

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 204-977

**Drug Name:** AKR-963 Capsule 0.9 g oral

**Indication(s):** An adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia

**Applicant:** Trygg Pharma

**Date(s):** Submission January 31, 2013; Review due date October 15, 2013; Action goal date November 22, 2013

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## 1 EXECUTIVE SUMMARY

This is a 505(b)(2) application. Trygg developed AKR-963 for the treatment of hypertriglyceridemia relying upon the Agency's previous findings of safety and effectiveness for the reference drug, Lovaza (omega-3-acid ethyl esters) capsules (NDA 21-654). The indication is as an adjunct to diet to reduce triglyceride levels (TG) in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia. AKR-963 is a 1160 mg capsule containing approximately 465 mg/capsule EPA<sub>ee</sub> and approximately 374 mg/capsule DHA<sub>ee</sub> and minor omega-3-acid ethyl esters. The company conducted a bioequivalence study in a fed state (administered after a high fat meal), TRGG-963-005 after learning from the bioequivalence and bioavailability studies 003 (low fat meal) and 004 (fasted vs. fed (high fat)) that a high fat meal was required for adequate absorption of omega-3. To address the concern, the FDA advice to the sponsor was 'The Agency recognized that the sponsor is not solely relying on bioequivalence for the demonstration of safety and efficacy; a clinical study was also conducted. Safety and efficacy will be determined on the totality of the data submitted.' (pre-NDA meeting dated December 10, 2012). Bioequivalence was demonstrated in study 005 (see the clinical pharmacology review).

The sponsor proposed product label includes the results from three trials comparing Lovaza to placebo (one of which is an add-on to simvastatin) and the results from study TRGG-963-002. This review focuses on study TRGG-963-002. Study TRGG-963-002 titled 'A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase III Study to Assess Efficacy and Safety of AKR-963 Therapy in Subjects with Severe Hypertriglyceridemia.' was a 3-arm study. Approximately 250 patients with hypertriglyceridemia (TG $>500$  and  $\leq 1500$  mg/dL) were randomized 100 to AKR-963, 100 to Lovaza (active reference) and 40 to placebo (vegetable oil). The sponsor's primary, secondary, and tertiary statistical tests for percent change in TG from baseline to Week 12 were respectively:

1. superiority of AKR-963 (test drug) to placebo
2. superiority of Lovaza (reference drug) to placebo
3. non-inferiority of AKR-963 to Lovaza by a margin of 15%

The study demonstrated marginal results for superiority of AKR-963 vs. placebo ( $p=0.041$ ) and Lovaza vs. placebo ( $p=0.023$ ). The 95% confidence interval (CI) for the difference in the effects of AKR-963 and Lovaza was (-6.0%, +10.5%), which ruled out the pre-specified non-inferiority margin of 15%. See Table 1 for further details on these analyses. As the estimated effect of Lovaza was not only smaller than 15% but quite different from the studies used to determine the margin of 15%, it does not appear that the margin of 15% is appropriate for this study. The re-analyses submitted by sponsor (see Appendix) yielded smaller p-values and a smaller upper limit (8.7%) for the 95% CI for the difference in the effects of AKR-963 and Lovaza.

**Table 1 Study results of TG (mg/dL) % change from baseline to Week 12 - Period A**

	<b>AKR-963 vs. placebo</b>	<b>Lovaza vs. placebo</b>	<b>Non-inferiority: AKR-963 vs. Lovaza</b>
Estimate (95% CI)	-12.2 (-23.9, -0.4)	-14.0 (-26.9, -1.1)	+2.3 (-6.0, 10.5)
p-value	0.041	0.023	

Based on the primary efficacy analysis (p=0.041) and the supportive reanalysis, it is concluded that AKR-963 is superior to placebo in TG percent change (reduction) from baseline to Week 12. The estimated effects for Lovaza and AKR-963 from this trial tended to be smaller than estimated effects seen by Lovaza in previous studies (see Figures 18 and 19 in the Appendix). The modest treatment effect might be due to the lack of instructions on drug administration in the fed or fasting state. The bioequivalence study demonstrated that absorption of active drugs is optimal after a fatty meal. The generalizability of the 002 trial results may be affected by when the drugs were administered (i.e., not necessarily after a fatty meal). The issue on the estimated effect of Lovaza being smaller in this study than historically (i.e., the constancy assumption may not hold) raises concern on the appropriateness of using a 15% non-inferiority margin in this trial. Based on the 002 trial results it is not clear that AKR-963 is truly non-inferior to (i.e., not unacceptably worse than) Lovaza on TG percent change from baseline to Week 12. The sponsor proposes to include statements in the product label that (b) (4)

We recommend not including proposed statements in the product label on (b) (4)

## 2 INTRODUCTION

### 2.1 Overview

The sponsor submitted a single 3-arm Phase 3 trial. Treatment arms were AKR-963 (n=104), Lovaza (n=103) and placebo (n=43). The primary, secondary, and tertiary statistical tests for percent change in TG from baseline to Week 12 were:

1. superiority of AKR-963 (test drug) to placebo
2. superiority of Lovaza (reference drug) to placebo
3. non-inferiority of AKR-963 to Lovaza by a margin of 15%

The margin was derived by preservation ½ of the -31% upper bound of the 95% confidence interval from the historical data of Lovaza vs. placebo (Fig 1. red).

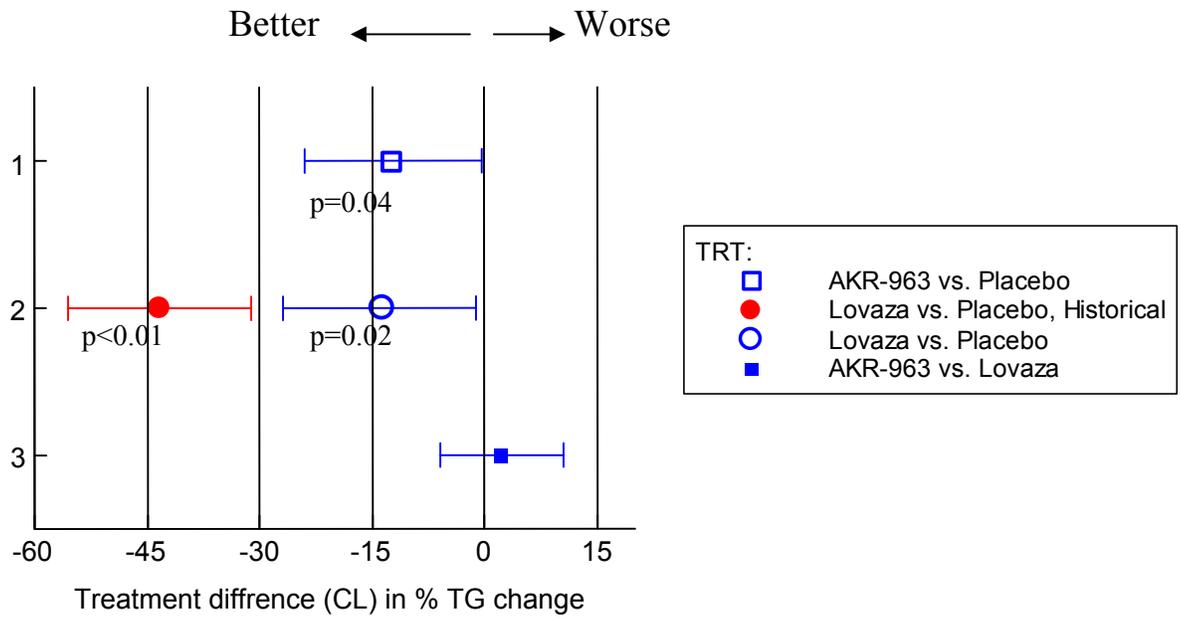
Issues of the study were:

1. The marginal result for AKR vs. placebo.
2. Validity of the 15% margin. The non-inferiority margin should be smaller than the effect of the active control in the setting of the non-inferiority trial. It appears that this may be the case for this clinical trial. The absolute value of the median difference between lovaza and placebo was 14% which is smaller than the margin. Also, an assumption critical to the interpretation of any

non-inferiority trial is the so called constancy assumption. It does not appear that the constancy assumption holds here. The constancy assumption is that the effect of Lovaza seen in a meta-analysis of previous placebo-controlled studies of Lovaza applies to (unbiasly estimates) the effect of Lovaza in the non-inferiority trial. One can only evaluate whether the constancy assumption is valid directly if the trial has a placebo arm, and most NI trials don't. But this one does. The Lovaza effect (-14%) in the current study was smaller than its historical effect (-45%) with non-overlapping 95% confidence intervals. Therefore, the margin of 15% should not be used to evaluate non-inferiority in this trial.

Figure 1 displays the 95% confidence intervals of the 3 study comparisons in blue and the historical 95% confidence interval of Lovaza vs. placebo in red.

**Figure 1 Treatment differences (CI) for current study and historical data**



## 2.2 Data Sources

Analysis dataset data definition (submission dated January 31, 2013):

<\\cdsesub1\evsprod\nda204977\0000\m5\datasets\trgg-963-002\analysis\adam\datasets\>

Information amendment (submission dated July 3, 2013):

<\\cdsesub1\evsprod\nda204977\0008\m1\us\111-info-amendment\1113-efficacy-amend\efficacy.pdf>

<\\cdsesub1\evsprod\nda204977\0008\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\severe-hypertriglyceridemia\5351-stud-rep-contr\trgg-963-002-reassessment\report-body.pdf>

## 3 STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Design and Endpoints

Study TRGG-963-002 was a randomized, double-blind, placebo and active controlled trial. Treatment arms were AKR-963, Lovaza (active control reference) and placebo. The 505(b)(2) application relies on FDA's findings of safety and effectiveness for the reference drug, Lovaza (omega-3-acid ethyl esters) capsules which was approved under NDA 21-654 in 2006. The proposed indication for AKR-963 is for use as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia ( $TG \geq 500$  mg/dL).

Approximately 240 patients were to be randomized at 68 sites in the US. The 5:5:2 randomization was stratified by baseline TG ( $<750$  mg/dL or  $\geq 750$  mg/dL), diabetes status (no diabetes, diabetes with  $HbA1c < 8.0\%$ , or diabetes with  $HbA1c \geq 8.0\%$ ), and statin use (yes or no).

The up to 82-week study consisted of a 6 week 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) (Figure 2).

**Figure 2 Study design**

Diet Lead-In				Double-Blind Treatment Period A				Double-Blind Treatment Period B					Safety Extension Period Period C					
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	Visit	E1	E2	E3	EFinal
Week	-6	-2	-1	0	2	6	11	12	20	28	36	44	52	Week	52	60	68	
	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓					
	AKR-963 3,600 mg (n=100)				AKR-963 3,600 mg (n=120)				<b>AKR-963 3,600 mg</b>									
	LOVAZA 3,600 mg (n=100)				LOVAZA 3,600 mg (n=120)				<b>LOVAZA 3,600 mg</b>									
	Placebo (n=40)																	

The primary efficacy variable was TG percent change from baseline to the end of Period A (Week 12).

Secondary efficacy variables were percent changes from baseline to Period A for the following:

- non-high-density lipoprotein cholesterol (non-HDL-C),
- very low-density lipoprotein cholesterol (VLDL-C),
- low-density lipoprotein cholesterol (LDL-C), and
- high-density lipoprotein cholesterol (HDL-C).

### **The null hypotheses:**

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

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

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

### **Baseline definition:**

Only fasting measurements will be considered valid for baseline. For TG, baseline is defined as the average of the measurements at Visit 2 (Week -2), Visit 3 (Week -1), Visit 3 repeat if it occurs, and Visit 4 (Week 0). If any of these measurements are missing, the average of the remaining measurements will be used as baseline. For all other outcome variables, baseline is defined as the measurement at Visit 4 (Week 0). If this measurement is missing, the last measurement taken prior to randomization will be used as baseline.

### **Endpoint definition**

Only fasting measurements taken less than 1 week after the last dose of study medication will be considered valid for endpoint. For TG, endpoint is defined as the average of the measurements at Visit 7 (Week 11) and Visit 8 (Week 12). If either of these measurements is missing, the other measurement will be used as endpoint. If both of these measurements are missing, the last measurement taken during Period A (LOCF) will be used as endpoint.

### **3.1.2 Statistical Methodologies**

#### **Sample size**

The sponsor planned sample size accounted for multiple comparisons to placebo which turned out not necessary. Therefore, the power is more than 90%.

The plan is to randomize 240 patients (100/active treatment group and 40 placebo group) to have a total of 204 evaluable patients for the entire study (14% to 20% attrition rate). An evaluable sample size of 85 patients/active treatment group and 34 patients in the placebo group provides 90% power (0.025 2-sided alpha adjusting to account for multiple comparisons to placebo) to detect a difference of 22% in TG % change between active treatment and placebo, assuming a 30% standard deviation.

For the non-inferiority comparison of (AKR-Lovaza), the evaluable sample size of 85/group (100 randomized per group) provides 90% power (alpha=0.025) assuming a 30% standard deviation and a margin of 15%.

The study randomized a total of 254 patients with 106, 105 and 43 patients to AKR-963, Lovaza and placebo, respectively.

### **Study population:**

The MITT (Modified Intent-to-Treat) population was the primary analysis population for efficacy evaluation. The MITT population included all randomized patients who consumed at least 1 dose of study medication and provided at least 1 post-randomization blood sample for efficacy evaluation. Four randomized patients without post-randomization data were excluded from the MITT population (2 each in the active treatment groups). The exposure of all 4 patients were less than 4 weeks (<1 week for 3 patients and 3 weeks for one Lovaza patient). The reasons for early withdrawal were 'By patient' and 'Other' (1 each/active treatment group).

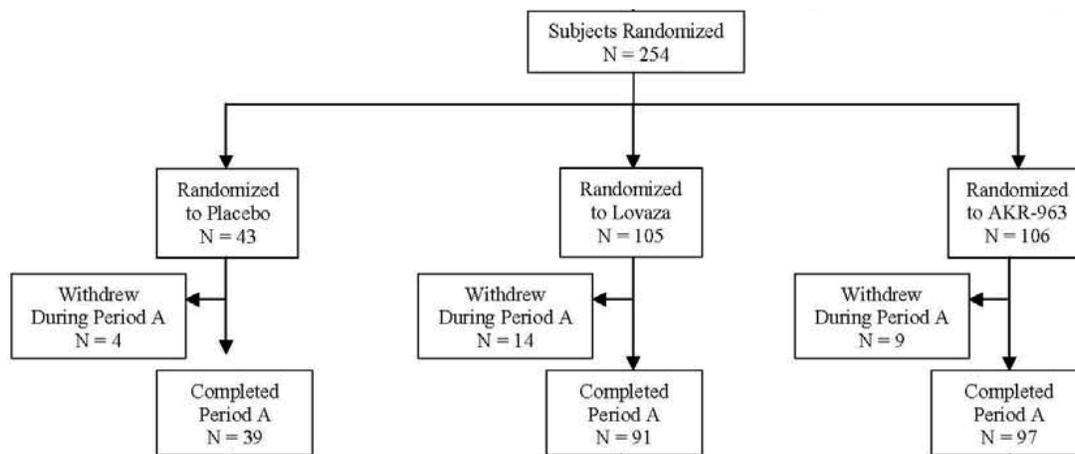
### **Statistical analysis plan (SAP) efficacy analyses:**

Analysis of variance (ANOVA) was the pre-specified primary analysis to assess the percent change in TG from baseline to period A. The model will include treatment, baseline TG category, diabetes status, and concurrent statin use as factors. However, prior to the performing of parametric analysis (ANOVA), the normality assumptions of residuals will be tested using Shapiro-Wilk test. If significant departures from normality are observed (p-value < 0.01), an analysis based on ranks of percent change will be performed. Medians of differences and Hodges-Lehmann 95% confidence intervals will be calculated, and p-values will be obtained from Wilcoxon rank-sum tests.

### 3.1.3 Patient Disposition, Demographic and Baseline Characteristics

Out of a total of 254 patients randomized, 27 (10.6%) patients withdrew from Period A. In total 227 (89.4%) patients completed Period A. Figure 3 displays patient disposition and Table 2 the reason for discontinuation.

**Figure 3 Patient disposition**



**Table 2 Reason for discontinuation**

Reason for Discontinuation	Treatment		
	Akr-963 n=106	Lovaza n=105	Placebo n=43
Adverse event	2 (2%)	2 (2%)	0
Other	3 (3%)	4 (4%)	1 (2%)
Protocol violation	0	3 (3%)	1 (2%)
Withdrawal by subject	4 (4%)	5 (5%)	2 (5%)
Completer	97 (92%)	91 (87%)	39 (91%)

Table 3 displays patient demographics and baseline characteristics. The mean age of patients was 50.9 years. Most patients were male (72.4%), Caucasian (91.7%) and less than 65 years of age (93.3%). Most patients were not taking a statin at baseline. 62.6% of patients were not diabetic. Median TG level at baseline was 675 mg/dl. 57.5% of patients were in baseline TG <750 mg/dL category.

**Table 3 Patient demographics and characteristics**

Characteristic	Placebo (N = 43)	Lovaza (N = 105)	AKR-963 (N = 106)	Total (N = 254)
Age (years)				
n	43	105	106	254
Mean (SD)	51.7 (11.14)	51.2 (9.06)	50.4 (9.88)	50.9 (9.75)
Age group (n, %)				
<65 years	39 (90.7%)	97 (92.4%)	101 (95.3%)	237 (93.3%)
≥65 years	4 (9.3%)	8 (7.6%)	5 (4.7%)	17 (6.7%)
Sex (n, %)				
Male	32 (74.4%)	77 (73.3%)	75 (70.8%)	184 (72.4%)
Female	11 (25.6%)	28 (26.7%)	31 (29.2%)	70 (27.6%)
Ethnicity (n, %)				
Not Hispanic or Latino	35 (81.4%)	88 (83.8%)	87 (82.1%)	210 (82.7%)
Hispanic or Latino	8 (18.6%)	17 (16.2%)	19 (17.9%)	44 (17.3%)
Race (n, %)				
White/Caucasian	38 (88.4%)	94 (89.5%)	101 (95.3%)	233 (91.7%)
Black/African or African American	2 (4.7%)	6 (5.7%)	3 (2.8%)	11 (4.3%)
Asian	1 (2.3%)	3 (2.9%)	0 (0.0%)	4 (1.6%)
Native Hawaiian or Pacific Islander	1 (2.3%)	1 (1.0%)	0 (0.0%)	2 (0.8%)
American Indian or Alaska Native	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.4%)
Multiple	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.4%)
Other	1 (2.3%)	0 (0.0%)	1 (0.9%)	2 (0.8%)
Diabetes status (n, %)				

<b>Characteristic</b>	<b>Placebo (N = 43)</b>	<b>Lovaza (N = 105)</b>	<b>AKR-963 (N = 106)</b>	<b>Total (N = 254)</b>
No diabetes	28 (65.1%)	65 (61.9%)	66 (62.3%)	159 (62.6%)
Diabetes with HbA <sub>1c</sub> <8.0%	11 (25.6%)	25 (23.8%)	27 (25.5%)	63 (24.8%)
Diabetes with HbA <sub>1c</sub> ≥8.0%	4 (9.3%)	15 (14.3%)	13 (12.3%)	32 (12.6%)
Statin use (n, %)				
No	33 (76.7%)	84 (80.0%)	84 (79.2%)	201 (79.1%)
Yes	10 (23.3%)	21 (20.0%)	22 (20.8%)	53 (20.9%)
Triglycerides category (n, %)				
<750 mg/dL	24 (55.8%)	65 (61.9%)	57 (53.8%)	146 (57.5%)
≥750 mg/dL	19 (44.2%)	40 (38.1%)	49 (46.2%)	108 (42.5%)
Triglycerides [1] (mg/dL)				
n	43	105	106	254
Mean (SD)	750.8 (252.65)	732.4 (235.85)	789.1 (257.01)	759.2 (248.12)
Median	624.0	655.3	715.3	675.0

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

2. Baseline was defined as the Visit 4 (Week 0) measurement. If this measurement was missing, the last measurement taken prior to randomization was used as the baseline value.

HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; SD = standard deviation; VLDL-C = very low-density lipoprotein cholesterol.

## Missing data

A total of 24 patients (10%) of the 250 patients (MITT population) had missing TG data during Phase A (endpoint TG not an average of weeks 11 and 12).

**Table 4 Last data point for subjects not having both Week 11 and Week 12 TG**

Treatment	Week (last data point)				
	Week 1 (unscheduled)	Week 2	Week 6	Week 11 (Week 12 missing)	Week 12 (week 11 missing)
AKR (n=104)	0	3	2	1	1
Lovaza (n=103)	1	4	3	2	3
Placebo (n=43)	1	1	2	0	0

## Sponsor's analyses and conclusion

The primary endpoint was TG percent change from baseline to endpoint. Table 5 displays the median % change in TG from baseline Period A endpoint for the MITT population. Table 5 was sponsor's Table 8 without the unnecessary p-value adjustment for the 2 active vs. placebo comparisons.

**Table 5 TG (mg/dL) % change from baseline to Period A endpoint - MITT**

Analysis Variable	Placebo	Lovaza	AKR-963 (N = 104)
n [1]	43	103	104
Baseline [2] median (Q1, Q3)	624 (555, 948)	655 (546, 879)	702 (577, 949)
Endpoint [3] median (Q1, Q3)	611 (459, 779)	495 (338, 693)	513.5 (398, 766)
Median (Q1, Q3) percent change	-17.4 (-32.1, 16.0)	-26.8 (-46.5, -7.2)	-24.7 (-39.2, -5.8)
Median of differences relative to placebo			
Estimate		-14.0	-12.2
95% CI		(-26.9, -1.1)	(-23.9, -0.4)
p-value		0.0234	0.0412
Median of differences relative to Lovaza			
Estimate			2.3
95% CI			(-6.0, 10.5)
p-value			0.5768

95% CIs were estimated with the Hodges-Lehmann method. P-values were from the Wilcoxon rank-sum test.

1. Includes subjects with non-missing values at baseline and Period A endpoint.

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

3. Endpoint was defined as the average of the measurements taken at Visit 7 (Week 11) and Visit 8 (Week 12).

If either of these measurements were missing, the other measurement was used as the endpoint TG value.

If both of these measurements were missing, the last measurement taken during Period A (last observation carried forward) was used as the endpoint TG value.

CI = confidence interval; Q1 = first quartile; Q3 = third quartile; TG = triglycerides.

The sponsor concluded that 'After 12 weeks of double-blind treatments in the MITT Population, the % reduction in TG with AKR-963 was non-inferior to that with Lovaza, based on the prespecified non-inferiority margin of 15%. Similar findings in the Per-Protocol Population and

the results of sensitivity analyses support the robustness of this result. The median % change in fasting TG compared to placebo was -14.0% (p=0.0234) for Lovaza and -12.2% (p=0.0412) for AKR-963, demonstrating the assay sensitivity for evaluating non-inferiority of the two active treatments.

### Reviewer’s analysis

The 3-arm design of test drug, active control and placebo provided the trial with internal validation. The placebo group affords an opportunity to test for non-inferiority directly without explicit use of a fixed margin.

To take advantage of the 3-arm design, the difference between AKR-963 and Lovaza can be compared to a fixed percentage, e.g. 50% of the estimated treatment effect of Lovaza observed in the trial and incorporate it into the test statistic. The non-inferiority on TG change of AKR-963 to Lovaza can be claimed if the 2-sided p-value is  $\leq 0.05$ .

Let D be the mean treatment difference between AKR-963 and Lovaza in TG percent change from baseline. The 2-arm null hypothesis of inferiority using a margin of 15% can be expressed as  $H_0 : D > 15\%$  which is against the alternative hypothesis of non-inferiority,  $H_A : D \leq 15\%$ . The 3-arm null hypothesis is  $D > 0.5 (U_{\text{Lovaza}} - U_{\text{placebo}})$  vs.  $D \leq 0.5 (U_{\text{placebo}} - U_{\text{Lovaza}})$  which is equivalent to:

$$D - 0.5 (U_{\text{placebo}} - U_{\text{Lovaza}}) > 0 \text{ vs. } D - 0.5 (U_{\text{placebo}} - U_{\text{Lovaza}}) \leq 0.$$

where  $U_{\text{placebo}} - U_{\text{Lovaza}}$  is the mean treatment difference between placebo and Lovaza in TG percent change from baseline.

The hypothesis testing results using percent change from baseline is summarized in Table 6. The p values for both tests was greater than 0.05. Using this internal validation method, the non-inferiority of AKR-963 to Lovaza (based on AKR-963 retaining more than 50% of the Lovaza effect) cannot be claimed.

**Table 6 Descriptive statistics of TG % change from baseline to Period A endpoint**

Treatment for Period 01	Triglyceride Percent Change from Baseline					
	n	Median	Mean	Std Dev	Minimum	Maximum
AKR-963	104	-24.7%	-21.5%	32%	-76.5%	129%
LOVAZA	103	-26.8%	-21.5%	37.1%	-79.7%	134%
PLACEBO	43	-17.4%	-4.6%	50.6%	-73.2%	229%

**Table 7 ANOVA of non-inferiority using current trial data**

	Estimate	SE	Lower	Upper	P value
% change	-8%	4.9%	-17.7%	+1.6%	0.05
% change (log transformed)	-6.2%	5.8%	-16.1%	4.9%	0.13

\*ANOVA model included fixed factors of treatment, baseline TG strata, statin use and diabetes status

### 3.1.4 Results and Conclusions

Table 8 presents medians of baseline, endpoint TG (mg/dL) and TG % change from baseline to endpoint. The -17% median TG % change of placebo was unexpected. It is unknown if using vegetable oil as placebo has some effect on TG.

**Table 8 TG (mg/dL) and % change from baseline to Period A descriptive statistics – MITT**

<b>Analysis Variable</b>	<b>AKR-963 (N = 104)</b>	<b>Lovaza (N = 103)</b>	<b>Placebo (N = 43)</b>
Baseline median (Q1, Q3)	702 (577, 949)	655 (546, 879)	624 (555, 948)
Endpoint median (Q1, Q3)	513.5 (398, 766)	495 (338, 693)	611 (459, 779)
% change median (Q1, Q3)	-24.7 (-39.2, -5.8)	-26.8 (-46.5, -7.2)	-17.4 (-32.1, 16.0)

The median shift of Hodges-Lehmann is the median of all pairwise differences between treatment groups. The p-value is from Wilcoxon rank test. The test results vs. placebo is marginal.

**Table 9 Hodges-Lehmann median shift and 95% CL on % TG change**

	<b>Lovaza vs. placebo</b>	<b>AKR-963 vs. placebo</b>	<b>AKR-963 – Lovaza Non-inferiority</b>
Estimate (95% CI)	<b>-14.0 (-26.9, -1.1)</b>	<b>-12.2 (-23.9, -0.4)</b>	<b>+2.3 (-6.0, 10.5)</b>
p-value	0.023	0.041	

Figure 4 displays boxplots for TG % change from baseline to Weeks 2, 6 and Period A endpoint (LOCF). The medians were connected over time. Data points for each visit were on left of the boxplot. The interquartile range (IQR) (the middle 50% of the values) is represented by the rectangle's top and bottom. The adjacent values are represented by vertical lines (whiskers) extending from the top and bottom of the rectangle. Observations beyond those values are represented by outliers (triangles). The uppermost adjacent value is 75% value + 1.5 x IQR. The lowermost adjacent value is the 25% value - 1.5 x IQR. The box of placebo (green) is higher than the active treatment groups (blue and red).

Figure 4 Boxplot of TG % change by weeks

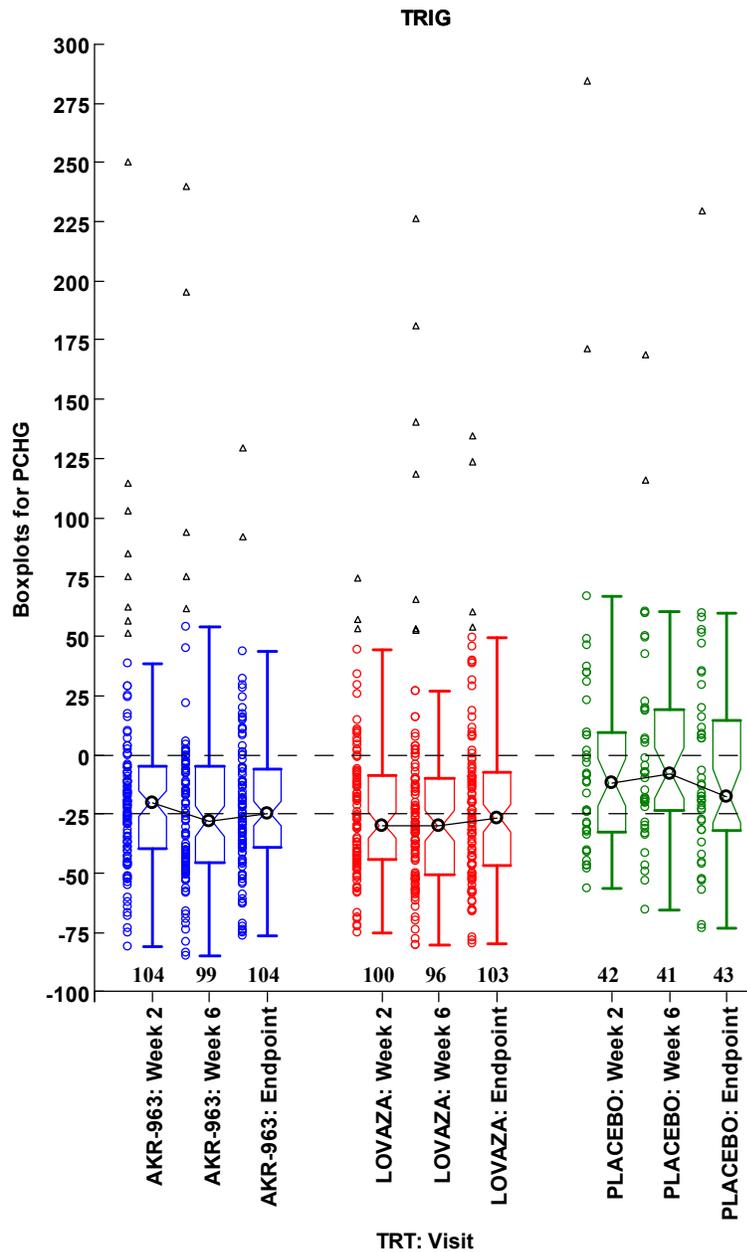


Figure 5 displays the cumulative distribution of TG % change from baseline to endpoint. The 50 percentile of the y-axis corresponds to the median TG% change of the x-axis. At lower left side of the curve, it showed that approximately 15% of patients of AKR-963 and placebo had at least 50% reduction (22% of Lovaza patients had at least 50% reduction). Approximately 80% and 65% of patients in active treatment groups and placebo group, respectively, had a TG % change  $\leq 0$ .

Figure 5 Cumulative distribution curves for TG % change

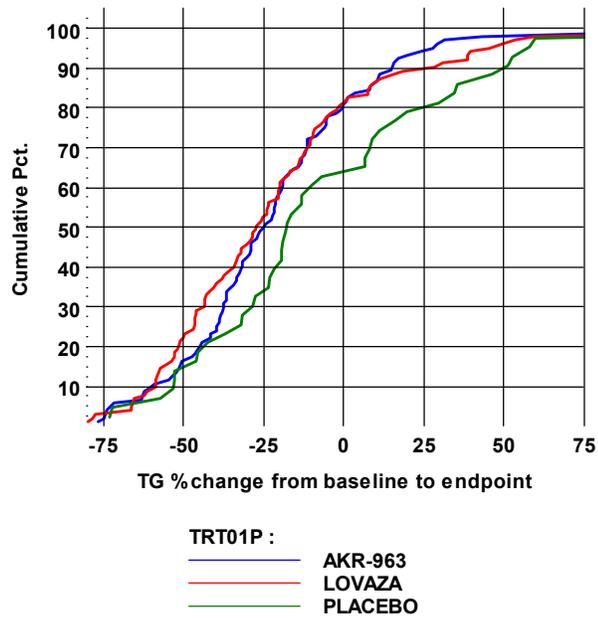


Figure 6 displays the median TG percent change from baseline during Phase A. The completers population presents the same patients from time point to time point. TG reduction of active treatments had a small increase while the reduction of placebo increased from week 6 to endpoint.

Figure 6 Median TG % change over time - Completers

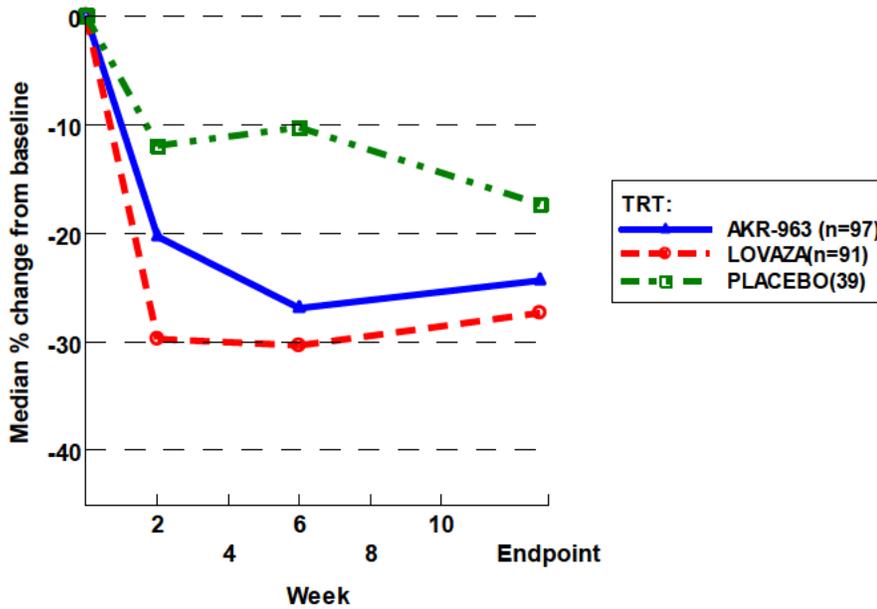


Figure 7 displays boxplots of primary and key secondary efficacy variables. LDL percent change from baseline of active treatment increased compared to placebo.

Figure 7 Boxplots for % change to endpoint of primary and secondary endpoints

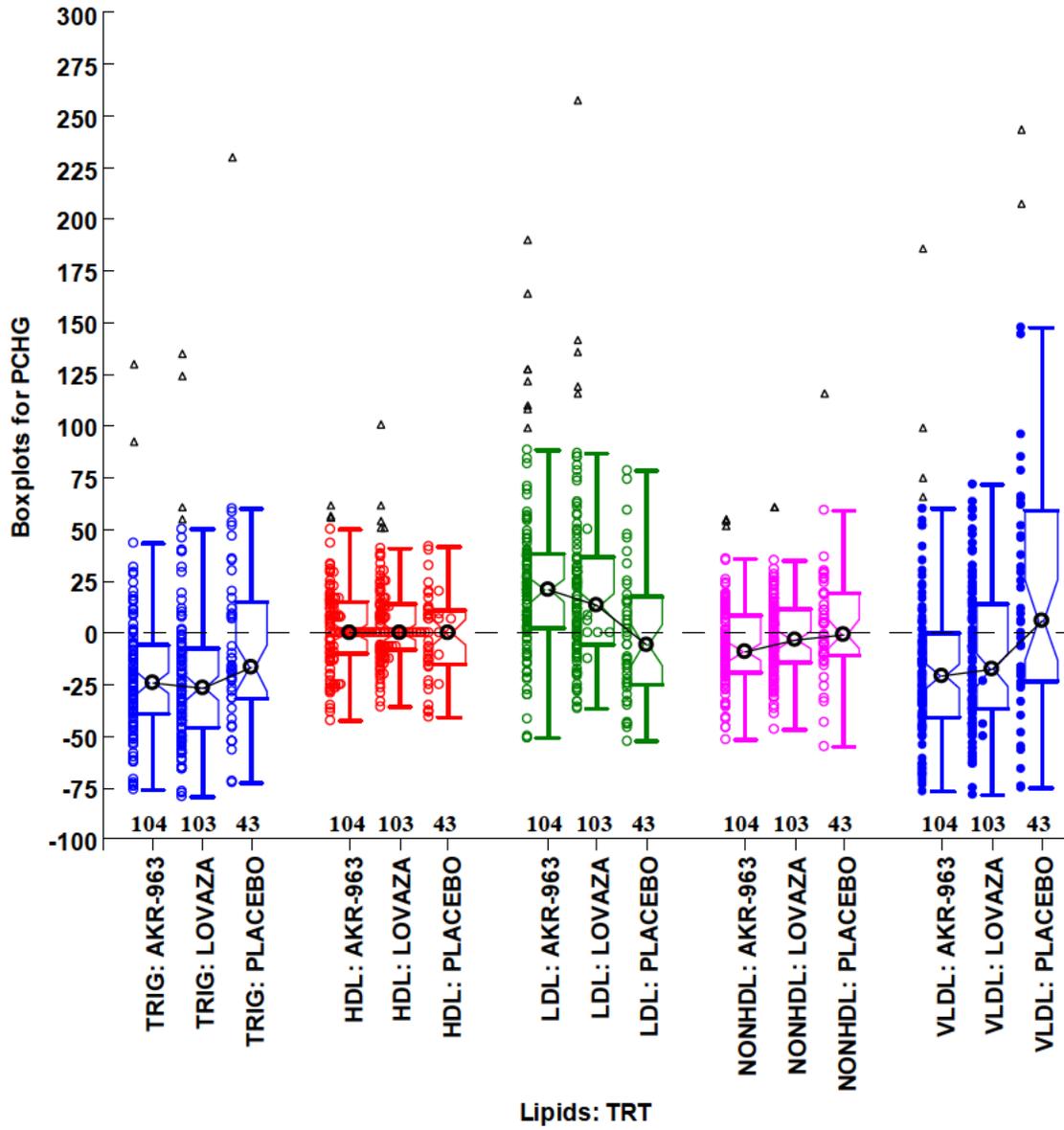
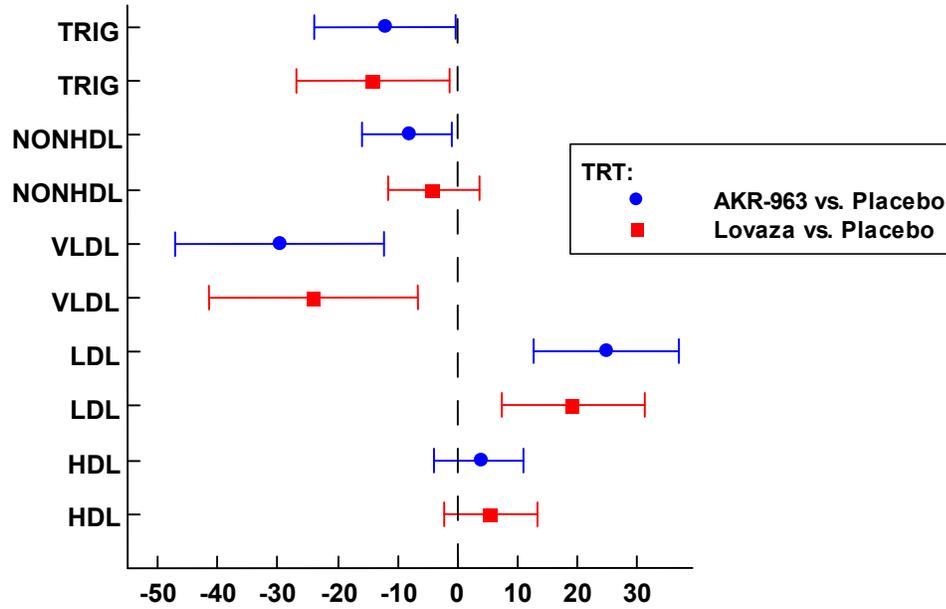


Figure 8 displays treatment difference vs. placebo with confidence intervals. For secondary efficacy variables, LDL and VLDL, the 95% confidence intervals excluded zero.

**Figure 8 Hodges-Lehmann estimates and 95% CI for treatment difference of percent change from baseline (vs. Placebo)**



## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup of gender, race, age and baseline stratification factors, statin use (Y/N), diabetes status (Y/N) and baseline TG (<750, ≥750 mg/dL) were examined using the nonparametric method of median shift and Hodges Lehmann 95% confidence intervals. These analyses were exploratory in nature. No interpretation is provided because of potential confounding factors.

### 4.1 Gender, Race, Age, and Geographic Region

The study was conducted in the US, therefore, no geographic region subgroup.

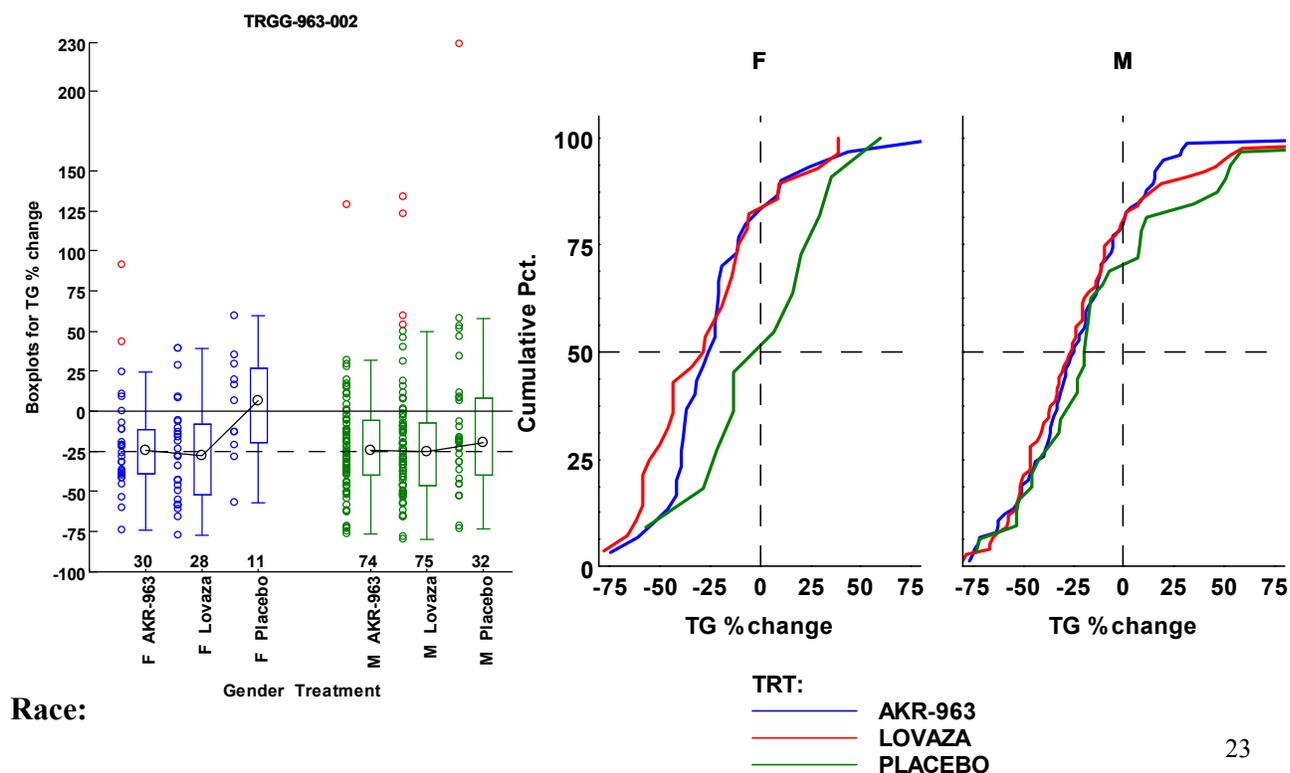
#### Gender:

Table 10 displays the exploratory analysis of TG % change to Period A endpoint by gender. Figure 9 displays Box plots and cumulative distribution curves of TG % change by gender.

**Table 10 Median shift (95% CI) by gender**

Gender n(%) (AKR, Lovaza, Placebo)	AKR vs. Placebo	Lovaza vs. Placebo	AKR-963 vs. Lovaza
Female n=69 (28%) (30, 28, 11)	-26% (-50, -4)	-30% (-54, -4)	+5% (-11, +21)
Male n=181 (72%) (74, 75, 32)	-7% (-21, +6)	-8% (-22, +6)	+1% (-9, +11)

**Figure 9 Boxplots for TG percent change from baseline by gender**

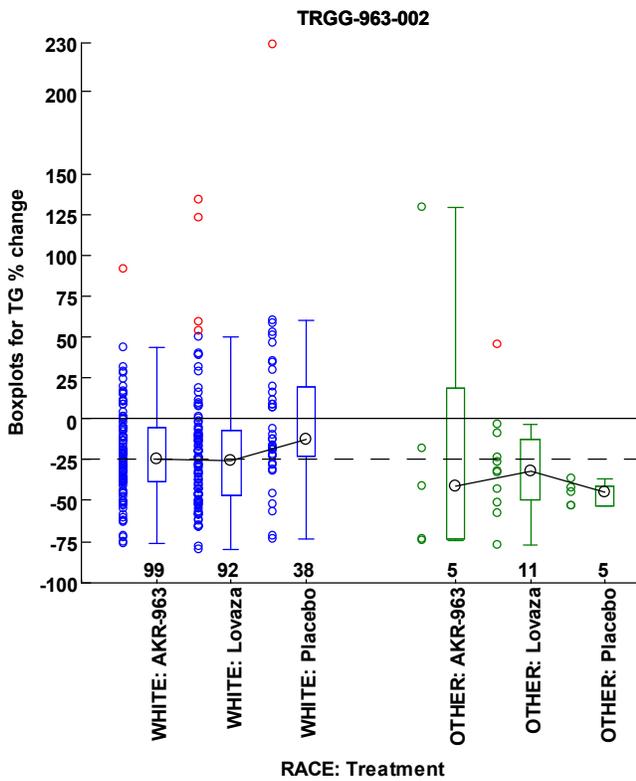


The majority of patients were Caucasians (92%).

**Table 11 TG % change median shift (95% CI) by race**

Race n(%) (AKR, Lovaza, Placebo)	AKR vs. Placebo	Lovaza vs. Placebo	AKR-963 vs. Lovaza
White n=229 (92%) (99, 92, 38)	-17% (-30, -6)	-20% (-33, -6)	+2% (-6, +11)
Other n=21 (8%) (5, 11, 5)	+4% (-32, +174)	+13% (-10, +41)	-9% (-133, +50)

**Figure 10 Boxplots for TG percent change from baseline by race (Caucasians and other)**



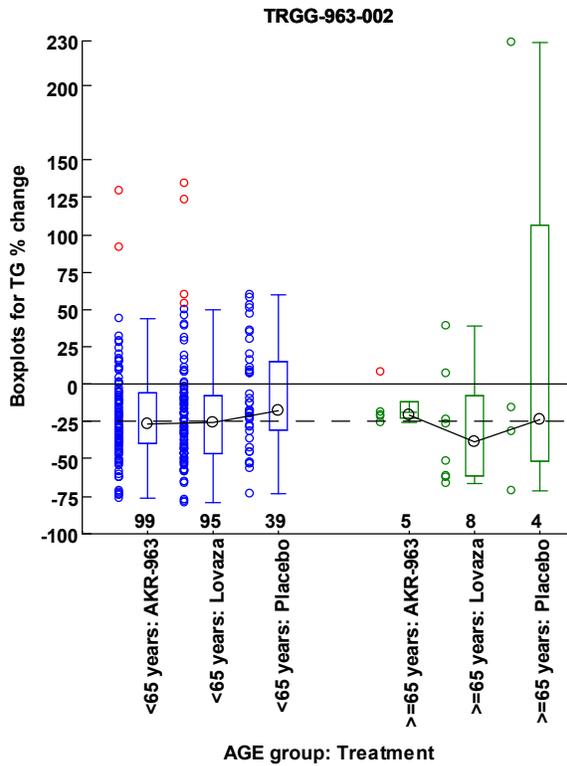
**Age group (<65, ≥65):**

93% of patients were less than 65 years of age.

**Table 12 Median shift (95% CI) by age group**

Age group n(%) (AKR, Lovaza, Placebo)	AKR vs. Placebo	Lovaza vs. Placebo	AKR-963 vs. Lovaza
<65 years n=233 (93%) (99, 95, 39)	-14% (-26, -1)	-14% (-27, -1)	+1% (-8, +9)
≥65 years n=17 (7%) (5, 8, 4)	+8% (-255, +80)	-15% (-280, +55)	+30% (-31, +45)

**Figure 11 Boxplots for TG percent change from baseline by age group**



## 4.2 Other Special/Subgroup Populations

### Baseline TG (<750 mg/dL, ≥750 mg/dL)

Figure 12 displays the cumulative distribution curves of TG percent change from baseline by baseline TG strata (sample size in legend). The median % change of placebo patients in TG baseline <750 mg/dL stratum was +7% and it was -25% in the baseline TG ≥750 mg/dL stratum.

**Table 13 Median shift (95% CI) by baseline TG group**

Baseline TG n(%) (AKR, Lovaza, Placebo)	AKR vs. Placebo	Lovaza vs. Placebo	AKR-963 vs. Lovaza
<750 mg/dL n=145 (58%) (57, 64, 24)	-24% (-40, -9)	-24% (-40, -7)	+0.1% (-10, +10)
≥750 mg/dL n=105 (42%) (47, 39, 19)	+1% (-15, +18)	-6% (-23, +12)	+7% (-8, +21)
All n=250 (100%) (104, 103, 43)	-12% (-24, +0.4)	-14% (-27, +1)	+2% (-6, +10)

**Figure 12 Cumulative distribution of % change from baseline to endpoint by baseline TG strata**

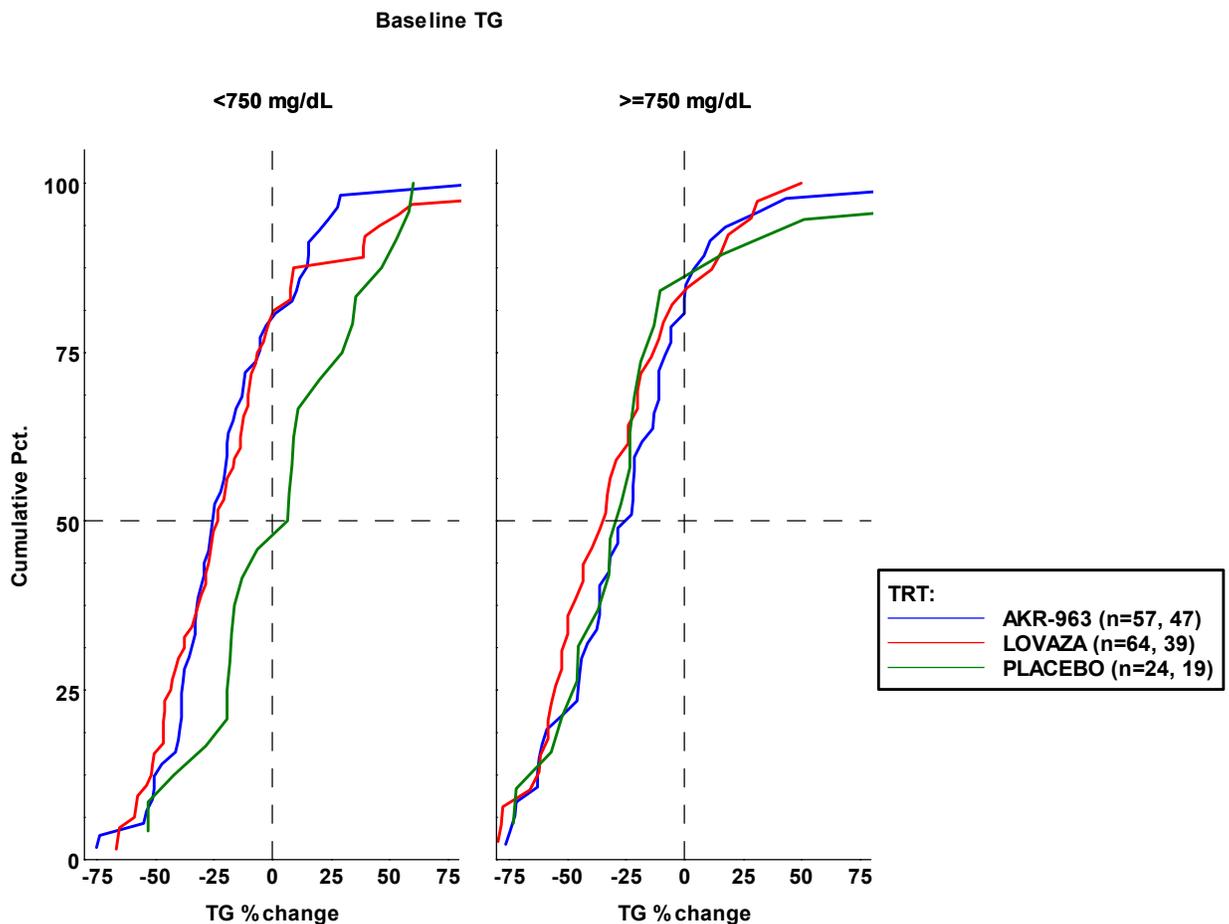


Figure 13 Median TG % change over time by baseline TG strata

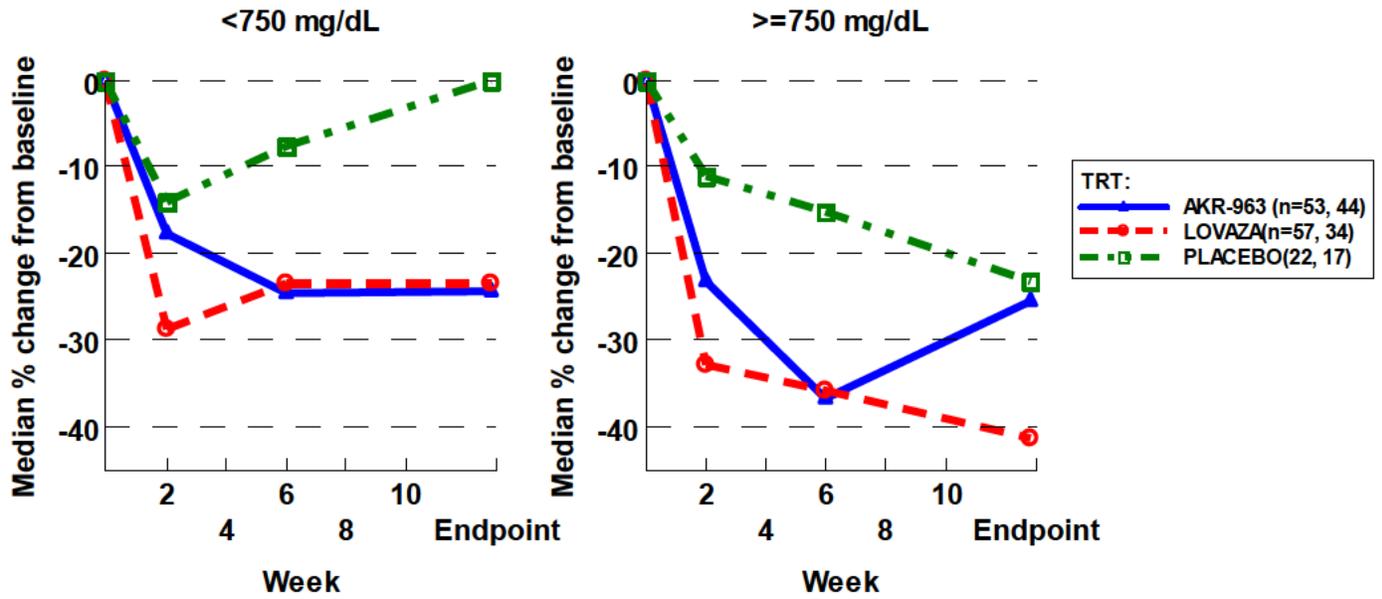
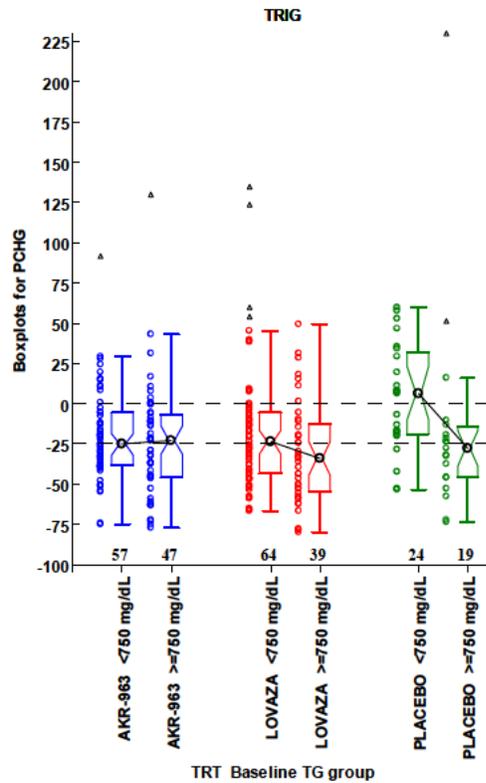


Figure 14 Boxplots for TG % change from baseline by baseline TG strata



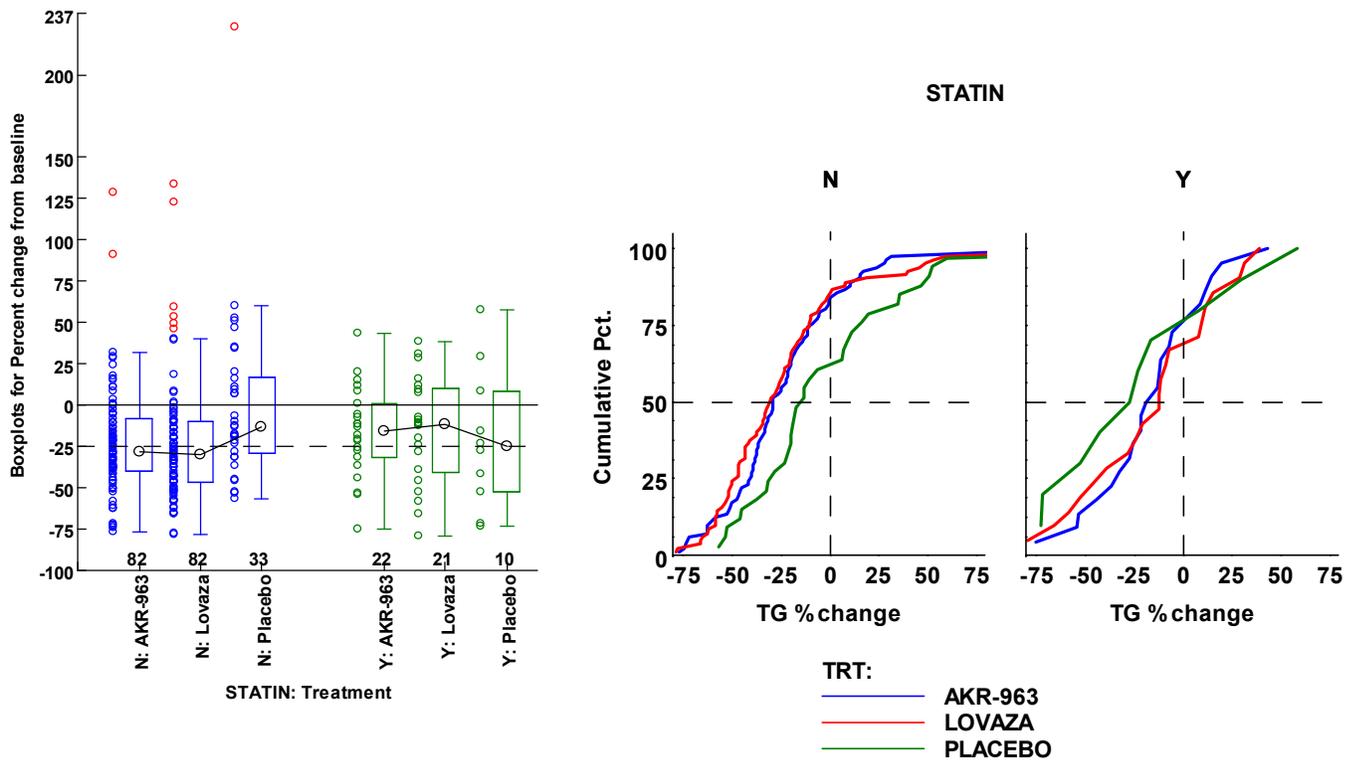
**Statin Use:**

Approximately 80% of the patients were in the No statin use stratum. Table 14 displays treatment differences from placebo and 95% CIs by baseline statin use.

**Table 14 TG change from baseline median shift (95% CI) by baseline statin use**

Baseline statin n(%) (AKR, Lovaza, Placebo)	AKR vs. Placebo	Lovaza vs. Placebo	AKR-963 vs. Lovaza
No n= 197 (79%) (82, 82, 33)	-18% (-31, -5)	-20% (-33, -7)	+3% (-6, +12)
Yes n=53 (21%) (22, 21, 10)	+9% (-22, +37)	+8% (-25, +41)	-1% (-21, +19)

**Figure 15 Boxplots for TG percent change from baseline by baseline statin use**



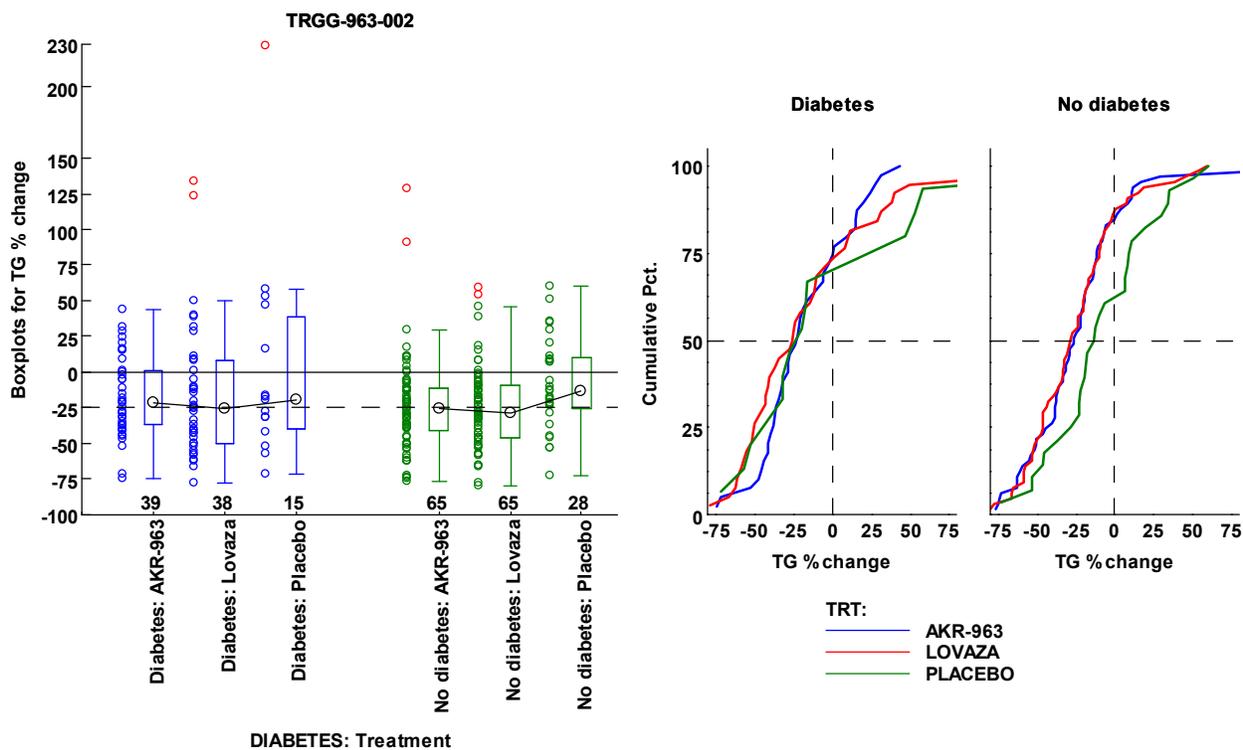
## Diabetes:

The diabetes stratum was reclassified into no diabetes and diabetes (combining strata HbA1c <8 and HbA1c ≥ 8%). Approximately 40% of patients were diabetics.

**Table 15 TG change from baseline median shift (95% CI) by baseline diabetic status**

Baseline diabetes n(%) (AKR, Lovaza, Placebo)	AKR vs. Placebo	Lovaza vs. Placebo	AKR-963 vs. Lovaza
No n=158 (63%) (65, 65, 28)	-17% (-31, -3) p=0.02	-17% (-32, -4) p=0.01	+1% (-9, +10) p=0.86
Yes n=92 (37%) (39, 38, 15)	-4% (-28, +17) p=0.66	-9% (-34, +16) p=0.49	+5% (-12, +19) p=0.55

**Figure 16 Boxplots and cumulative distribution curves by diabetes status**



## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

1. The borderline statistical significance when comparing AKR-963 to placebo.
2. The margin of 15% seems not to apply to the three arm study.
3. The generalizability of the trial results to practice.

#### Summary

- Internal to this study, the AKR-963 treatment arm “demonstrated” superior change in TG from baseline to Week 12 when compared to placebo.
  - Borderline statistical significance (and from one study)
  - Multiple sensitivity analyses were performed. The results are consistent with borderline statistical significance (and from one study)
- The effect of Lovaza (compared to placebo) is smaller in this study than in prior studies of Lovaza.
  - The upper limit of the 95% CI for the historical Lovaza effect was -31%
- The above
  - The results indicate that the constancy assumption did not hold, and a 15% margin does not seem to apply for the setting of this study
  - Raises questions on the generalizability/external validity of the results of the three arm study

### 5.2 Conclusions and Recommendations

The 3-arm study, AKR-963, Lovaza (active control reference) and placebo randomized in a ratio of 5:5:2, demonstrated marginal results for superiority of AKR-963 vs. placebo ( $p=0.041$ ) and Lovaza vs. placebo ( $p=0.023$ ). The non-inferiority margin of 15% derived from 2 small studies from Lovaza NDA. The sponsor’s re-analyses (Appendix) support the conclusion that this study is not a negative study in a sense that the 2 active drug comparisons vs. placebo with  $p<0.05$  for TG percent change provided internal validity for the non-inferiority trial and the 10.5% upper 95% confidence bound (<15% margin) of the +2.3% difference (AKR-963 vs. placebo) was within the prespecified margin.

The Clinical Pharmacology indicated that fat meal might have an effect on study medication absorption. The trial protocol did not provide instruction on study to optimize the medication administration.

## APPENDICES

### Statistical review on responses from Trygg dated July 3, 2013 to FDA request dated May 21, 2013

On May 21, 2013, FDA sent a general advice letter to the sponsor requesting the sponsor to present their opinions on why the treatment effects of AKR-963 and Lovaza were far less than expected when compared with placebo in trial Trgg-963-002. In response the sponsor later submitted two documents – an Efficacy Information Amendment and a document entitled Reanalysis of the Primary Outcome for Trygg Pharma’s Protocol TRGG-963-002 prepared by Statistics Collaborative [REDACTED] <sup>(b) (4)</sup> dated June 26, 2013.

#### Re-analyses

The “Reanalysis” document stated that ‘The reanalyses, by accounting more completely for the totality of the data and for the distribution of the outcome variables, lead to narrower confidence intervals and smaller p-value.’ (1. Introduction)

For the comparisons to placebo the reanalyses applied mixed model repeated measure (MMRM) model to TG data at Weeks 2, 6, 11/12 (endpoint). The treatment effect was estimated from the comparison at Week 11/12. Observations at Week 2 and Week 6 serve only to reduce the variability.

The reanalyses applied a randomization test that accounted for the randomization strata to calculate the p-value (1-sided) and 95% confidence intervals. ‘We re-randomized the allocation of treatment label (AKR-963, Lovaza, or placebo) to subject within the original randomization strata 1000 times and calculated the test statistic from the corresponding t-test. The p-value from the randomization test is the proportion of t values that are smaller than the value observed in the actual dataset.’

Issues of sponsor’s post-hoc analysis:

1. The post-hoc analysis is not prespecified. Therefore, exploratory in nature.
2. Definition for ‘endpoint’ seems not following protocol to use Week 11 or Week 12 if either one is missing. The Modified method (Section 5.) stated that ‘Results using repeated measures used the original percent changes at weeks 2, 6, 11, and 12. Thus, our estimates will not be identical to the data on means previously submitted to the FDA.’ The definition for endpoint from sponsor’s footnote of Table 1 was ‘the average of the measurements taken at Visit 7 (Week 11) and Visit 8 (Week 12). The model did not use any imputation for missing data.’ It is not clear if the protocol defined endpoint as ‘the average of the measurements taken at Week 11 and Week 12 was followed. That is, if either of these measurements were missing, the other measurement was used.’

The randomization (permutation) test assumes the observations are exchangeable (within strata) under the null hypothesis. The allocation of treatment (AKR-963, Lovaza, or placebo) to subjects was re-randomized 1000 times with the simulated p-value as the proportion of t-statistics that are smaller than the value observed in the actual dataset (one-sided, Table 1).

**Table 16 Sponsor’s estimates for TG treatment effect - Superiority**

Analysis Variable	Lovaza (N = 103)	AKR-963 (N = 104)
<i>Tests for superiority</i>		
n	103	104
Mean of differences relative to placebo [1, 2]		
Estimate	-16.9	-16.8
95% CI calculated from randomization test	(-31.8, -5.0)	(-30.5, -3.4)
p-value (one-sided)	0.002	0.005

1. Baseline was defined as the average of the measurements taken at Visit 2 (Week -2), Visit 3 (Week -1), a repeat of Visit 3 (if applicable), and Visit 4 (Week 0). If any of these measurements were missing, the average of the available measurements was used to determine the baseline TG value. Endpoint was defined as the average of the measurements taken at Visit 7 (Week 11) and Visit 8 (Week 12). The model did not use any imputation for missing data. See text for an explanation of the model.
2. Calculated from longitudinal model (SAS PROC MIXED for estimate; randomization test for p-value and confidence intervals).

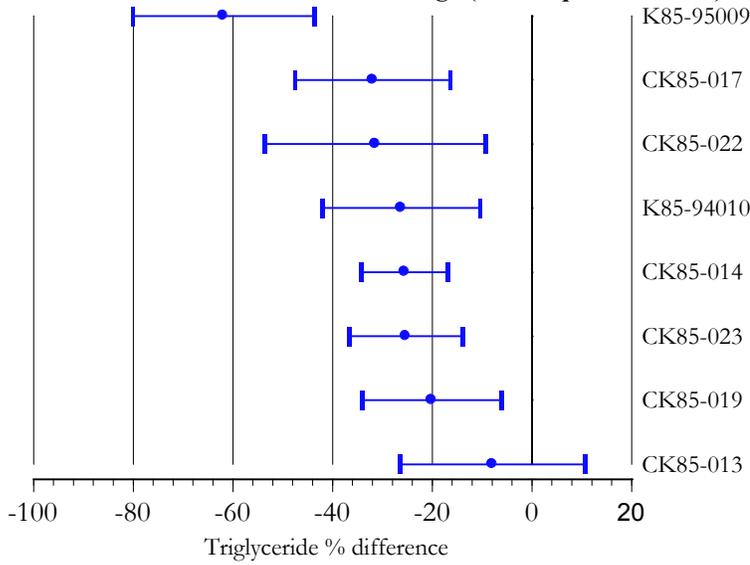
The re-analysis method for non-inferiority yielded 8.7% as the lower bound for the 95% CI on the difference (AKR-963 minus Lovaza) in mean change (from baseline to week 11/12) of TG. The confidence interval was based on an ANOVA model and incorporated a re-randomization procedure that accounted for the randomization strata.

### **Efficacy information amendment**

Concerning constancy assumption, the sponsor stated that “Notably, the pooled analysis of the 2 relatively small trials of Lovaza (conducted almost 2 decades ago) that formed the basis for FDA approval showed a median percent change from baseline (-44.9%) that was at least 50% greater than that of any controlled study that has been reported since. Thus, in response to the comments in the May 21, 2013, DMEP letter regarding the “constancy assumption”, the applicant believes that this assumption has been fulfilled if the data beyond these 2 original Lovaza studies are considered.”

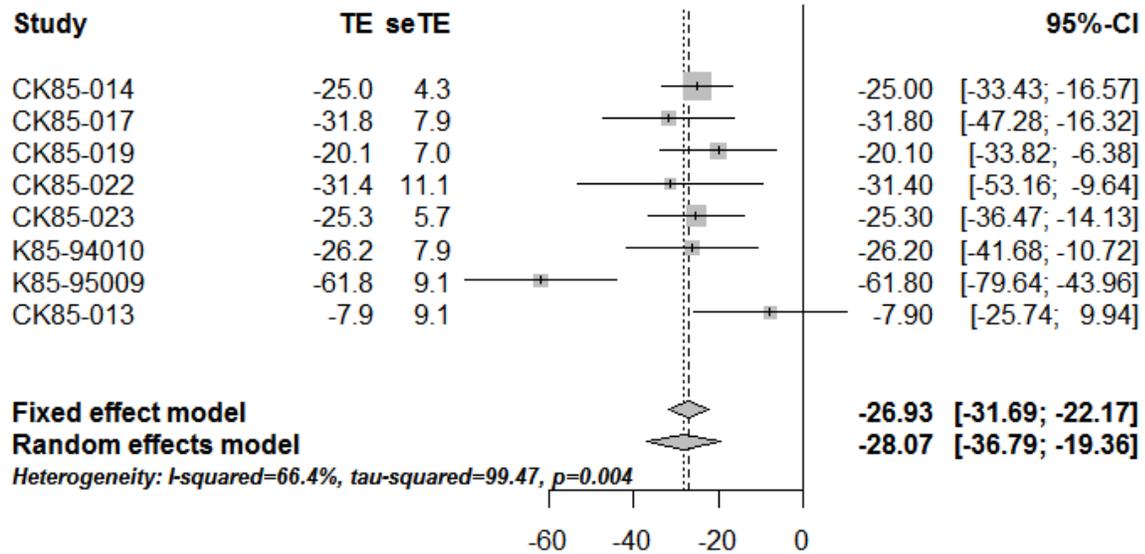
Figure 17 display treatment differences between Lovaza and placebo in TG % change by study from the historical data (NDA 21-654). The 15% margin was derived from 2 US studies pooled on basis of high baseline TG level (TG ≥ 500 mg/dL and < 2000 mg/dL) (K85-95009 and K85-94010). Note that the 95% CI from study K85-95009 does not overlap with the 95% CIs for studies CK85-014, CK85-019, CK85-023, K85-94010 and CK85-013.

**Figure 17 Treatment difference in TG % change (Least squared means) – Lovaza NDA data**

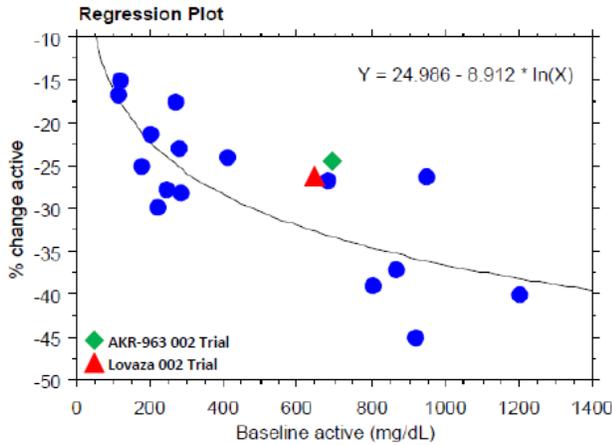


I performed a meta-analysis on all Lovaza NDA studies using random effects model (due to the significant heterogeneity,  $p=0.004$ ). The least squared mean (LSM) treatment differences and 95% confidence intervals in TG % change were estimated from ANCOVA model.

**Figure 18. Meta-analysis of Lovaza NDA studies**



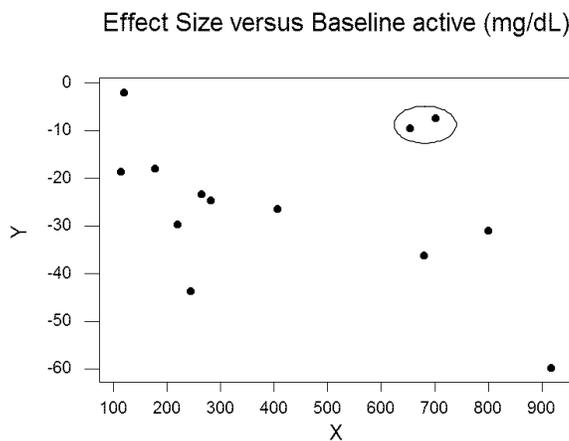
Additionally, concerning consistency of current data to all study data, the sponsor stated that “Because the studies summarized in *Table 1.11.3-3* include patients with differing levels of hypertriglyceridemia, it is important to demonstrate (*Figure 1.11.3-1*) that the percentage reduction in triglycerides from baseline is increased as the baseline level of triglycerides increases. The results of Study TRGG-963-002 are indicated as green (AKR-963) and red (Lovaza) points in *Figure 1.11.3-1*, and demonstrate that the findings are consistent with the body of data reported from studies in the indication being requested in NDA 204977.”



**Figure 1.11.3-1. Regression Plot Showing the Relationship (Unweighted) Between Baseline Triglyceride Serum Concentrations and the Triglyceride Percent Change From Baseline**

Instead of presenting the % change of active drugs, Figure 19 displays the effect size (active treatment median minus placebo median) by median baseline TG. The difference in medians is used as the effect size as that was the information available for all studies. The smaller effect size of current trial data (circled, AKR-963 and Lovaza) did not demonstrate consistency with the rest of studies.

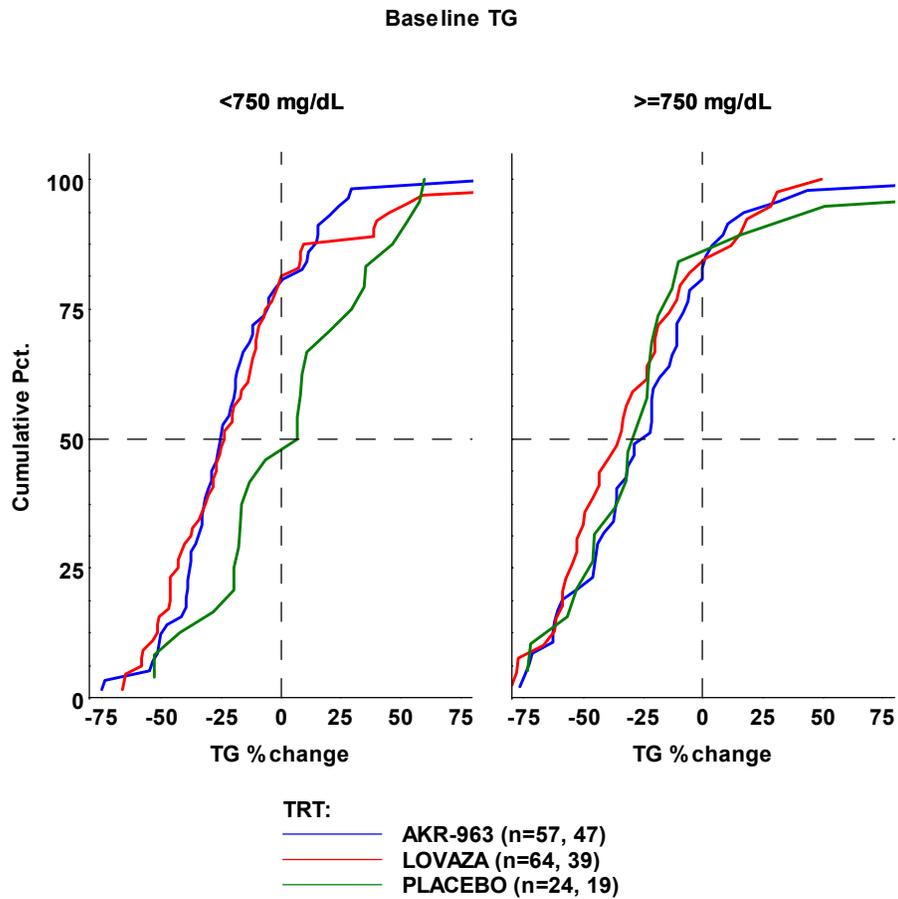
**Figure 19 TG % change effect size versus baseline TG of active treatment**



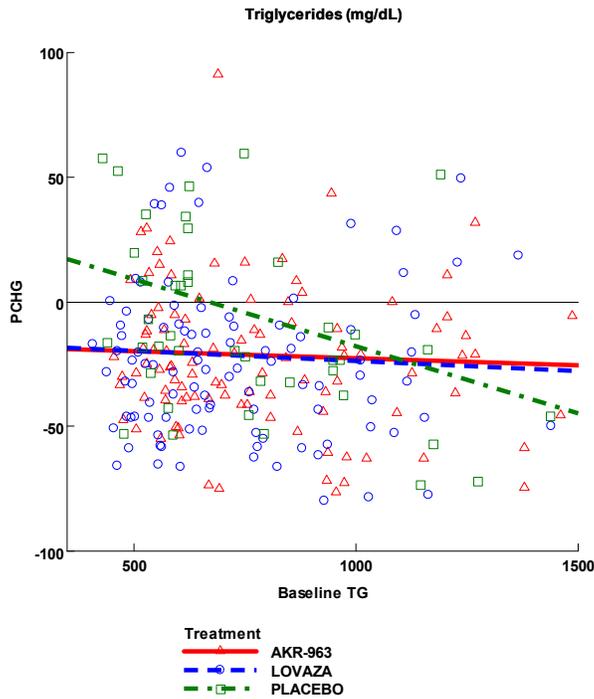
Furthermore, the current patient level data did not ‘... demonstrate that the percentage reduction in TG from baseline is increased as the baseline level of TG increases.’ (Figures 20 & 21). Figure 20 displays the cumulative distribution curves of TG percent change from baseline by baseline TG strata (sample size in legend). In baseline TG < 750 mg/dL stratum, median of AKR-963 was -25%. In baseline TG ≥ 750 mg/dL stratum, the median was -22%. The almost flat regression lines of the active drugs did not demonstrate the increase of TG % reduction as baseline TG increased (Fig 21). Table below shows correlation of TG % change and baseline TG was very low for the active drugs.

Treatment	n	r	r <sup>2</sup>	p-value Rho=0
AKR-963	104	-0.044	0.002	0.66
Lovaza	103	-0.052	0.003	0.60
Placebo	43	-0.268	0.072	0.08

Figure 20 Cumulative distribution of % change from baseline to endpoint by baseline TG strata



**Figure 21 TG % change from baseline by baseline TG**



**Conclusion on sponsor’s reanalyses:**

The sponsor’s reanalyses on TG percent change from baseline to Week 12 applied re-randomization test (re-randomize within the baseline strata of TG group, statin use and diabetes status) and mixed model repeated measure (MMRM) for Weeks 2, 6 and 12 data was a reasonable approach to deal with the significant departure from normality of residuals. The reanalysis support the primary efficacy analysis of active treatment vs. placebo, however, the analyses were post-hoc analyses.

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/s/  
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LEE PING PIAN  
10/15/2013

MARK D ROTHMANN  
10/15/2013  
I concur

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 204-977**

**Applicant: Trygg Pharma**

**Stamp Date: January 31, 2013**

**Drug Name: AKR-963**

**NDA/BLA Type: 505 (b) (2)  
reference LOVAZA**

**Reviewer: Lee Ping Pian**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?   Yes**

If the NDA/BLA is not fileable from the statistical 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.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	na			
Appropriate references for novel statistical methodology (if present) are included.	na			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	na			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5\_Statistics Filing Checklist for a New NDA 024-977

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

### Brief summary of controlled clinical trials

The following table contains information on the relevant trial contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
<b>TRGG-963-002</b>	<p><b>Randomized, double-blind, placebo-controlled, Parallel-group study in patients with severe hypertriglyceridemia (baseline TG&gt;500 and TG&lt;1500 mg/dL)</b></p> <p><b>Duration: up to 82 weeks with primary efficacy analysis at week 12 after randomization. (Fig 1)</b></p>	<p><b>Placebo: 43</b>  <b>Lovaza: 105</b>  <b>AKR-963: 106</b></p>	<p><b>TG % change from baseline to Period A (week 12). /ANCOVA with factors for treatment, baseline TG category, diabetes status, and concurrent statin use</b></p>	<p><b>Median % change from median baseline of 670 mg/dL TG:</b>  <b>-17% placebo,</b>  <b>-27% Lovaza,</b>  <b>-25% AKR-963</b></p> <p><b>Adjusted p-value vs. placebo: p=0.04 (both trt)</b></p> <p><b>Median difference of AKR-963 vs. Lovaza (CI):</b>  <b>2.3% (-6%, 11%)</b></p>

**Figure 1. Study design**

**Double-blind treatment periods:**

Randomization													
	Diet Lead-In			Double-Blind Treatment Period A					Double-Blind Treatment Period B				
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
Week	-6	-2	-1	0	2	6	11	12	20	28	36	44	52
	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
	AKR-963 3,600 mg (n=100)					AKR-963 3,600 mg (n=120)							
	LOVAZA 3,600 mg (n=100)					LOVAZA 3,600 mg (n=120)							
	Placebo (n=40)												

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Safety extension period:

<i>Safety Extension Period</i>				
<i>Period C</i>				
<i>Visit</i>	<i>E1</i>	<i>E2</i>	<i>E3</i>	<i>EFinal</i>
<i>Week</i>	<i>52</i>	<i>60</i>	<i>68</i>	

*AKR-963 3,600 mg*  
*LOVAZA 3,600 mg*

Lee Ping Pian

03/13/2013

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Reviewing Statistician

\_\_\_\_\_  
Date

Todd Sahlroot

03/13/2013

\_\_\_\_\_  
Supervisor/Team Leader

\_\_\_\_\_  
Date

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/s/  
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LEE PING PIAN  
04/04/2013

JON T SAHLROOT  
04/05/2013