1: March 24, 2012</li><li>• Period 2: April 07, 2012</li><li>• Period 3: April 21, 2012</li><li>• Period 4: May 05, 2012</li></ul>	<b>Phase of Development: I</b>
<b>Objective:</b> The primary objective of this study was to evaluate the comparative bioavailability between: <ul style="list-style-type: none"><li>• AKR-963 (omega-3-acid ethyl-esters) capsules from Trygg Pharma Inc., USA and</li><li>• Lovaza® capsules from GlaxoSmithKline, USA</li></ul> after a single-dose in healthy subjects under fasting and fed conditions.  The secondary objective of this study was to evaluate the effect of food on the study medications.	

<i>Name of Sponsor: Trygg Pharma Inc.</i>
<i>Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules</i>
<i>Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>
<b>Duration of treatment:</b> Single-dose treatment
<b>Criteria for Evaluation:</b>  <b>Pharmacokinetic:</b> All pharmacokinetic parameters are determined from plasma concentration data. <ul style="list-style-type: none"> <li>• Total EPA and Total DHA: AUC72, Cmax, Tmax (measured &amp; baseline-adjusted data)</li> <li>• EPA Ethyl-ester and DHA Ethyl-ester: AUCt, AUCinf, Cmax, Tmax, Kel, Thalf (measured data)</li> </ul> <b>Safety:</b> Subject safety was monitored throughout the study. Adverse event and vital signs information were documented. There was no formal safety analysis planned for this study.
<b>Statistical Methods:</b> Descriptive statistics are estimated for the pharmacokinetic parameters in each treatment.  Analysis of variance (ANOVA) was performed on log-transformed AUC72, AUCt, AUCinf and Cmax and on untransformed Tmax parameters. The significance of the sequence, period, treatment, and subject-within-sequence effects were tested.  The least-squares means, the differences between the treatments least-squares means, and the corresponding standard errors of these differences were estimated for log-transformed AUC72, AUCt, AUCinf and Cmax parameters.  Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated, as data permitted, for the following comparisons:  Total EPA and Total DHA <ul style="list-style-type: none"> <li>• Treatments A versus C (comparative bioavailability - fasting)</li> <li>• Treatments B versus D (comparative bioavailability - fed)</li> <li>• Treatments B versus A (food effect - test product)</li> <li>• Treatments D versus C (food effect - reference product)</li> </ul> EPA Ethyl-ester and DHA Ethyl-ester <ul style="list-style-type: none"> <li>• Treatments B versus D (comparative bioavailability - fed)</li> </ul> These statistics were used to evaluate the performance of the test formulation in relation to the reference product and the effect of food on the test and reference products.

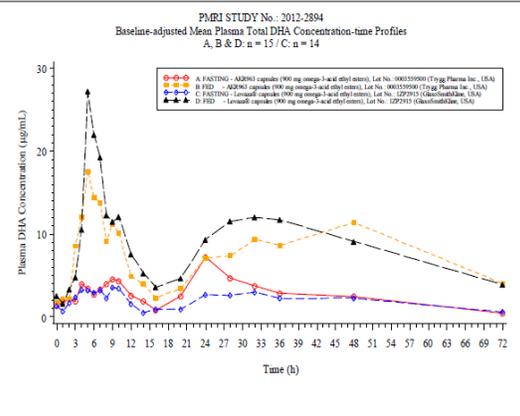
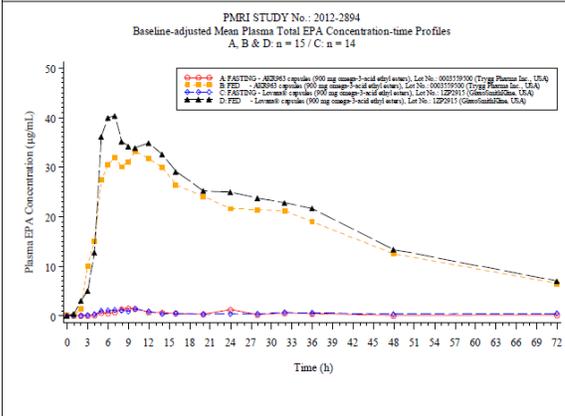
Name of Sponsor: Trygg Pharma Inc.

Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules

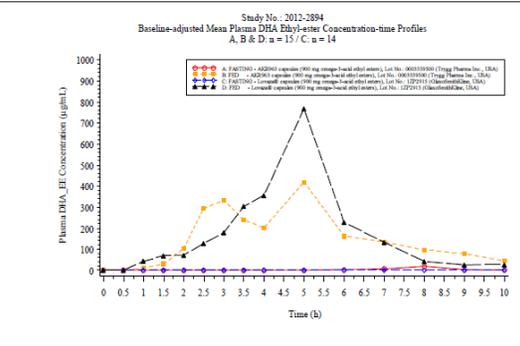
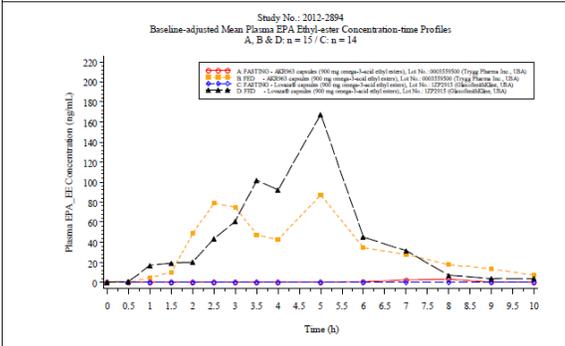
Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

**Summary-Conclusions:  
Pharmacokinetic Results:**

The following figure on the left highlights the finding that, in terms of comparative bioavailability, there is substantial absorption of EPA fatty acids in the fed state for both the innovator product (Lovaza) as well as AKR-963 compared to the fasting administration. This was also the case with DHA fatty acids (the following figure on the right) but to a lesser extent. Any further meaningful distinction in these profiles is difficult to interpret because of the large intra-subject variability. The coefficient of variation [CV] is as follows: EPA – Cmax (77%), AUC72 (117%) and DHA – Cmax (77%), AUC (86%).



The following figures (EPA Ethyl-esters on the left and DHA Ethyl-esters on the right) demonstrates that the pattern described above with the EPA and DHA fatty acids is similar for the respective ethyl esters of these fatty acids although at almost three orders of magnitude lower plasma concentrations. Also of note is the difference in the time course of the ethyl esters which appear to peak and then approach baseline levels within approximately 10 h post-dose.



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<b>Name of Sponsor:</b> <i>Trygg Pharma Inc.</i>
<b>Name of Finished Product:</b> <i>AKR-963 (omega-3-acid ethyl esters) capsules</i>
<b>Name of Active Ingredient:</b> <i>omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>
<p><b>Safety Results:</b></p> <p>There were no deaths, Serious Adverse Events (SAEs), or other significant adverse events in the study. All the reported AEs were mild and of the few reported AEs (a total of 19 AEs reported by 9 of the 16 subjects), there were no clinically relevant treatment differences. There were no clinically significant, treatment-emergent changes in clinical laboratory parameters, vital signs, or other physical examination findings for any subject in the trial.</p> <p>The overall conclusions of this study are as follows:</p> <ul style="list-style-type: none"> <li>• Blood concentrations of baseline-adjusted Total EPA fatty acids indicate that significant bioavailability is only attained for both the reference drug (Lovaza) or AKR-963 when taken after a high fat meal. This is similar but not as pronounced for baseline-adjusted Total DHA fatty acids.</li> <li>• The absorption of EPA Ethyl-ester and DHA Ethyl-ester is negligible under fasting conditions.</li> <li>• The maximum concentrations obtained for the Ethyl-ester compounds are substantially lower (EPA approximately 235 times and DHA approximately 35 times) when compared to the concentrations from the Total EPA and Total DHA fatty acids.</li> <li>• The timeframe for changes in EPA Ethyl-ester and DHA Ethyl-esters plasma concentrations was approximately 10 hours post-dose versus the approximately 72 hours for the baseline-adjusted Total EPA and Total DHA fatty acids. Although it is anticipated that that concentrations of these Ethyl-ester analytes can be obtained after 10 hours.</li> <li>• While all analytes (Total EPA and EPA Ethyl-ester and Total DHA and DHA Ethyl-ester) had low test-to-reference ratios, the limited sample size and high variability of this study may lead to an inadequate conclusion regarding the true mean values and the intra-subject variability.</li> <li>• Both treatments under either fasted or fed conditions were well tolerated by all subjects in the study.</li> </ul>
<b>Date of Report:</b> Final Report Version 2: December 2012

#### 4.1.2 Definite BE Study Under Fed Condition (TRGG-963-005)

<i>Name of Sponsor: Trygg Pharma Inc.</i>	
<i>Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules</i>	
<i>Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>	
<b>Title of Study:</b> A Replicate, Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters Capsules under Fed Conditions	
<b>Investigators:</b> Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C) Tomislav Buconjic, M.D., M.Sc., CCFP Andrea S. Gershon, M.D., FRCP(C), M.Sc. Robert C. Wu, M.D., FRCP (C), M.Sc.	
<b>Study Centre(s):</b> <b>Clinical Facility:</b> Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6 <b>Clinical Laboratory:</b> Alpha Laboratories Incorporated 1262 Don Mills Road North York, Ontario, Canada, M3B 2W7 <b>Analytical, Pharmacokinetic, Statistical and Report Issuing Facility:</b> <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span>	
<b>Study Periods:</b> <ul style="list-style-type: none"> <li>• Period 1: April 29, 2012</li> <li>• Period 2: May 13, 2012</li> <li>• Period 3: May 27, 2012</li> <li>• Period 4: June 10, 2012</li> </ul>	<b>Phase of Development: I</b>
<b>Objective:</b> The objective of this study was to evaluate the comparative bioavailability between: <ul style="list-style-type: none"> <li>• AKR-963 (omega-3-acid ethyl-esters) capsules from Trygg Pharma Inc., USA and</li> <li>• Lovaza® capsules from GlaxoSmithKline, USA,</li> </ul> after a single-dose in healthy subjects under fed conditions.	

<i>Name of Sponsor: Trygg Pharma Inc.</i>
<i>Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules</i>
<i>Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>
<p><b>Methodology:</b></p> <ul style="list-style-type: none"> <li>• This is an open-label, single-dose, randomized, 4-period, 2-sequence, 2-treatment, replicate, crossover study, designed to evaluate the comparative bioavailability of two formulations of omega-3 fatty acid ethyl esters, administered to healthy male and female subjects under fed conditions.</li> <li>• Subjects were randomly assigned to one of the two dosing sequences ABAB or BABA under fed conditions.</li> <li>• 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.</li> </ul>
<p><b>Number of subjects (planned and analyzed):</b></p> <ul style="list-style-type: none"> <li>• Forty-four (44) subjects were dosed in Period 1. All 44 subjects are included in the safety dataset.</li> <li>• Thirty-seven (37) subjects completed all periods of the study.</li> <li>• Thirty-nine (39) subjects are included in the pharmacokinetic and statistical analyses. <ul style="list-style-type: none"> <li>○ Subject 09 (BABA) and Subject 18 (BABA) completed Periods 1, 2, and 3 of the study. Both subjects completed at least two periods of the study taking the reference product twice, thus, were included in the pharmacokinetic analysis and the statistical analysis.</li> </ul> </li> </ul>
<p><b>Main criteria for inclusion:</b>  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/m<sup>2</sup>, who were judged to be healthy based on a medical history, ECG, laboratory evaluation and physical examination and vital signs measurements.</p>
<p><b>Test Product (Treatment A):</b>  AKR-963 (omega-3-acid ethyl esters) capsules  (Trygg Pharma Inc., USA)  Lot No.: 0003559500  Expiry Date: 5/2013  Dose: 4 capsules  Mode of Administration: Oral under fed conditions</p>
<p><b>Test Product (Treatment B):</b>  Lovaza® capsules  (GlaxoSmithKline, USA)  Lot No.: 1ZP2915  Expiry Date: 9/2014  Dose: 4 capsules  Mode of Administration: Oral under fed conditions</p>

<i>Name of Sponsor: Trygg Pharma Inc.</i>
<i>Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules</i>
<i>Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>
<b>Duration of treatment:</b> Single-dose treatment
<b>Criteria for Evaluation:</b>  <b>Pharmacokinetic:</b> All pharmacokinetic parameters are determined from measured and baseline-adjusted plasma concentration data: <ul style="list-style-type: none"> <li>Total EPA, Total DHA, Free EPA, and Free DHA: AUC72, Cmax, Tmax</li> <li>EPA Ethyl-ester and DHA Ethyl-ester: AUCt, AUCinf, Cmax, Tmax, Kel, Thalf</li> </ul> Free EPA and Free DHA were measured and presented for information only. <b>Safety:</b> Subject safety was monitored throughout the study. Adverse event and vital signs information were documented. There was no formal safety analysis planned for this study.
<b>Statistical Methods:</b> Descriptive statistics are estimated for the pharmacokinetic parameters in each treatment.  Analysis of variance (ANOVA) was performed on the log-transformed (natural logarithm) AUC72, AUCt, AUCinf, and Cmax parameters using PROC MIXED in SAS®. The significance of the sequence, period, treatment, and subject-within-sequence effects were tested.  For each pharmacokinetic parameter, estimates were obtained for the treatment mean values, $\mu_T$ and $\mu_R$ , for the difference between the treatment means with the corresponding 90% confidence interval, and for the within-subject variance for the reference treatment ( $\sigma_{WR}^2$ ).  The estimate of the within-subject standard deviation for the reference drug product ( $s_{WR}$ ) defined the bioequivalence approach and criterion that was used for the assessment of AUC72, AUCt, AUCinf, and Cmax: <ul style="list-style-type: none"> <li>If <math>s_{WR} &lt; 0.294</math>: the standard, unscaled average bioequivalence approach (ABE) was used. <i>Bioequivalence criterion:</i> The 90% confidence interval of the ratio of geometric means of the test to reference product should be within 80.00–125.00%.</li> <li>If <math>s_{WR} \geq 0.294</math>: the reference-scaled average bioequivalence approach (RSABE) was used. <i>Bioequivalence criteria:</i> <ol style="list-style-type: none"> <li>The ratio of geometric means of the test to reference product should be within 80.00–125.00%.</li> <li>The upper 95% bound of the confidence interval for the expression <math>(\bar{Y}_T - \bar{Y}_R)^2 - \theta \cdot s_{WR}^2</math> should be negative or equal to zero (<math>\leq 0</math>).</li> </ol> </li> </ul> The bioequivalence assessment was based on the AUC72, AUCt, AUCinf, and Cmax.

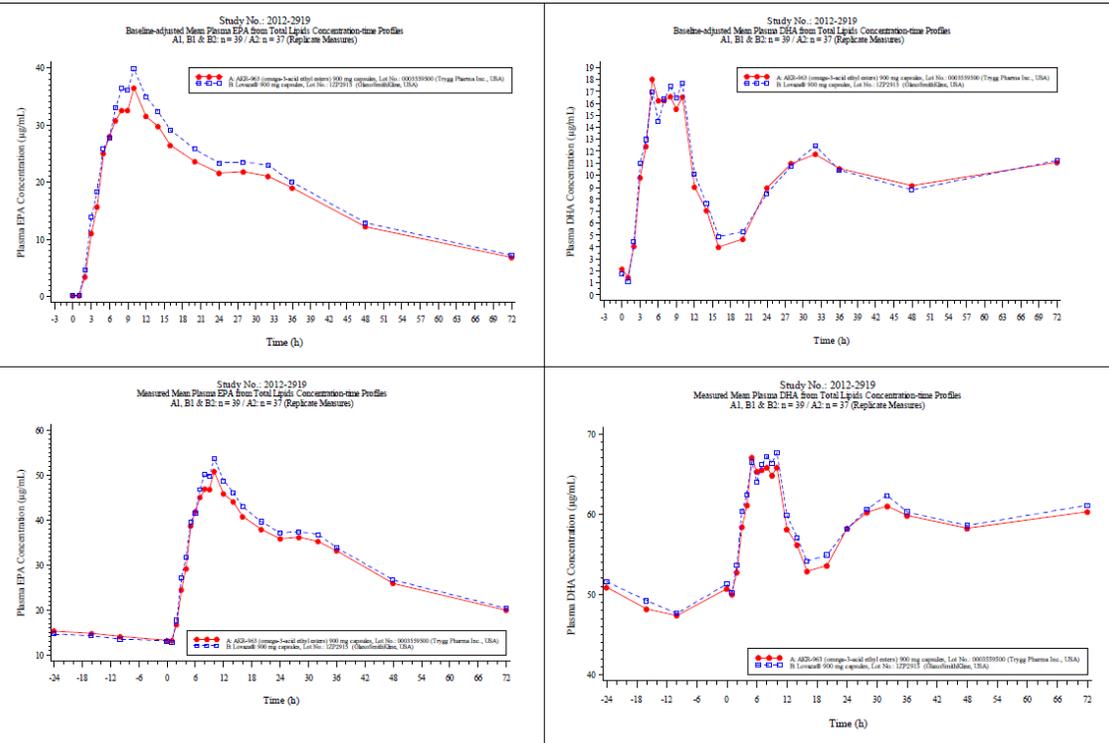
Name of Sponsor: Trygg Pharma Inc.

Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules

Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

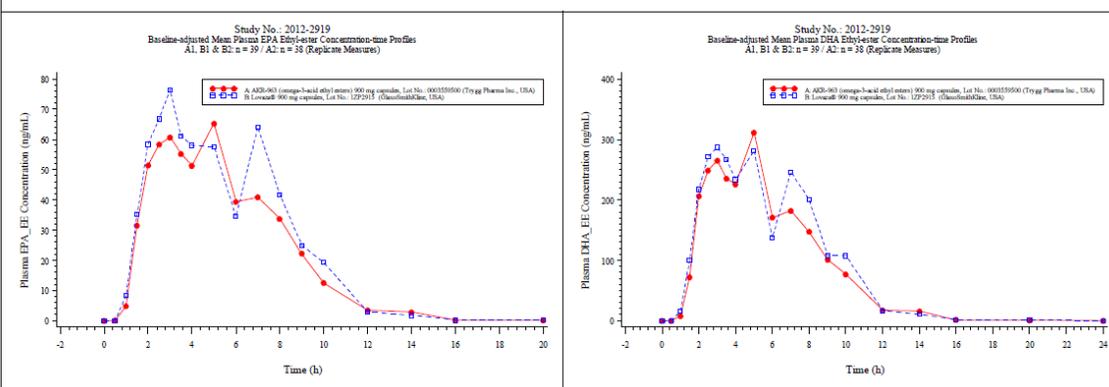
**Summary-Conclusions:**  
**Pharmacokinetic Results:**

The following figures summarize the similarities between the two treatments for mean plasma concentration-time profiles of the baseline-adjusted EPA from Total Lipids (top left panel), DHA from Total Lipids (top right panel), measured EPA from Total Lipids (bottom left panel), and measured DHA from total Lipids (bottom right panel).



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, as well as the corresponding EPA Ethyl-ester (top left panel) and DHA Ethyl-ester (top right panel)

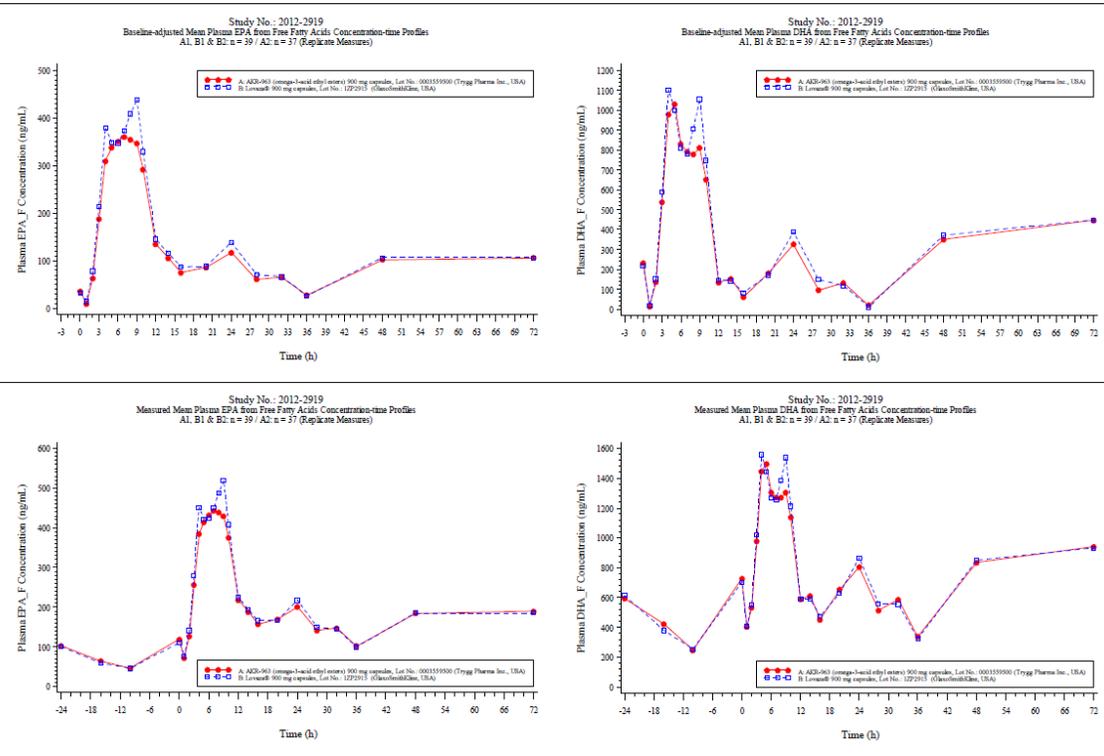


Name of Sponsor: Trygg Pharma Inc.

Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules

Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

The same similarity was observed in the mean concentration time profiles of the EPA and DHA from Free Fatty Acids: baseline-adjusted (first row) or measured (second row).



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The following tables provide a summary results of the pharmacokinetic and statistical analyses for the EPA and DHA from:

- Total Lipids of Plasma
- Ethyl-esters
- Free Fatty Acids of Plasma

Name of Sponsor: Trygg Pharma Inc.

Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules

Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

Total Lipids of Plasma											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Total EPA Data</i>											
AUC <sub>0-72</sub> (µg* <i>h</i> /mL)	A <sub>1</sub>	1218.16	41	1144.40	A vs. B	91.22	84.48 - 98.49	A: 36	N/A	N/A	
	A <sub>2</sub>	1259.32	31								
	B <sub>1</sub>	1345.60	33	1254.56							
	B <sub>2</sub>	1325.03	34								
Cmax (µg/mL)	A <sub>1</sub>	44.79	33	44.97	A vs. B	89.78	85.35 - 94.43	A: 21	N/A	N/A	
	A <sub>2</sub>	49.50	36								
	B <sub>1</sub>	53.37	34	50.09							
	B <sub>2</sub>	51.41	30								
<i>Based on Measured Total EPA Data</i>											
AUC <sub>0-72</sub> (µg* <i>h</i> /mL)	A <sub>1</sub>	2223.60	33	2161.23	A vs. B	96.68	93.96 - 99.48	A: 8	N/A	N/A	
	A <sub>2</sub>	2264.66	32								
	B <sub>1</sub>	2316.12	30	2235.40							
	B <sub>2</sub>	2335.85	31								
Cmax (µg/mL)	A <sub>1</sub>	59.31	31	59.13	A vs. B	92.92	89.34 - 96.64	A: 15	N/A	N/A	
	A <sub>2</sub>	63.79	33								
	B <sub>1</sub>	66.94	31	63.64							
	B <sub>2</sub>	65.65	30								

Total Lipids of Plasma											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Total DHA Data</i>											
AUC <sub>0-72</sub> (µg* <i>h</i> /mL)	A <sub>1</sub>	664.62	34	667.74	A vs. B	103.88	94.40 - 114.32	A: 24	N/A	N/A	
	A <sub>2</sub>	754.79	35								
	B <sub>1</sub>	696.49	39	642.79							
	B <sub>2</sub>	728.11	41								
Cmax (µg/mL)	A <sub>1</sub>	25.95	43	26.40	A vs. B	91.01	84.58 - 97.94	A: 29	N/A	N/A	
	A <sub>2</sub>	32.49	49								
	B <sub>1</sub>	31.06	47	29.01							
	B <sub>2</sub>	31.97	36								
<i>Based on Measured Total DHA Data</i>											
AUC <sub>0-72</sub> (µg* <i>h</i> /mL)	A <sub>1</sub>	4142.03	26	4138.54	A vs. B	99.16	97.66 - 100.68	A: 6	N/A	N/A	
	A <sub>2</sub>	4362.48	28								
	B <sub>1</sub>	4189.26	25	4173.73							
	B <sub>2</sub>	4409.73	26								
Cmax (µg/mL)	A <sub>1</sub>	74.33	27	75.95	A vs. B	96.10	93.29 - 98.99	A: 13	N/A	N/A	
	A <sub>2</sub>	82.68	30								
	B <sub>1</sub>	79.72	26	79.03							
	B <sub>2</sub>	83.19	27								

The variability of both EPA and DHA from Total Lipids was low. The intra-subject-within-reference standard deviation, s<sub>WR</sub>, was lower than the cutoff value of 0.294 and therefore the standard average bioequivalence method was used.

The 90% confidence intervals for baseline-adjusted and measured AUC<sub>72</sub> and Cmax parameters are within the 80.00-125.00% bioequivalence range for both EPA and DHA.

**Name of Sponsor:** Trygg Pharma Inc.

**Name of Finished Product:** AKR-963 (omega-3-acid ethyl esters) capsules

**Name of Active Ingredient:** omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

For both EPA Ethyl-esters and DHA Ethyl-esters, the ratio of the geometric means of the test to reference product for AUCt, AUCinf, and Cmax were all within the 80.00-125.00% range and the upper 95% bound of the confidence interval of the RSABE criterion is negative.

<i>Ethyl-esters</i>											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Measured/Baseline-Adjusted EPA Ethyl-ester Data</i>											
AUC <sub>0-t</sub> (ng*h/mL)	A <sub>1</sub>	381.378	46	N/A	A vs. B	88.73	N/A	-	N/A	N/A	N/A
	A <sub>2</sub>	421.040	52								
	B <sub>1</sub>	482.751	49	N/A							
	B <sub>2</sub>	429.334	49	N/A							
AUC <sub>0-inf</sub> (ng*h/mL)	A <sub>1</sub>	427.012	39	N/A	A vs. B	96.24	N/A	-	N/A	N/A	N/A
	A <sub>2</sub>	414.545	51								
	B <sub>1</sub>	502.955	50	N/A							
	B <sub>2</sub>	453.773	48	N/A							
C <sub>max</sub> (ng/mL)	A <sub>1</sub>	183.500	64	N/A	A vs. B	83.42	N/A	-	N/A	N/A	N/A
	A <sub>2</sub>	192.450	68								
	B <sub>1</sub>	237.067	67	N/A							
	B <sub>2</sub>	201.410	58	N/A							

<i>Ethyl-esters</i>											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV %	Geometric			Lower	Upper			
<i>Based on Measured/Baseline-Adjusted DHA Ethyl-ester Data</i>											
AUC <sub>0-t</sub> (ng*h/mL)	A <sub>1</sub>	1699.232	43	N/A	A vs. B	92.20	N/A	-	N/A	N/A	N/A
	A <sub>2</sub>	1868.335	48								
	B <sub>1</sub>	2026.347	40	N/A							
	B <sub>2</sub>	1866.066	46	N/A							
AUC <sub>0-inf</sub> (ng*h/mL)	A <sub>1</sub>	1762.930	39	1733.262	A vs. B	92.04	83.70	-	101.21	A: 25 B: 26	N/A
	A <sub>2</sub>	2096.299	45								
	B <sub>1</sub>	2052.842	43	1883.138							
	B <sub>2</sub>	2106.363	39								
C <sub>max</sub> (ng/mL)	A <sub>1</sub>	683.003	56	N/A	A vs. B	86.47	N/A	-	N/A	N/A	N/A
	A <sub>2</sub>	769.526	62								
	B <sub>1</sub>	859.846	56	N/A							
	B <sub>2</sub>	767.172	54	N/A							

**Name of Sponsor:** Trygg Pharma Inc.

**Name of Finished Product:** AKR-963 (omega-3-acid ethyl esters) capsules

**Name of Active Ingredient:** omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

<b>Free Fatty Acids of Plasma</b>											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (SWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV %	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Free EPA Data</i>											
<b>AUC<sub>0-72</sub></b> (ng*h/mL)	A <sub>1</sub>	7465.2	37	7678.6	A vs. B	92.18	87.26 - 97.38	A: 25	B: 15	0.153	
	A <sub>2</sub>	8915.7	33								
	B <sub>1</sub>	8414.2	31								
	B <sub>2</sub>	9146.5	36								
<b>C<sub>max</sub></b> (ng/mL)	A <sub>1</sub>	698.0	51	N/A	A vs. B	90.86	N/A - N/A	N/A	N/A	0.314	
	A <sub>2</sub>	773.4	43								
	B <sub>1</sub>	793.6	56								
	B <sub>2</sub>	883.2	62								
<i>Based on Measured Free EPA Data</i>											
<b>AUC<sub>0-72</sub></b> (ng*h/mL)	A <sub>1</sub>	13338.2	42	13008.2	A vs. B	96.84	93.68 - 100.11	A: 11	B: 10	0.105	
	A <sub>2</sub>	14616.2	43								
	B <sub>1</sub>	13701.2	35								
	B <sub>2</sub>	14950.8	43								
<b>C<sub>max</sub></b> (ng/mL)	A <sub>1</sub>	782.9	46	753.3	A vs. B	92.48	84.04 - 101.76	A: 30	B: 28	0.280	
	A <sub>2</sub>	854.9	40								
	B <sub>1</sub>	868.6	51								
	B <sub>2</sub>	965.8	57								

*Name of Sponsor: Trygg Pharma Inc.*

*Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules*

*Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)*

<b>Free Fatty Acids of Plasma</b>										
Parameter TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
	Arithmetic	CV %	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Free DHA Data</i>										
<b>AUC<sub>0-72</sub></b> (ng* <i>h</i> /mL)	A <sub>1</sub>	19996.0	50	19833.7	<b>A vs. B</b>	88.99	81.66 - 96.96	A: 39	0.214	N/A
	A <sub>2</sub>	25222.4	41							
	B <sub>1</sub>	22408.8	37							
	B <sub>2</sub>	25423.9	41	22288.5						
<b>C<sub>max</sub></b> (ng/mL)	A <sub>1</sub>	1958.6	48	N/A	<b>A vs. B</b>	94.97	N/A - N/A	N/A	0.358	-0.064739
	A <sub>2</sub>	2321.6	43							
	B <sub>1</sub>	2145.4	59							
	B <sub>2</sub>	2487.3	57	N/A						
<i>Based on Measured Free DHA Data</i>										
<b>AUC<sub>0-72</sub></b> (ng* <i>h</i> /mL)	A <sub>1</sub>	52432.6	41	51569.1	<b>A vs. B</b>	97.61	94.72 - 100.58	A: 12	0.093	N/A
	A <sub>2</sub>	58080.2	38							
	B <sub>1</sub>	53140.2	33							
	B <sub>2</sub>	58734.3	36	52833.1						
<b>C<sub>max</sub></b> (ng/mL)	A <sub>1</sub>	2457.5	39	2474.1	<b>A vs. B</b>	97.11	89.70 - 105.15	A: 27	0.283	N/A
	A <sub>2</sub>	2823.0	36							
	B <sub>1</sub>	2612.3	48							
	B <sub>2</sub>	2995.4	49	2547.6						

Due to large variability ( $s_{WR} > 0.294$ ) the reference-scaled approach was used for the baseline-adjusted C<sub>max</sub> of both EPA and DHA from free fatty acids. The results meet bioequivalence criteria: test/reference ratios are within the 80.00-125.00% range and the upper 95% bound of the confidence interval of the RSABE criterion is negative.

The standard average bioequivalence method was used for baseline-adjusted AUC<sub>72</sub> and for measured AUC<sub>72</sub> and C<sub>max</sub> for both Free EPA and Free DHA. The 90% confidence intervals for all these parameters are within the 80.00-125.00% bioequivalence range.

<i>Name of Sponsor: Trygg Pharma Inc.</i>
<i>Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules</i>
<i>Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>
<p><b>Safety Results:</b></p> <p>There were no deaths, Serious Adverse Events (SAEs), or other significant adverse events in the study. All the reported AEs were mild (a total of 78 AEs reported by 30 of the 44 subjects). There were no clinically relevant treatment differences. There were no clinically significant, treatment-emergent changes in clinical laboratory parameters, vital signs, or other physical examination findings for any subject in the trial</p> <p>The study drugs were both well tolerated by all subjects in the study.</p> <p><b>Overall Conclusion:</b></p> <p>The bioequivalence criteria are fulfilled for parent drugs, EPA ethyl-ester, and DHA ethyl-ester, for EPA and DHA from Total Lipids and from Free Fatty Acids based on both measured and baseline-adjusted concentrations.</p> <p>Therefore, the test product (AKR-963 (omega-3-acid ethyl esters) capsules from Trygg Pharma Inc., USA) is bioequivalent to the reference product (Lovaza® capsules from GlaxoSmithKline, USA) in healthy subjects after a single, oral dose, under fed conditions.</p>
<b>Date of Report:</b> Final Report: December 2012

### 4.1.3 Definite BE Study Under Fasted Condition (TRGG-963-006)

<b>Name of Sponsor:</b> <i>Trygg Pharma Inc.</i>	
<b>Name of Finished Product:</b> <i>AKR-963 (omega-3-acid ethyl esters) capsules</i>	
<b>Name of Active Ingredient:</b> <i>omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>	
<b>Title of Study:</b> A Replicate, Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters Capsules under Fasting Conditions	
<b>Investigators:</b> Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C) Tomislav Buconjic, M.D., M.Sc., CCFP Robert C. Wu, M.D., FRCP (C), M.Sc.	
<b>Study Centre(s):</b>	
<b>Clinical Facility:</b>	Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6
<b>Clinical Laboratory:</b>	Alpha Laboratories Incorporated 1262 Don Mills Road North York, Ontario, Canada, M3B 2W7
<b>Analytical, Pharmacokinetic, Statistical and Report Issuing Facility:</b>	(b) (4)
<b>Study Periods:</b> <b>Period 1:</b> November 7, 2012 <b>Period 2:</b> November 21, 2012 <b>Period 3:</b> December 5, 2012 <b>Period 4:</b> December 19, 2012	<b>Phase of Development:</b> I
<b>Objective:</b> The objective of this study was to evaluate the comparative bioavailability between: <ul style="list-style-type: none"> <li>AKR-963 (omega-3-acid ethyl-esters) capsules from Trygg Pharma Inc., USA and</li> <li>Lovaza® capsules from GlaxoSmithKline, USA,</li> </ul> after a single-dose in healthy subjects under fasting conditions.	

**Name of Sponsor:** Trygg Pharma Inc.

**Name of Finished Product:** AKR-963 (omega-3-acid ethyl esters) capsules

**Name of Active Ingredient:** omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

**Methodology:**

- This is an open-label, single-dose, randomized, 4-period, 2-sequence, 2-treatment, replicate, crossover study, designed to evaluate the comparative bioavailability of two formulations of omega-3 fatty acid ethyl esters, administered to healthy male and female subjects under fasting conditions.
- Subjects 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 subjects (planned and analyzed):**

- Fifty (50) subjects were dosed in Period 1.
- Forty-eight (48) subjects completed the study.
- Subject 34 completed Period 1, 2, and 3 of the study, receiving Treatments B, A, and B, respectively. Subject 34 completed at least two periods of the study where the reference product was administered and in accordance with the protocol was included in the pharmacokinetic and statistical analyses.
- A number of subjects were removed from pharmacokinetic and statistical analyses due to having data from baseline-adjusted concentration time profiles with less than 4 consecutive non-zero values. Below is a breakdown of the number of subjects included in pharmacokinetic and statistical analyses by analyte.

Analyte	Treatment	n
Total EPA (Baseline-adjusted)	A1	38
	B1	41
	A2	37
	B2	39
Total DHA (Baseline-adjusted)	A1	33
	B1	37
	A2	31
	B2	36
Free EPA (Baseline-adjusted)	A1	49
	B1	49
	A2	46
	B2	47
Free DHA (Baseline-adjusted)	A1	49
	B1	49
	A2	47
	B2	47

<b>Name of Sponsor:</b> <i>Trygg Pharma Inc.</i>
<b>Name of Finished Product:</b> <i>AKR-963 (omega-3-acid ethyl esters) capsules</i>
<b>Name of Active Ingredient:</b> <i>omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>
<p><b>Main criteria for inclusion:</b>  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/m<sup>2</sup>, who were judged to be healthy based on a medical history, ECG, laboratory evaluation and physical examination and vital signs measurements.</p>
<p><b>Test Product (Treatment A):</b>  AKR-963 (omega-3-acid ethyl esters) capsules  (Trygg Pharma Inc., USA)  Lot No.: 0003559500  Expiry Date: 5/2013  Dose: 4 capsules  Mode of Administration: Oral under fasting conditions</p> <p><b>Test Product (Treatment B):</b>  Lovaza® capsules  (GlaxoSmithKline, USA)  Lot No.: 1ZP2915  Expiry Date: 9/2014  Dose: 4 capsules  Mode of Administration: Oral under fasting conditions</p>
<p><b>Duration of treatment:</b>  Single-dose treatment</p>
<p><b>Criteria for Evaluation:</b>  <b>Pharmacokinetic:</b>  All pharmacokinetic parameters are determined from measured and baseline-adjusted plasma concentration data:</p> <ul style="list-style-type: none"> <li>• Total EPA, Total DHA, Free EPA, and Free DHA: AUC<sub>72</sub>, C<sub>max</sub>, T<sub>max</sub></li> </ul> <p>Free EPA and Free DHA were measured and presented for information only.</p> <p><b>Safety:</b>  Subject safety was monitored throughout the study. Adverse event and vital signs information were documented. There was no formal safety analysis planned for this study.</p>

**Name of Sponsor:** Trygg Pharma Inc.

**Name of Finished Product:** AKR-963 (omega-3-acid ethyl esters) capsules

**Name of Active Ingredient:** omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

**Statistical Methods:**

Descriptive statistics are estimated for the pharmacokinetic parameters in each treatment.

Analysis of variance (ANOVA) was performed on the log-transformed (natural logarithm) AUC72 and Cmax parameters using PROC MIXED in SAS®. The significance of the sequence, period, treatment, and subject-within-sequence effects were tested.

For each pharmacokinetic parameter, estimates were obtained for the treatment mean values,  $\mu_T$  and  $\mu_R$ , for the difference between the treatment means with the corresponding 90% confidence interval, and for the within-subject variance for the reference treatment ( $\sigma^2_{WR}$ ).

The estimate of the within-subject standard deviation for the reference drug product ( $s_{WR}$ ) defined the bioequivalence approach and criterion that was used for the assessment of AUC72 and Cmax:

- If  $s_{WR} < 0.294$ : the standard, unscaled average bioequivalence approach (ABE) was used.  
*Bioequivalence criterion:*  
The 90% confidence interval of the ratio of geometric means of the test to reference product should be within 80.00–125.00%.
- If  $s_{WR} \geq 0.294$ : the reference-scaled average bioequivalence approach (RSABE) was used.  
*Bioequivalence criteria:*
  1. The ratio of geometric means of the test to reference product should be within 80.00–125.00%.
  2. The upper 95% bound of the confidence interval for the expression  $(\bar{Y}_T - \bar{Y}_R)^2 - \theta \cdot s_{WR}^2$  should be negative or equal to zero ( $\leq 0$ ).

The bioequivalence assessment was based on the log-transformed AUC72 and Cmax for baseline-adjusted Total EPA and Total DHA.

The log-transformed AUC72 and Cmax based on baseline-adjusted Free EPA and Free DHA were analyzed similarly and presented as supportive evidence.

Name of Sponsor: Trygg Pharma Inc.

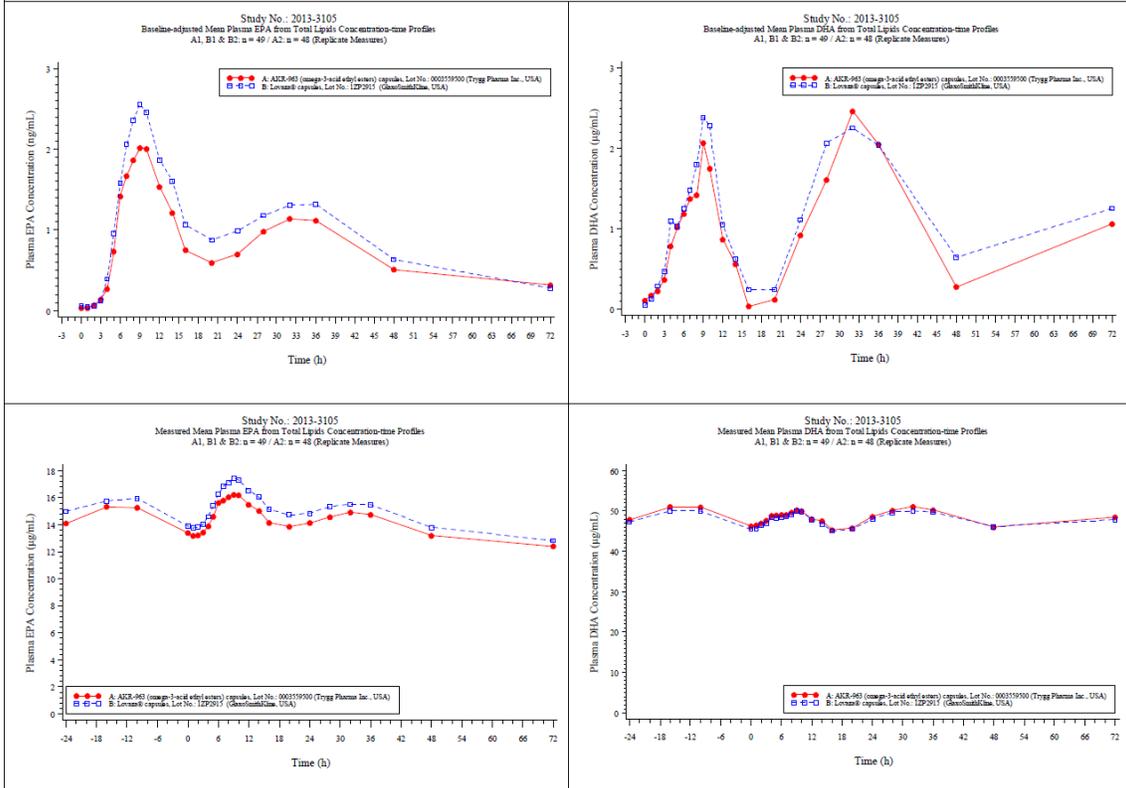
Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules

Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

Summary-Conclusions:

Pharmacokinetic Results:

The following figures summarize the similarities between the two treatments for mean plasma concentration-time profiles of the baseline-adjusted EPA from Total Lipids (top left panel), DHA from Total Lipids (top right panel), measured EPA from Total Lipids (bottom left panel), and measured DHA from total Lipids (bottom right panel).



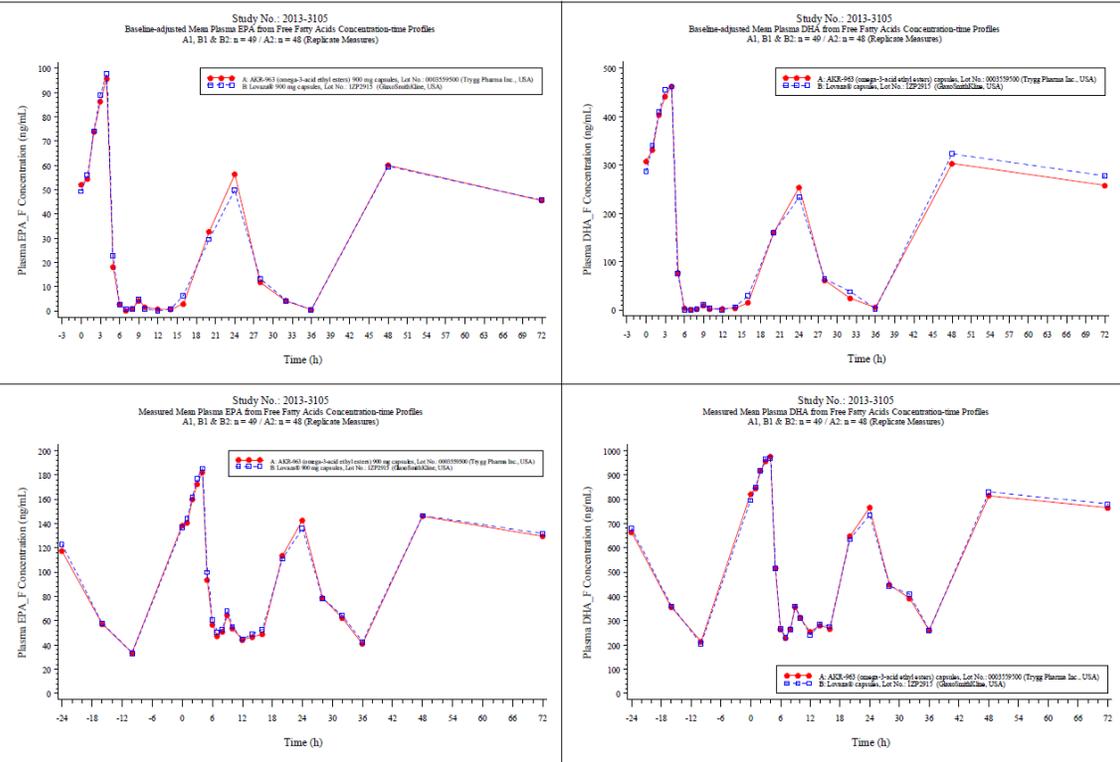
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Name of Sponsor: Trygg Pharma Inc.

Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules

Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

The same similarity was observed in the mean concentration time profiles of the EPA and DHA from Free Fatty Acids: baseline-adjusted (first row) or measured (second row).



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The following tables provide a summary results of the pharmacokinetic and statistical analyses for the EPA and DHA from:

- Total Lipids of Plasma
- Free Fatty Acids of Plasma

<i>Name of Sponsor: Trygg Pharma Inc.</i>											
<i>Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules</i>											
<i>Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>											
<b>Total Lipids of Plasma</b>											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Total EPA Data</i>											
<b>AUC<sub>0-72</sub></b> ( $\mu\text{g}^*\text{h}/\text{mL}$ )	A <sub>1</sub>	81.29	205	N/A	<b>A vs. B</b>	87.78	N/A - N/A		N/A	N/A	-0.468892
	A <sub>2</sub>	52.44	83								
	B <sub>1</sub>	90.21	157	N/A					N/A	0.956	
	B <sub>2</sub>	65.58	84								
<b>Cmax</b> ( $\mu\text{g}/\text{mL}$ )	A <sub>1</sub>	4.37	164	N/A	<b>A vs. B</b>	81.94	N/A - N/A		N/A	N/A	-0.048073
	A <sub>2</sub>	3.09	56								
	B <sub>1</sub>	4.14	102	N/A					N/A	0.466	
	B <sub>2</sub>	4.16	60								
<i>Based on Measured Total EPA Data</i>											
<b>AUC<sub>0-72</sub></b> ( $\mu\text{g}^*\text{h}/\text{mL}$ )	A <sub>1</sub>	1027.17	43	929.54	<b>A vs. B</b>	95.43	92.74 - 98.19		A: 11	N/A	N/A
	A <sub>2</sub>	979.26	47								
	B <sub>1</sub>	1097.59	44	974.06					B: 13	0.129	
	B <sub>2</sub>	1009.58	45								
<b>Cmax</b> ( $\mu\text{g}/\text{mL}$ )	A <sub>1</sub>	17.88	54	15.76	<b>A vs. B</b>	92.98	89.12 - 97.01		A: 17	N/A	N/A
	A <sub>2</sub>	16.79	50								
	B <sub>1</sub>	19.15	48	16.95					B: 17	0.166	
	B <sub>2</sub>	17.83	44								

**Name of Sponsor:** Trygg Pharma Inc.

**Name of Finished Product:** AKR-963 (omega-3-acid ethyl esters) capsules

**Name of Active Ingredient:** omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

<b>Total Lipids of Plasma</b>											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Total DHA Data</i>											
AUC <sub>0-72</sub> ( $\mu\text{g}^*\text{h/mL}$ )	A <sub>1</sub>	83.85	66	N/A	A vs. B	101.08	N/A - N/A		N/A	N/A	-0.310813
	A <sub>2</sub>	73.46	85								
	B <sub>1</sub>	90.92	71	N/A							
	B <sub>2</sub>	98.15	72	N/A							
Cmax ( $\mu\text{g/mL}$ )	A <sub>1</sub>	6.09	83	N/A	A vs. B	103.51	N/A - N/A		N/A	N/A	-0.045635
	A <sub>2</sub>	5.20	49								
	B <sub>1</sub>	5.48	50	N/A							
	B <sub>2</sub>	5.65	32	N/A							
<i>Based on Measured Total DHA Data</i>											
AUC <sub>0-72</sub> ( $\mu\text{g}^*\text{h/mL}$ )	A <sub>1</sub>	3452.06	31	3321.34	A vs. B	100.89	99.24 - 102.57		A: 7	N/A	N/A
	A <sub>2</sub>	3472.59	33								
	B <sub>1</sub>	3441.36	31	3292.02					B: 7	0.076	
	B <sub>2</sub>	3430.52	32								
Cmax ( $\mu\text{g/mL}$ )	A <sub>1</sub>	54.04	34	51.63	A vs. B	101.57	99.59 - 103.58		A: 8	N/A	N/A
	A <sub>2</sub>	53.92	33								
	B <sub>1</sub>	53.05	31	50.83					B: 8	0.089	
	B <sub>2</sub>	53.08	31								

Due to large variability ( $s_{WR} > 0.294$ ) the reference-scaled approach was used for the baseline-adjusted AUC72 and Cmax of both Total EPA and Total DHA. The results meet bioequivalence criteria: test/reference ratios are within the 80.00-125.00% range and the upper 95% bound of the confidence interval of the RSABE criterion is negative.

Measured Total EPA and Total DHA were assessed using the standard average bioequivalence method for both AUC72 and Cmax. The 90% confidence intervals for all these parameters are within the standard 80.00-125.00% bioequivalence range.

**Name of Sponsor:** Trygg Pharma Inc.

**Name of Finished Product:** AKR-963 (omega-3-acid ethyl esters) capsules

**Name of Active Ingredient:** omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

<b>Free Fatty Acids of Plasma</b>											
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion
		Arithmetic	CV%	Geometric			Lower	Upper			
<i>Based on Baseline-Adjusted Free EPA Data</i>											
AUC <sub>0-72</sub> ( $\mu\text{g}^*\text{h/mL}$ )	A <sub>1</sub>	2332.5	85	N/A	A vs. B	94.86	N/A - N/A	N/A	N/A	-0.113530	
	A <sub>2</sub>	2483.1	87								
	B <sub>1</sub>	2211.6	64	N/A							
	B <sub>2</sub>	2527.2	55								
C <sub>max</sub> ( $\mu\text{g/mL}$ )	A <sub>1</sub>	134.9	59	114.0	A vs. B	101.63	95.29 - 108.40	A: 23	N/A	N/A	
	A <sub>2</sub>	131.2	73								
	B <sub>1</sub>	126.7	61	112.2							
	B <sub>2</sub>	133.0	51								
<i>Based on Measured Free EPA Data</i>											
AUC <sub>0-72</sub> ( $\mu\text{g}^*\text{h/mL}$ )	A <sub>1</sub>	7601.6	63	6680.3	A vs. B	96.96	93.47 - 100.57	A: 15	N/A	N/A	
	A <sub>2</sub>	7538.7	65								
	B <sub>1</sub>	7616.7	50	6890.0							
	B <sub>2</sub>	7660.5	53								
C <sub>max</sub> ( $\mu\text{g/mL}$ )	A <sub>1</sub>	223.0	59	191.3	A vs. B	99.74	95.83 - 103.82	A: 16	N/A	N/A	
	A <sub>2</sub>	213.3	66								
	B <sub>1</sub>	217.2	56	191.8							
	B <sub>2</sub>	216.0	54								

<i>Name of Sponsor: Trygg Pharma Inc.</i>
<i>Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules</i>
<i>Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>

<i>Free Fatty Acids of Plasma</i>												
Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)	Intra-Sub Within Ref SD (sWR)	95% Upper Bound for RSABE Criterion	
		Arithmetic	CV%	Geometric			Lower	Upper				
<i>Based on Baseline-Adjusted Free DHA Data</i>												
AUC <sub>0-72</sub> (µg* <i>h</i> /mL)	A <sub>1</sub>	11716.7	62	N/A	A vs. B	93.82	N/A -	N/A	N/A	N/A		
	A <sub>2</sub>	12842.5	65									
	B <sub>1</sub>	12443.9	61	N/A								
	B <sub>2</sub>	13958.6	54									
C <sub>max</sub> (µg/mL)	A <sub>1</sub>	611.7	45	562.1	A vs. B	100.10	94.90 -	105.59	A: 23	N/A		
	A <sub>2</sub>	622.5	52									
	B <sub>1</sub>	611.6	52	561.5							B: 22	0.224
	B <sub>2</sub>	638.7	45									
<i>Based on Measured Free DHA Data</i>												
AUC <sub>0-72</sub> (µg* <i>h</i> /mL)	A <sub>1</sub>	42385.4	47	39512.1	A vs. B	98.69	95.70 -	101.77	A: 12	N/A		
	A <sub>2</sub>	43912.4	46									
	B <sub>1</sub>	42796.6	43	40038.2							B: 13	0.144
	B <sub>2</sub>	44222.3	44									
C <sub>max</sub> (µg/mL)	A <sub>1</sub>	1127.3	45	1043.3	A vs. B	100.43	97.31 -	103.65	A: 13	N/A		
	A <sub>2</sub>	1138.0	47									
	B <sub>1</sub>	1130.4	46	1038.8							B: 14	0.143
	B <sub>2</sub>	1127.3	45									

Due to large variability ( $s_{WR} > 0.294$ ) the reference-scaled approach was used for the baseline-adjusted AUC72 of both EPA and DHA from free fatty acids. The results meet bioequivalence criteria: test/reference ratios are within the 80.00-125.00% range and the upper 95% bound of the confidence interval of the RSABE criterion is negative.

The standard average bioequivalence method was used for baseline-adjusted C<sub>max</sub> and for measured AUC72 and C<sub>max</sub> of both EPA and DHA from free fatty acids. The 90% confidence intervals for all these parameters are within the standard 80.00-125.00% bioequivalence range.

<i>Name of Sponsor: Trygg Pharma Inc.</i>
<i>Name of Finished Product: AKR-963 (omega-3-acid ethyl esters) capsules</i>
<i>Name of Active Ingredient: omega-3 fatty acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)</i>

**Safety Results:**

There was one death (unexpected and not related to the study drug with the cause still under investigation) but no other Serious Adverse Events or severe adverse events in this study.

With the exception of one AE (Subject 34, Death), all AEs were mild in severity. Of the reported AEs (a total of 59 AEs reported by 27 of the 50 subjects), there were no clinically relevant treatment differences.

There were no clinically significant, treatment-emergent changes in clinical laboratory parameters, vital signs, or other physical examination findings for any subject in the trial.

**Overall Conclusion:**

The bioequivalence criteria are met for baseline-adjusted and measured EPA and DHA from total lipids and free fatty acids.

Therefore, the test product (AKR-963 (omega-3-acid ethyl esters) capsules from Trygg Pharma Inc., USA) is bioequivalent to the reference product (Lovaza® capsules from GlaxoSmithKline, USA) in healthy subjects after a single, oral dose, under fasting conditions.

**Date of Report:** Final Report: January 2013

## 4.2 OCP Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
<b>NDA Number</b>	204977 / 505(b)(2)		<b>Brand Name</b>	OMTRYG™ (Proposed)
<b>OCP Division (I, II, III, IV, V)</b>	DCP II		<b>Generic Name</b>	AKR-963 (omega-3-acid ethyl esters)
<b>Medical Division</b>	DMEP		<b>Drug Class</b>	Anti-hyperlipidemic
<b>OCP Reviewer</b>	Manoj Khurana, Ph.D.		<b>Indication(s)</b>	As an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ( $\geq 500$ mg/dL) hypertriglyceridemia.
			<b>Dosage Form</b>	Soft gelatin capsule (liquid filled) 900 mg
<b>OCP Team Leader</b>	Immo Zadezensky, Ph.D.		<b>Dosing Regimen</b>	4-Capsules Once Daily / 2-Capsules Twice Daily
<b>Date of Submission</b>	01/31/2013		<b>Route of Administration</b>	Oral
<b>Estimated Due Date of OCP Review</b>	10/01/2013		<b>Sponsor</b>	Trygg Pharma Inc
<b>PDUFA Due Date</b>	11/22/2013		<b>Priority Classification</b>	Standard
<b>Division Due Date</b>				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 1:				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		Efficacy/Safety Trial – TRGG-963-002*
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	1		TRGG-963-003* (Unsuccessful)
replicate design; single / multi dose:	X	3		Pilot Trial - TRGG-963-004* Definitive Trial- TRGG-963-005* Fasted BE Trial - TRGG-963-006*
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		5		

**Proposed Labeling Changes to Section 12:**

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

The mechanism of action of (b) (4)s not completely understood. Potential mechanisms of action include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal  $\beta$ -oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. **Omega-3-acid 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.

(b) (4)

**12.3 Pharmacokinetics**

(b) (4) [Section 2.5, Section 2.7.1](#)  
[Study TRGG-963-005](#)  
[StudyTRGG-963-006](#)

In healthy volunteers and in patients with hypertriglyceridemia, EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters.

Delete RLD

**Specific Populations:** *Age:* Uptake of EPA and DHA into serum phospholipids in subjects treated with **omega-3-acid ethyl esters** was independent of age (<49 years versus  $\geq 49$  years).

(b) (4)

*Gender:* Females tended to have more uptake of EPA into serum phospholipids than males. The clinical significance of this is unknown.

*Pediatric:* Pharmacokinetics of (b) (4) have not been (b) (4)

(b) (4)

**Table 1.14.1.2-1. Annotated Draft Labeling Text**

Proposed Package Insert for AKR-963 BRANDNAME	Annotation
<i>Renal or Hepatic Impairment:</i> (b) (4) has not been studied in patients with renal or hepatic impairment.	(b) (4)
<i>Drug-Drug Interactions: Simvastatin:</i> In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg with (b) (4) (b) (4) did not affect the extent (AUC) or rate ( $C_{max}$ ) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.	(b) (4)
<i>Atorvastatin:</i> in a 14-day study of 50 healthy adult subjects, daily co-administration of atorvastatin 80 mg with (b) (4) did not affect AUC or $C_{max}$ of exposure to atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin at steady state.	(b) (4)
<i>Rosuvastatin:</i> In a 14-day study of 48 healthy adult subjects, daily co-administration of rosuvastatin 40 mg with (b) (4) did not affect AUC or $C_{max}$ of exposure to rosuvastatin at steady state.	(b) (4)
<i>In vitro</i> studies using human liver microsomes indicated that clinically significant cytochrome P450 mediated inhibition by EPA/DHA combinations are not expected in humans.	(b) (4)

## Key Results Presented in the Filing Meeting Slides:


  
**NDA 204977 Filing Meeting**  
**Clinical Pharmacology Perspective**

**AKR-963 (omega-3-acid ethyl esters)**  
**Sponsor: Trygg Pharma, Inc.**  
**Submitted: 01/31/2013**

**Manoj Khurana, PhD**  
 Division of Metabolism and Endocrinology Products  
 Office of Clinical Pharmacology  
 03/21/2013

CDER, Office of Clinical Pharmacology


  
**Overview:**

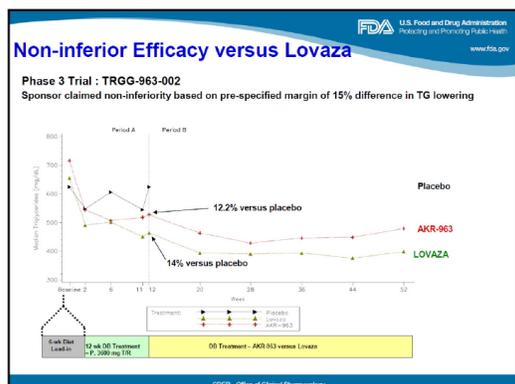
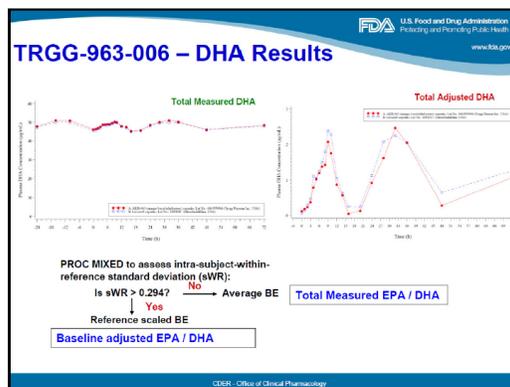
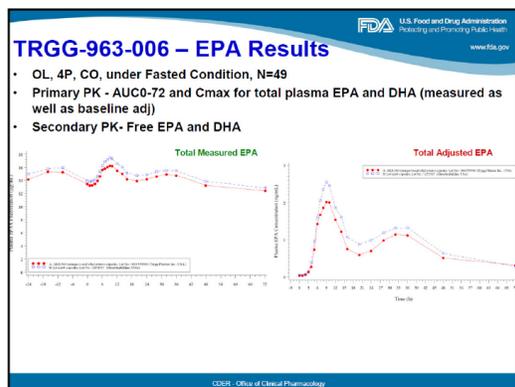
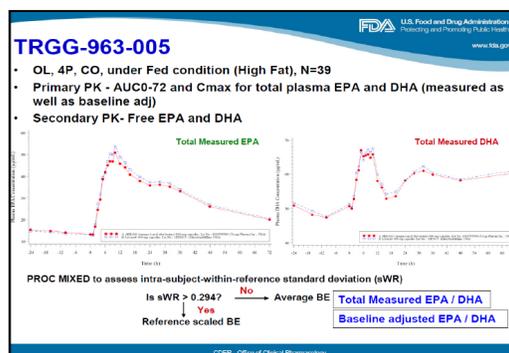
- **Type of Submission:** 505(b)(2) referring Lovaza (NDA021654)
- **Proposed Indication:**
  - adjunct to diet and exercise to reduce triglyceride levels in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia
- **Formulation:** Soft gelatin capsules:
  - 0.9 g
  - a mixture of at least 0.9 g omega-3-acid ethyl esters: ~465 mg of EPAee and 375 mg of DHAee
- **Recommended dose:**
  - 4-capsule dose as QD, or 2-capsule dose BID
    - AKR-963 has 900 mg strength
  - Lovaza is labeled as – 4 grams QD or 2 g BID
  - Sponsor proposed this change for all Lovaza dose related information throughout the label

CDER, Office of Clinical Pharmacology


  
**Clinical Pharmacology Evaluation of AKR-963 Formulation**

Clin. Pharm. Study	Key Design Features	Outcome
TRGG-963-003	DB, CO, 0-24h PK, BA <sub>adj</sub> -AUC <sub>1</sub> and C <sub>max</sub> for plasma EPA and DHA	Failed
TRGG-963-004 Pilot	DB, CO, 0-72h PK, BA <sub>adj</sub> -AUC <sub>1</sub> and C <sub>max</sub> for plasma EPA and DHA	NA
TRGG-963-005	OL, 4P, CO, 0-72h PK, AUC <sub>0-72</sub> and C <sub>max</sub> for plasma EPA and DHA (total and free), Fed (High Fat)	Claimed BE 90% CI within 80-125 Average/Ref-scaled BE analysis of unadjusted and adjusted
TRGG-963-006	OL, 4P, CO, 0-72h PK, AUC <sub>0-72</sub> and C <sub>max</sub> for plasma EPA and DHA (total and free), Fasted	Claimed BE 90% CI within 80-125 Average/Ref-scaled BE analysis of unadjusted and adjusted

CDER, Office of Clinical Pharmacology




  
**Application Filability and Consults**

- Yes, the application is filable from the clinical pharmacology perspective
- OSI consults - None
- Request for Sponsor: None

CDER, Office of Clinical Pharmacology

**Clinical Pharmacology Review Focus:**

- **What is the relative bioavailability of EPA and DHA from AKR-963 Capsules in comparison to Lovaza®, and does this data supports the claim of bioequivalence of AKR-963 to Lovaza®?**
- **Are sponsor's labeling changes acceptable?**

**GRMP Checklist:**

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR A NEW NDA/BLA**

**NDA/BLA Number: 204977    Applicant: Trygg Pharma Inc.    Stamp Date: 01/31/2013**

**Drug Name: AKR-963    NDA/BLA Type: (505(b)(2))  
(omega-3-acid ethyl esters)**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			BE is not pivotal as TBM formulation was used in Phase 3
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or			X	

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA\_BLA 110307

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR A NEW NDA/BLA**

	pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**YES**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Manoj Khurana	03/22/2013
Reviewing Pharmacologist	Date
Immo Zadezensky	03/22/2013
Team Leader/Supervisor	Date

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA\_BLA 110307

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MANOJ KHURANA  
11/14/2013

IMMO ZADEZENSKY  
11/14/2013

<b>BIOPHARMACEUTICS REVIEW</b>			
<b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 204-977	<b>Reviewer:</b>	
<b>Division:</b>	DMEP	Houda Mahayni, Ph.D.	
<b>Applicant:</b>	TRYGG Pharma	<b>Team Leader:</b>	
<b>Trade Name:</b>	--	Angelica Dorantes, Ph.D.	
<b>Generic Name:</b>	AKR-963 (omega-3-acid ethyl esters)	<b>Acting Supervisor:</b>	
<b>Indication:</b>	Adjunct to diet to reduce triglyceride levels in adult patients with severe ( $\geq 500$ mg/dL) hypertriglyceridemia	<b>Date Assigned:</b>	February 2, 2013
<b>Formulation/strength</b>	Soft gelatin capsule/ 900 mg	<b>Date of Review:</b>	October 16, 2013
<b>Route of Administration</b>	Oral		
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<b>Submission Dates</b>		<b>Date of Consult</b>	<b>PDUFA DATE</b>
		January 31, 2013 May 3, 2013 August 19, 2013	November 22, 2013
<b>Type of Submission:</b>	505 (b) (2)		
<b>Key review points</b>	Rupture Test and acceptance criterion		

## TABLE OF CONTENTS

ITEM	PAGE NUMBER
I) Summary of Biopharmaceutics Findings	4
II) Recommendation	4
III) Biopharmaceutics Assessment - Question Based Review Approach	5
A) GENERAL ATTRIBUTES	5
1. What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?	
2. Is there any information on BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?	
B) DISSOLUTION INFORMATION	6
B.1. DISSOLUTION METHOD	6
3. What is the proposed dissolution method?	
4. What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?	
5. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?	
6. What data are available to support the discriminating power of the method?	
7. Is the proposed dissolution method biorelevant? What data are available to support this claim?	
8. Is the proposed method acceptable? If not, what are the deficiencies?	
B.2. ACCEPTANCE CRITERION	11
9. What is the proposed dissolution acceptance criterion for this product?	
10. What data are available to support the dissolution acceptance criterion?	
11. Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?	

**C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES**

**12**

12. What are the highlights of the drug product formulation development?
13. Are all the strengths evaluated in the pivotal clinical trials? If not, what data are available to support the approval of lower strengths?
14. Are there any manufacturing changes implemented to the clinical trial formulation (e.g. formulation changes, process changes, site change, etc.)? What information is available to support these changes?

**D) DISSOLUTION APPLICATIONS**

**12**

**D.1 BIOWAIVERS**

15. Is there a waiver request of in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?
16. Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR/IVIVC model?

**D.2 SURROGATES IN LIEU OF DISSOLUTION**

**13**

17. Are there any manufacturing parameters (e.g. <sup>(b) (4)</sup>, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

## I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

AKR-963 is 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®, which is being used as the basis for this 505 (b) (2) NDA application.

AKR-963 (omega-3-acid ethyl esters) is obtained by esterification of the body oil of fish species and subsequent purification processes. Its two main constituents are ethyl esters of eicosapenaenoic acid (EPA) and docosahexaenoic acid (DHA).

AKR-963 is a soft gelatin capsule. The proposed strength is 900 mg. The recommended dose is 4 g per day.

This review focuses on the evaluation of the acceptability of the rupture test and acceptance criterion.

### **Rupture Test and Acceptance Criterion:**

The Applicant adopted the USP <2040> rupture test and acceptance criterion of NMT 15 minutes for AKR-963 capsules to rupture.

The rupture test and acceptance criterion are acceptable.

In the NDA, the Applicant proposed using (b) (4) test and (b) (4) specification of (b) (4) minutes. FDA requested the Applicant to adopt USP <2040> rupture test and acceptance criterion. The Applicant agreed and updated the specification table and all relevant sections in the NDA. The acceptance criterion was based on the mean rupture results of clinical and stability batches.

## II) RECOMMENDATION

The ONDQA-Biopharmaceutics team reviewed NDA 204-977 for AKR-963 (omega-3-acid ethyl esters) soft gelatin capsules, 900 mg.

The USP <2040> rupture test and acceptance criterion of capsules rupturing in NMT 15 minutes are acceptable.

From the Biopharmaceutics perspective, NDA 204-977 for AKR-963 (omega-3-acid ethyl esters) soft gelatin capsule is recommended for approval.

**Houda Mahayni, Ph. D.**  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Angelica Dorantes, Ph.D.**  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

### III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

#### A) GENERAL ATTRIBUTES

1. *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

##### Drug Substance

AKR-963 (omega-3-acid ethyl esters) is obtained by esterification of the body oil of fish species from the families (b) (4)

(b) (4) Its two main constituents are ethyl esters of eicosapenaenoic acid (EPA) and docosahexaenoic acid (DHA). AKR-963 drug substance is sparingly soluble in aqueous solution at pH 3 to 7, and very soluble in ethanol, methanol, and acetone. (b) (4)

##### Drug Product

The drug product is a soft gelatin capsule containing a mixture of omega-3-acid ethyl esters of at least 900 mg, including approximately 465 mg EPA and 375 mg DHA. An identifying mark is printed on the capsules. The drug product is packaged in a white opaque high-density polyethylene bottle with a (b) (4) white opaque (b) (4) screw cap.

The components, their function, and quality are provided in Table 1.

**Table 1: Components and composition of AKR-963 capsules**

Component	Function	Quality Standard	Amount per Capsule (g)
<b>AKR-963 Drug Substance<sup>a</sup></b>		Trygg Pharma, Inc.	1.16
Total omega-3-acid ethyl esters	Active ingredient	(b) (4)	(b) (4)
<i>d</i> α-Tocopherol	(b) (4)	(b) (4)	(b) (4)
<b>Capsule Shell</b>	(b) (4)		
Gelatin	(b) (4)	NF, Ph Eur	
Glycerin	(b) (4)	USP, Ph Eur	
Purified water	(b) (4)	USP, Ph Eur	
<b>White Ink</b>	(b) (4)		
(b) (4)	(b) (4)	USP	
(b) (4)	(b) (4)	NF	
(b) (4)	(b) (4)	USP	
(b) (4)	(b) (4)	USP	
(b) (4)	(b) (4)	NF	
(b) (4)	(b) (4)	USP	
(b) (4)	(b) (4)	NF	
(b) (4)	(b) (4)	USP	

<sup>a</sup> = Each capsule contains 1.16 g of AKR-963 drug substance, which is composed of at least 900 mg of total omega-3-acid ethyl esters, approximately 465 mg EPA<sup>a</sup>, approximately 375 mg DHA<sup>a</sup>, and 4.6 mg *d*α-tocopherol.

<sup>b</sup> = Residual water content in the capsule shells is approximately (b) (4) %.

<sup>c</sup> = Removed during processing.

*2. Is there any information on BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?*

Not applicable.

**B) DISSOLUTION INFORMATION**

**B.1. DISSOLUTION METHOD**

*3. What is the proposed dissolution method?*

(b) (4)



FDA responded on July 22, 2013 in a General Advice Letter to the Applicant's responses of May 3, 2013 amendment which were provided in response to the FDA comments conveyed in the filing communication of April 8, 2013. The General Advice Letter provided FDA disagreement with the Applicant's responses of May 3, 2013 amendment. In summary, FDA did not agree with the Applicant's proposal to use the terminology "(b) (4)" for AKR-963 capsules and requested that the terminology of "rupture test" be used instead, and provided the following responses/requests to the Applicant's responses of May 3, 2013 amendment.

***FDA Response to the Applicant Response to FDA's Comment 1:***  
**AKR-963 Capsule is a soft gelatin that (b) (4); it ruptures and becomes a soft mass having no palpably firm core. (b) (4)**

Since your product cannot meet the above four criteria, the terminology should be change to a rupture test. Therefore, please correct all appropriate sections in the NDA to reflect rupture test and record the time taken for each capsule shell to rupture.

***FDA Response to the Applicant Response to FDA's Comment 2:***

It is not clear how you determined that the selected volume, apparatus, and speed are appropriate test conditions for your dosage form, as you did not provide the test method development report. Refer to USP<2040> Rupture Test for Soft Shell Capsules for test conditions (medium, apparatus, time, procedure, and tolerances) used for soft gelatin capsule and use these test conditions to assess the rupture time for your dosage form.

***FDA Response to the Applicant Response to FDA's Comment 3:***

You are requested to submit in tabulated and graphical form the individual, mean, and standard deviation data from the pivotal clinical batches and primary (registration) stability batches. This is accomplished by recording the time taken for each capsule shell to rupture (Refer to USP <2040>). It is not acceptable to record the maximum time for 6 capsules to rupture. Also, FDA sets tolerances based on the long-term stability data and not the accelerated conditions. Therefore, your proposal to revise the tolerances based on release and stability data need to take that into consideration. Based on the data provided at release and long-term stability, all the capsules tested rupture in NMT 15 minutes.

The Applicant responded to the General Advice Letter of July 22, 2013 on August 19, 2013 with acceptance of FDA's requests. The Applicant responses to each comment are provided below.

***The Applicant's Response to FDA Comment 1:***

In compliance with the request, the terminology in the proposed specification for AKR-963 capsules is revised to rupture in place of the test for (b) (4) time. The rupture test will be conducted in accordance with USP <2040>, and the time taken for each capsule shell to rupture will be recorded. The relevant CTD sections of the NDA are updated and replaced in this submission, as summarized in section 1.11.4.2. Please note that the (b) (4) testing conducted during development has not been changed to rupture (e.g., batch analysis data and stability data), because this testing was conducted in accordance with (b) (4). However, the CTD sections with commitments for release and stability testing for the commercial drug product are updated to reflect the terminology of rupture test (e.g., manufacturer responsibilities, proposed specification, analytical procedure, justification of specification, and postapproval stability commitment).

***The Applicant's Response to FDA Comment 2:***

In compliance with the request, the proposed specification and analytical procedures for AKR-963 capsules were revised to include a test for rupture in accordance with USP <2040> in place of the test for (b) (4) time. The rupture test is conducted using

500 mL water as the medium, apparatus 2 at 50 rpm, by placing 1 capsule with a sinker in each vessel and allowing it to sink before starting rotation of the blade. The time required for each capsule to rupture will be recorded. The requirements for the test will be met if all capsules rupture in not more than 15 minutes. If 1 or 2 capsules rupture in more than 15 minutes and not more than (b) (4) minutes, the test will be repeated on 12 additional capsules and the requirements are met if not more than 2 of the 18 capsules rupture in more than 15 minutes and not more than (b) (4) minutes. If capsules do not conform to this requirement, the test may be repeated (b) (4)

***The Applicant's Response to FDA Comment #3:***

In compliance with the request, rupture data for the pivotal clinical batches and primary stability (registration) batches, as well as other batches used during development, are provided in tabulated and graphical form in *Table 1.11.4-1* and *Figure 1.11.4-1*. The rupture test was conducted on capsules aged from 25 to 42 months, as noted in the tabulation. All rupture results are  $\leq 6$  minutes, which meet the USP <2040> requirements of rupturing in not more than 15 minutes. The proposed specification in *section 3.2.P.5.1* is updated to replace the (b) (4) time test with the rupture test per USP <2040> with the acceptance criterion of "meets requirements". The acceptance criterion is justified based on the aged capsule results, as described in the revised *section 3.2.P.5.6*. Future stability studies will be conducted using the rupture test, as noted in the revised stability commitment (*section 3.2.P.8.2*), as will future test intervals of ongoing studies.

(b) (4)

Also, the Applicant revised all relevant sections of the NDA to reflect the rupture testing per USP <2040> (b) (4)

**4. What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?**

Not Applicable. The Applicant used USP <2040>.

**5. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?**

Not applicable. The Applicant used USP <2040>.

**6. What data are available to support the discriminating power of the method?**

Not applicable. The Applicant used USP <2040>.

**7. Is the proposed dissolution method biorelevant? What data is available to support this claim?**

Not applicable

**8. Is the proposed method acceptable? If not, what are the deficiencies?**

The USP <2040> Rupture test is acceptable.

## **B.2. ACCEPTANCE CRITERION**

**9. What is the proposed dissolution acceptance criterion for this product?**

The proposed rupture acceptance criterion is **capsules rupturing in NMT 15 minutes.**

**10. What data are available to support the dissolution acceptance criterion?**

All rupture results are  $\leq 6$  minutes, which meet the USP <2040> requirements of rupturing in not more than 15 minutes.

**11. Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?**

The acceptance criterion is acceptable, as rupture data for the pivotal clinical batches and primary stability (registration) batches, as well as other batches used during development, including rupture results of capsules aged from 25 to 42 months support the acceptance criteria.

**C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES**

**12. What are the highlights of the drug product formulation development?**

The to-be-marketed formulation is the same as the formulation used for stability studies, toxicology studies, and all clinical trials.

**13. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?**

Not Applicable, as the product has one dosage strength.

**14. Are there any manufacturing changes implemented to the clinical trial formulation (e.g. formulation changes, process changes, site change, etc.)? What information is available to support these changes?**

No manufacturing changes were implemented to the clinical trial formulation. All batches were manufactured by Swiss Caps using AKR-963 drug substance manufactured by (b) (4)

**D) DISSOLUTION APPLICATIONS**

**D.1 BIOWAIVERS**

**15. Is there a request for waiver of in vivo BA or BE data (Biowaiver)? What is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?**

Not applicable.

**16. Is there any IVIVC or IVIVR information submitted? What is the regulatory application of the IVIVC or IVIVR in the submission? What data is provided to support the acceptability of the IVIVC or IVIVR model?**

There is no IVIVC or IVIVR data included in the submission.

## D.2 SURROGATES IN LIEU OF DISSOLUTION

*17. Are there any manufacturing parameters (e.g. (b) (4), drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?*

No, there are no manufacturing parameters being proposed as surrogates in lieu of dissolution testing. Note that the rupture test was used as a quality control test instead of dissolution test because the product is a soft gelatin capsule and the drug substance is oil.

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/s/  
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HOUDA MAHAYNI  
10/16/2013

ANGELICA DORANTES  
10/16/2013

Office of Clinical Pharmacology  
New Drug Application Filing and Review Form

**General Information About the Submission**

	Information		Information
<b>NDA Number</b>	204977 / 505(b)(2)	<b>Brand Name</b>	OMTRYG™ (Proposed)
<b>OCP Division (I, II, III, IV, V)</b>	DCP II	<b>Generic Name</b>	AKR-963 (omega-3-acid ethyl esters)
<b>Medical Division</b>	DMEP	<b>Drug Class</b>	Anti-hyperlipidemic
<b>OCP Reviewer</b>	Manoj Khurana, Ph.D.	<b>Indication(s)</b>	As an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ( $\geq 500$ mg/dL) hypertriglyceridemia.
		<b>Dosage Form</b>	Soft gelatin capsule (liquid filled) 900 mg
<b>OCP Team Leader</b>	Immo Zadezensky, Ph.D.	<b>Dosing Regimen</b>	4-Capsules Once Daily / 2-Capsules Twice Daily
<b>Date of Submission</b>	01/31/2013	<b>Route of Administration</b>	Oral
<b>Estimated Due Date of OCP Review</b>	10/01/2013	<b>Sponsor</b>	Trygg Pharma Inc
<b>PDUFA Due Date</b>	11/22/2013	<b>Priority Classification</b>	Standard
<b>Division Due Date</b>			

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 1:				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		Efficacy/Safety Trial – TRGG-963-002*
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	1		TRGG-963-003* (Unsuccessful)
replicate design; single / multi dose:	X	3		Pilot Trial - TRGG-963-004* Definitive Trial- TRGG-963-005* Fasted BE Trial - TRGG-963-006*
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		5		

<b>*Trials with Electronic Data-sets</b>		
<b>Filability</b>		
	<b>“X” if yes</b>	<b>Comments</b>
<b>Is Application filable?</b>	<b>X</b>	<b>Comments to the Sponsor: None.</b>
<b>Submission in Brief: See the details below.</b>	<b>Reviewer’s Comments for project manager: None</b>	

### Submission in Brief:

Trygg Pharma, Inc. (Trygg), is seeking US marketing approval for AKR-963 capsules (Proposed Trade Name: OMTRYG™) under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, relying upon the Agency’s previous findings of safety and effectiveness for the reference listed drug (RLD), Lovaza® (omega-3-acid ethyl esters) Capsules, oral (NDA 21-654, GlaxoSmithKline). The proposed indication of AKR-963 capsule is “an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia”, which is identical to Lovaza.

This NDA is supported by data from one safety/efficacy trial and two BA/BE trials:

<b>Type of Study</b>	<b>Study Identifier Location of Study Report</b>	<b>Objective(s) of the Study</b>	<b>Study Design and Type of Control</b>
Efficacy and Safety – Controlled	<a href="#">TRGG-963-002</a>  <a href="#">Section 5.3.5.1</a>	<b>Primary:</b> to evaluate the efficacy of AKR-963 as adjunctive therapy to diet for the treatment of severe hypertriglyceridemia  <b>Secondary and Tertiary:</b> To evaluate additional efficacy and safety endpoints with AKR-963 for the treatment of severe hypertriglyceridemia and to assess its effects on other lipids and markers for cardiovascular risk, body weight, blood pressure, and HOMA-IR	Randomized, double-blind, placebo controlled, parallel-group non-inferiority of AKR-963 vs Lovaza design Up to 76 weeks of treatment consisting of: <ul style="list-style-type: none"> <li>• <b>Diet Lead In Period:</b> 6-week diet-only</li> <li>• <b>Period A:</b> a 12-week double-blind, AKR-963 vs Lovaza, placebo controlled treatment period</li> <li>• <b>Period B:</b> a 40-week double-blind AKR-963 vs Lovaza treatment period</li> <li>• <b>Period C:</b> an up to 24-week double-blind safety extension treatment period</li> </ul>
Comparative BA and BE	<a href="#">TRGG-963-003</a>  <a href="#">Section 5.3.1.2</a>	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 ( $\leq 15\%$ of kcal) meal

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control
Comparative BA and BE	<a href="#">TRGG-963-004</a> <a href="#">Section 5.3.1.2</a>	<b>Primary:</b> To evaluate the comparative BA of AKR-963 and Lovaza after a single dose in healthy subjects under fasting and fed conditions <b>Secondary:</b> To evaluate the effect of food on 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
Comparative BA and BE	<a href="#">TRGG-963-005</a> <a href="#">Section 5.3.1.2</a>	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
Comparative BA and BE	<a href="#">TRGG-963-006</a> <a href="#">Section 5.3.1.2</a>	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

As reported by the Sponsor, the AKR-963 versus Lovaza Product Comparison is mentioned below:

	Lovaza	AKR-963 Capsules
Route of administration	Oral	
Active Ingredient	Omega-3-acid ethyl esters	
Product source	Fish oil	
Expressed Strength (g)	1 <sup>b</sup>	0.9
Total omega-3-acid ethyl esters (mg/capsule) <sup>a</sup>	At least 900	
EPAec (mg/capsule)	Approximately 465	
DHAec (mg/capsule)	Approximately 375	
Minor omega-3-acid ethyl esters	Not specified in RLD label	(b) (4)
Dosage form	Capsule	
Inactive ingredients	Gelatin, glycerol, water, $\alpha$ -tocopherol (in a carrier of soybean oil)	Gelatin, glycerol, water, $\alpha$ -tocopherol (in a carrier of sunflower oil)
Capsule fill weight (g)	1	1.16
<sup>a</sup> =	(b) (4)	
<sup>b</sup> =	The RLD label states the description as each 1-gram capsule of Lovaza contains at least 900 mg of ethyl esters of omega-3 fatty acid sourced from fish oil. These are predominately a combination of ethyl esters of EPA - approximately 465 mg and DHA – approximately 375 mg.	

**Proposed Labeling Changes to Section 12:**

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

The mechanism of action of (b) (4) is not completely understood. Potential mechanisms of action include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal  $\beta$ -oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. **Omega-3-acid 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.

(b) (4)

**12.3 Pharmacokinetics**

**Systemic Bioavailability:**

(b) (4)  
(b) (4)

Section 2.5, Section 2.7.1  
Study TRGG-963-005  
Study TRGG-963-006

In healthy volunteers and in patients with hypertriglyceridemia, EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters.

Delete RLD

(b) (4)

**Specific Populations:** *Age:* Uptake of EPA and DHA into serum phospholipids in subjects treated with **omega-3-acid ethyl esters** was independent of age (<49 years versus  $\geq$ 49 years).

*Gender:* Females tended to have more uptake of EPA into serum phospholipids than males. The clinical significance of this is unknown.

*Pediatric:* Pharmacokinetics of (b) (4) have not been (b) (4)

**Table 1.14.1.2-1. Annotated Draft Labeling Text**

**Proposed Package Insert for AKR-963 BRANDNAME**

**Annotation**

*Renal or Hepatic Impairment:* (b) (4) has not been studied in patients with renal or hepatic impairment.

(b) (4)

*Drug-Drug Interactions: Simvastatin:* In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg with (b) (4) (b) (4) did not affect the extent (AUC) or rate ( $C_{max}$ ) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.

*Atorvastatin:* in a 14-day study of 50 healthy adult subjects, daily co-administration of atorvastatin 80 mg with (b) (4) did not affect AUC or  $C_{max}$  of exposure to atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin at steady state.

*Rosuvastatin:* In a 14-day study of 48 healthy adult subjects, daily co-administration of rosuvastatin 40 mg with (b) (4) did not affect AUC or  $C_{max}$  of exposure to rosuvastatin at steady state.

*In vitro* studies using human liver microsomes indicated that clinically significant cytochrome P450 mediated inhibition by EPA/DHA combinations are not expected in humans.

## Key Results Presented in the Filing Meeting Slides:

 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
 www.fda.gov

# NDA 204977 Filing Meeting Clinical Pharmacology Perspective

**AKR-963 (omega-3-acid ethyl esters)**  
**Sponsor: Trygg Pharma, Inc.**  
**Submitted: 01/31/2013**

**Manoj Khurana, PhD**  
 Division of Metabolism and Endocrinology Products  
 Office of Clinical Pharmacology  
 03/21/2013

CDER - Office of Clinical Pharmacology

 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
 www.fda.gov

## Overview:

- **Type of Submission:** 505(b)(2) referring Lovaza (NDA021654)
- **Proposed Indication:**
  - adjunct to diet and exercise to reduce triglyceride levels in adult patients with severe ( $>=500$  mg/dL) hypertriglyceridemia
- **Formulation:** Soft gelatin capsules:
  - 0.9 g
  - a mixture of at least 0.9 g omega-3-acid ethyl esters: ~465 mg of EPAee and 375 mg of DHAee
- **Recommended dose:**
  - 4-capsule dose as QD, or 2-capsule dose BID
    - AKR-963 has 900 mg strength
  - Lovaza is labeled as – 4 grams QD or 2 g BID
  - Sponsor proposed this change for all Lovaza dose related information throughout the label

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## Clinical Pharmacology Evaluation of AKR-963 Formulation

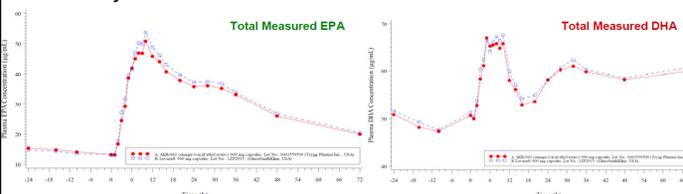
Clin. Pharm. Study	Key Design Features	Outcome
TRGG-963-003	DB, CO, 0-24h PK, BAdj-AUCt and Cmax for plasma EPA and DHA	Failed
TRGG-963-004 Pilot	DB, CO, 0-72h PK, BAdj-AUCt and Cmax for plasma EPA and DHA	NA
TRGG-963-005	OL, 4P, CO, 0-72h PK, AUC0-72 and Cmax for plasma EPA and DHA (total and free), Fed (High Fat)	Claimed BE 90% CI within 80-125 Average/Ref-scaled BE analysis of unadjusted and adjusted
TRGG-963-006	OL, 4P, CO, 0-72h PK, AUC0-72 and Cmax for plasma EPA and DHA (total and free), Fasted	Claimed BE 90% CI within 80-125 Average/Ref-scaled BE analysis of unadjusted and adjusted

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## TRGG-963-005

- OL, 4P, CO, under Fed condition (High Fat), N=39
- Primary PK - AUC0-72 and Cmax for total plasma EPA and DHA (measured as well as baseline adj)
- Secondary PK- Free EPA and DHA



PROC MIXED to assess intra-subject-within-reference standard deviation (sWR)

Is sWR > 0.294? No → Average BE

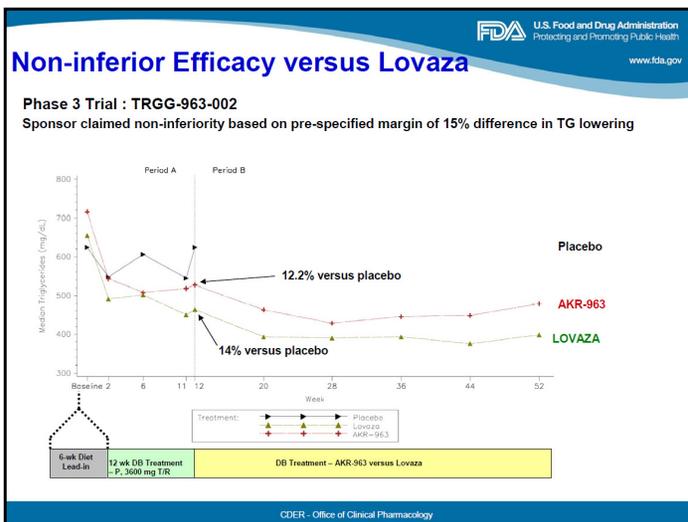
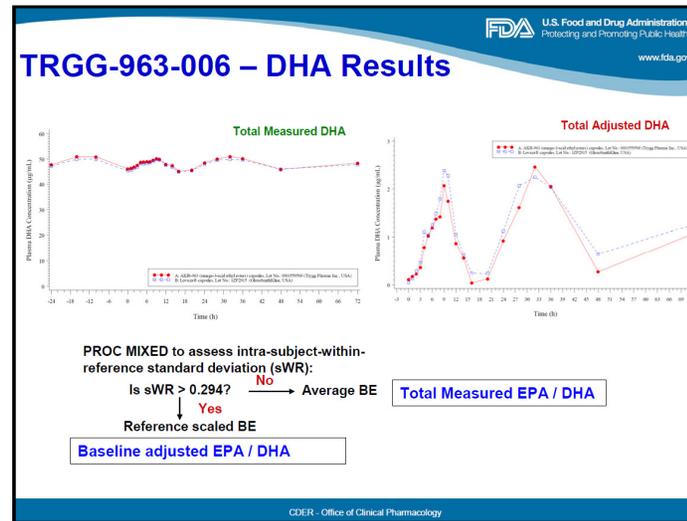
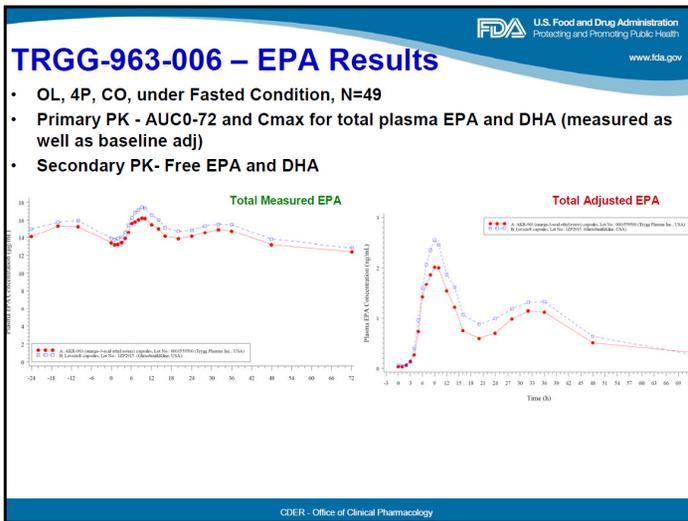
Yes ↓

Reference scaled BE

Total Measured EPA / DHA

Baseline adjusted EPA / DHA

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**Application Filability and Consults**

- Yes, the application is filable from the clinical pharmacology perspective
- OSI consults - None
- Request for Sponsor: None

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**Clinical Pharmacology Review Focus:**

- **What is the relative bioavailability of EPA and DHA from AKR-963 Capsules in comparison to Lovaza®, and does this data supports the claim of bioequivalence of AKR-963 to Lovaza®?**
- **Are sponsor's labeling changes acceptable?**

**GRMP Checklist:**

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR A NEW NDA/BLA**

**NDA/BLA Number: 204977    Applicant: Trygg Pharma Inc.    Stamp Date: 01/31/2013**

**Drug Name: AKR-963    NDA/BLA Type: (505(b)(2))  
(omega-3-acid ethyl esters)**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			BE is not pivotal as TBM formulation was used in Phase 3
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or			X	

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA\_BLA 110307

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR A NEW NDA/BLA**

	pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**YES**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Manoj Khurana	03/22/2013
Reviewing Pharmacologist	Date
Immo Zadezensky	03/22/2013
Team Leader/Supervisor	Date

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA\_BLA 110307

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MANOJ KHURANA  
03/22/2013

IMMO ZADEZENSKY  
03/22/2013

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

<b>NDA Number</b>	204-977
<b>Submission Date</b>	January 31, 2013
<b>Product name, generic name of the active</b>	AKR-963 (omega-3-acid ethyl esters)
<b>Dosage form and strength</b>	Soft gelatin capsules, 900 mg
<b>Indication</b>	Adjunct to diet to reduce triglyceride levels in adult patients with severe ( $\geq 500$ mg/dL) hypertriglyceridemia
<b>Applicant</b>	TRYGG Pharma
<b>Clinical Division</b>	DMEP
<b>Type of Submission</b>	505(b)(2) NDA (RLD: Lovaza®)
<b>Biopharmaceutics Reviewer</b>	Houda Mahayni, Ph.D.
<b>Biopharmaceutics Team Leader</b>	Angelica Dorantes, Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b>A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Does the application contain dissolution data?		x	<p>AKR-963 capsules are soft gelatin with immediate release characteristics. The Applicant proposed using (b) (4) testing in lieu of dissolution testing, as the drug substance is liquid and the dosage form provides immediate release after the capsule rupture.</p> <p>It is noted that the Applicant used the terminology of (b) (4) test for a soft gelatin capsule which is not appropriate terminology for a soft gelatin capsule. The Applicant will be asked to change the terminology to rupture test, as it is the terminology used by USP for soft gelatin capsules.</p>
2.	Is the dissolution test part of the DP specifications?		x	<p>A (b) (4) test is part of the DP specifications. The proposed (b) (4) specification is (b) (4) minutes. The Applicant stated that the (b) (4) time is set in accordance with the limit provided in the USP monograph for Omega-3-Acid Ethyl Esters Capsules.</p>

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

3.	Does the application contain the dissolution method development report?	x	<p>The Applicant followed the compendial method of the European Pharmacopoeia (<i>Ph Eur</i> 2.9.1 apparatus B). Six capsules are tested and the stop time for (b) (4) is determined as the time that the last capsule ruptures.</p> <div style="background-color: #cccccc; height: 150px; width: 100%; margin-top: 10px;">(b) (4)</div>
4.	Is there a validation package for the analytical method and dissolution methodology?	x	The Applicant is using the European Pharmacopoeia compendial method.
5.	Does the application include a biowaiver request?	x	The Applicant proposed one dosage strength (900 mg), and the proposed commercial formulation is the same as the formulation used for stability studies and all clinical trials.
6.	Is there enough information to assess the extended release designation claim?	X	Not applicable. This is an IR formulation.
7.	Does the application include an IVIVC model?	x	
8.	Does the application include information/data on in vitro alcohol dose-dumping potential?	x	Not applicable, as the dosage form is immediate-release.
9.	Is information such as BCS classification mentioned, and supportive data provided?	x	
10.	Is information on mixing the product with foods or liquids included?	x	
11.	Is there any in vivo BA or BE information in the submission?	x	Several BA studies are included. These studies will be reviewed by OCP.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

12.	Is there any design space proposed using in vitro release as a response variable?		X	Not applicable. This NDA does not contain QbD elements.
13.	Is the control strategy related to in vitro drug release?		X	Not applicable. This NDA does not contain QbD elements.

**PRODUCT QUALITY - BIOPHARMACEUTICS  
FILING REVIEW**

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
14.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		<ul style="list-style-type: none"> <li>• The NDA is fileable from Biopharmaceutics Perspective.</li> <li>• The acceptability of the proposed (b) (4) test and proposed specification limit will be a review issue.</li> </ul>
15.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not Applicable.
16.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not Applicable.
17.	Are there any <b>potential review</b> issues identified?		x	(b) (4)

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

18.	<p>Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?</p>	X	<ul style="list-style-type: none"> <li>• The terminology of (b) (4) test for a soft gelatin capsule is not appropriate. It is requested that you change the terminology to rupture test, as it reflects the terminology used by USP for soft gelatin capsules.</li> <li>• Provide the specified liquid medium, the experimental conditions (volume, temperature, time, etc.), and the procedure to assess the (b) (4) of your dosage form. Also, provide your testing plan if 1 or 2 capsules fail to disintegrate completely and how many times you plan to repeat the test and the number of capsules you plan to test to meet the proposed specification.</li> <li>• Your proposed (b) (4) specification (b) (4) minutes is not justified. Provide the (b) (4) data (individual, mean, SD, in tabulated and graphical form) from the pivotal clinical batches and primary (registration) stability batches.</li> </ul>
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*{See appended electronic signature page}*

Houda Mahayni, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Angelica Dorantes, Ph.D.  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HOUDA MAHAYNI  
03/15/2013

ANGELICA DORANTES  
03/15/2013