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RESEARCH**

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STATISTICAL REVIEW(S)



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Statistical Review and Evaluation

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

Tesamorelin (TH9507) is a synthetic analog of human growth hormone releasing factor developed for the treatment of excess abdominal fat in HIV patients with lipodystrophy.

The submission included one phase 2 study (referred to as Study 8) and two phase 3 studies (referred to as Studies 10 & 11/12) to evaluate subcutaneous tesamorelin (TH9507) vs. placebo in the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy. The phase 3 studies were similarly designed with a 26-week main phase for efficacy assessment using VAT (Visceral Adipose Tissue) percent change from baseline to week 26 as the primary efficacy endpoint and a 26-week extension phase which re-randomized patients who completed the TH9507 treatment in the main phase to continue on TH9507 or placebo. The efficacy objective of the 26-week withdrawal extension phase was to explore the efficacy of TH9507 following discontinuation. The placebo-treated patients in the main phase were switched to TH9507 (2 mg) in the extension phase.

Study 11 was undertaken to confirm the findings of Study 10.

1.1 Conclusions and Recommendations

Based on results from studies 10 and 11, 2 mg subcutaneous tesamorelin (TH9507) was statistically significantly superior to placebo in VAT reduction, the primary efficacy endpoint, from baseline to week 26 (Table 1 and Fig 1). Triglycerides and the patient reported outcome, belly appearance distress, were not consistently statistically different from placebo. IGF-1 was statistically significantly increased in the TH9507 group compared to placebo in both studies.

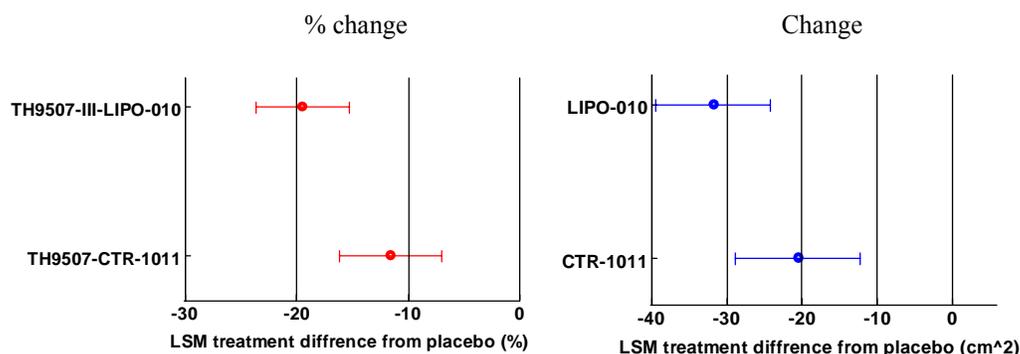
Results from the re-randomized extension withdrawal phase showed that VAT increased when TH9507 was discontinued. Continuation of TH9507 2 mg treatment to week 52 was necessary in order to maintain the effect of the drug beyond week 26.

Table 1 ANCOVA* results for VAT % change and change from baseline to Week 26 – ITT, LOCF

Study		TH9507 (2 mg)		Placebo		Treatment difference from placebo LSM, (SE), [95% CI], p-value
		n	Mean	n	Mean	
10	Baseline (SD)	272	178.3 (76.9)	136	171.0 (76.9)	
	% change (SE)		-17.8% (1.6)		+2.2% (2.2)	-19.6% (2.7) [-23.7, -15.3] p<0.001
	Change (SE)	272	-27.4 (2.2)	136	+4.4 (3.2)	-31.9 (3.9) [-39.5, -24.3] p<0.001
11	Baseline (SD)	268	186.5 (86.6)	126	194.9 (95.5)	
	% change (SE)		-13.8% (1.5)		-2.4% (2.2)	-11.7% (2.7) [-16.2, -7.1] p<0.001
	Change (SE)	268	-21.0 (2.4)	126	-0.4 (3.5)	-20.6 (4.2) [-28.8, -12.3] p<0.001

*Analysis of covariance model with treatment as fixed effect and baseline VAT as covariate

Figure 1 LSMEAN difference from placebo at 26 Week



1.2 Brief Overview of Clinical Studies

Egrifita (tesamorelin acetate for injection) is a synthetic human growth hormone releasing factor analogue (hGRF) developed for treatment of HIV-associated lipodystrophy.

The NDA included one Phase 2 study (LIPO 008) and two Phase 3 studies (LIPO-010 and TH9507-CRT-1011), referred to subsequently as studies 8, 10 and 11, respectively.

Study 8 was a multicenter, randomized, double-blind, placebo-controlled study evaluating two doses of TH9507, 1 mg and 2 mg, administered daily by subcutaneous injection over a period of 12 weeks in patients with HIV-associated lipodystrophy.

The 2 phase 3 studies were double-blind, randomized, placebo-controlled studies to assess efficacy and safety of once daily injection of 2mg/day of Egrifita for 26 weeks in HIV patients with excess abdominal fat accumulation. The studies were composed of a main phase and an extension phase; the initial randomized phase of 26 weeks was followed by a randomized withdrawal extension of 26 weeks. TH9507-treated patients completed the main phase were re-randomized to TH9507 or placebo and the 26-week placebo-treated completers were switched to TH9507. The purpose of the extension was to collect long-term safety data and to explore duration of effect after the main study treatment.

Both studies randomized approximately 400 patients in a 2:1 ratio. In the protocol, the 2 randomization strata were Site and IGT/Diabetes condition (fasting blood glucose value > 6 mmol/L (108 mg/dL) at screening). The maximum number of IGT/Diabetes patients should not exceed 30% of total number of patients randomized to the study.

For Study 10, randomization was stratified by testosterone use and IGT/Diabetes condition (FBG>108 mg/dL, [6mmol/L] at screening). For study 11, randomization was supposed to stratify for site and IGT/Diabetes condition. However, due to an error in the IVRS specifications, patients were randomized according to their diabetes (yes/no) status.

Visit weeks were 6, 13, 19 and 26 during treatment period. CT scan for VAT and SAT were conducted at screening, Weeks 13 and 26.

Table 2 summarizes the two phase 3 studies.

Table 2 Phase 3 study summary

	LIPO 010 Main	CTR 1011 Main
Study location (# sites, % patients)	USA (37, 94%) Canada (6, 6%)	USA (25, 73%) Canada (8, 8%) Europe (13, 18%)
Duration	26 weeks	26 weeks
N (ITT) by treatment: # and (% Male/% Female)	P:137 (84%/16%) T: 273 (87%/13%)	P:126 (83%/17%) T: 270 (84%/16%)
Inclusion	Age 18-65 HIV-associated lipodystrophy Stable ART ≥8 weeks CD4>100 cells/mm ³ Viral load<10,000 copies/mL BMI>20 kg/m ² Waist circumference: Male: 95 cm and waist/hip ratio 0.94 Female: 94 cm and waist/hip 0.88	Age 18-65 HIV-associated lipodystrophy Stable ART ≥8 weeks CD4>100 cells/mm ³ Viral load<10,000 copies/mL BMI>20 kg/m ² Waist circumference: Male: 95 cm and waist/hip ratio 0.94 Female: 94 cm and waist/hip 0.88
Primary endpoint	VAT percent change from baseline to week 26	VAT percent change from baseline to week 26
	LIPO 010 Extension	CTR 1012 Extension
Study center	USA (26) Canada (5)	USA (23) Canada (6) Europe (10)
Duration	26 weeks	26 weeks
N (ITT) by treatment sequence main – extension: # and (% Male/% Female)	Re-randomized T main completers (1:3 ratio): T – P: 50 (86%, 14%) T – T: 154 (88%, 12%) P switch to T: P – T:111 (86%, 14%)	Re-randomized T main completers (1:1 ratio): T – P: 85 (89%, 11%) T – T: 92 (90%, 10%) P switch to T P – T: 86 (87%, 13%)
Inclusion	Patients completed LIPO 010 FBG < 8.33 mmol/L	Patients completed CTR 1011 FBG < 8.33 mmol/L
Primary endpoint	52-week safety	52-week safety

The glycemic criteria for removing patients from the main phase were hyperglycemia symptoms, FBG ≥ 180mg/dL (test and retest after 7 days). Patients with FBG ≤ 180 mg/dL at any time who displayed symptoms related to hyperglycemia were to be immediately removed from the study and treated with appropriate therapy. For extension phase, patients with verified FBG >150 mg/dL at week 26 were not permitted to enter the extension phase. Once enrolled in the extension, the main phase guidelines were to be applied.

1.3 Statistical Issues and Findings

The efficacy analysis performed in the extension study comparing the two re-randomized groups, T-P and T-T was for proof-of-concept. The purpose of the efficacy analysis was to evaluate the effect of stopping TH9507 after 26 weeks of treatment vs. continuing treatment for an additional 26 weeks. The analysis of variance for change from baseline to week 52 in the extension phase should use values at week 26 re-randomization for baseline not week 0 for baseline as the sponsor used.

The study randomization was stratified by testosterone use and glucose intolerance/diabetes (yes or no). The analysis of covariance should incorporate the factors in the model.

2. INTRODUCTION

2.1 Overview

Tesamorelin is a synthetic growth hormone releasing factor (GHR) analog. The intended indication is treatment of excess abdominal fat in HIV-infected patients with lipodystrophy.

Based on the results from a 12-week phase 2 study, it was determined that the 2 mg dosage of TH9507 was appropriate for phase 3 trials. The design for the phase 3 study should include a main treatment-period of 26 weeks followed by a randomized withdrawal period for 26 weeks ‘to explore the duration of effects following the end of treatment and to gather safety data.’

2.2 Data Sources

The analysis datasets for individual studies were not consistent in format. The integrated efficacy dataset were used. Numerous modifications and corrections were made during the review process.

The links for the analysis datasets are:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study 8

Randomization was stratified by gender and sites (3 US and 4 Canada). Table 11 presents patient disposition and Figure 18 the percentage of patients in study by time.

Table 3 Patient disposition – ITT population, Study 8

Reason for Discontinuation	Treatment			
	1mg N=19	2mg N=21	Placebo N=21	Total N=61
Completed	17 (89%)	15 (71%)	16 (76%)	48 (79%)
Adverse event	0	3 (14%)	1 (5%)	4 (7%)
Fulfills one of the withdrawal criteria	1 (5%)	0	0	1 (2%)
Lack of compliance	0	1 (5%)	0	1 (2%)
Withdrawal consent	1 (5%)	2 (10%)	4 (19%)	7 (11%)

Figure 2 Percentage of patients in study by time – Study 8

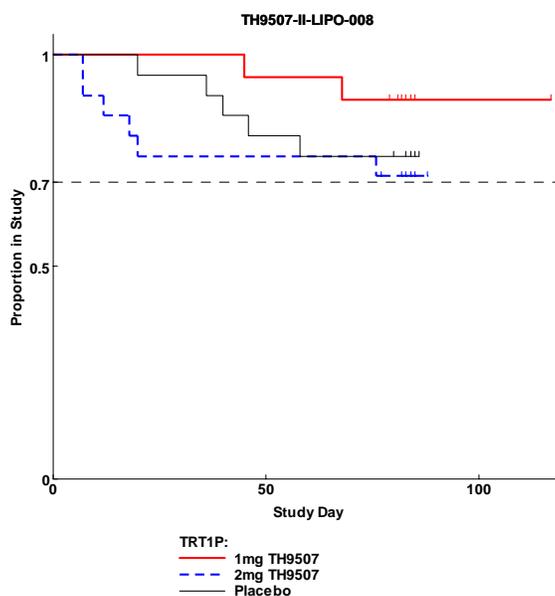


Table 4 displays descriptive statistics and Table 5 the analysis results for VAT. The main planned analysis for efficacy was ANOVA on VAT change from baseline to week 12. The efficacy results showed that 1mg was similar to placebo; therefore, TH9507 2 mg was selected for the phase 3 studies.

Table 4 VAT descriptive statistics – ITT, LOCF

Treatment	Label	N	Mean	Std Dev	Median	Min	Max
Placebo	Baseline Value	15	200	78	194	93	362
	Change from Baseline	15	-12	31	-6	-90	19
1mg TH9507	Baseline Value	17	158	57	156	56	273
	Change from Baseline	17	-12	28	-7	-74	28
2mg TH9507	Baseline Value	15	162	57	167	89	284
	Change from Baseline	15	-19	27	-19	-50	35

Table 5 Analysis results for VAT – ITT

	Placebo n=15	1 mg n=17	2 mg n=15
Baseline	200 (78)	158 (57)	162 (57)
LSM Change (SE)	-12 (8)	-12 (7)	-19 (7)
*LSM Difference from placebo		+0.4 (11)	-7 (11)
[2-sided 95% CI]		[-21, 22]	[-29, 15]
p-value		p=0.97	p=0.52
% change (SE)	-4% (5)	-5% (4)	-13% (5)
**LSM % Difference from placebo		-0.2% (6)	-9% (7)
[2-sided 95% CI]		[-13, 13]	[-22, 5]
p-value		p=0.98	p=0.19

* ANOVA model with treatment as fixed effect

** ANCOVA model with treatment as fixed effect and baseline as covariate

Studies 10 and 11

Randomization ratio was 2:1 (active:placebo) in the 26-week main phase. Patients completed the TH9507 2 mg in main phase were re-randomized in a 3:1 ratio for study 10 and 1:1 for study 11 to continue on TH9507 or placebo in the extension. Patients who completed placebo main phase were treated with TH9507 in the extension.

The main inclusion criteria were: Age: 18 to 65, HIV: positive, CD4: >100 cells/mm³, Viral load: <10,000 copies/mL, abdominal fat accumulation: Male: waist circumference ≥95 cm and waist-to-hip ratio ≥0.94, Female: ≥94 cm and ≥0.88, respectively.

Sample size calculation was based on both the VAT percent change and the PRO change from baseline. For VAT percent change, in order to detect a treatment difference of 8%, a total of 255 patients (170 TH9507 : 85 placebo) in a 2:1 ratio was required assuming a standard deviation of

18.5%, a power of 90% and a 2-sided significant level of 5%. Assuming a drop out rate of 33%, a total of 381 patients (254 TH9507 : 127 placebo) were planned.

For PRO, the sample size of 255 (170 active: 85 placebo) patients was to detect a difference of 25 points (one scale unit) (SD=67, active and 65 placebo) in the Belly Size Evaluation scale with 80% power and to detect a difference of 12.5 (SD=25 active and 33 placebo) (one scale unit) in the Belly Appearance Distress scale with 90% power.

Study Endpoints

The primary efficacy endpoint was the percent change from baseline to week 26 in visceral adipose tissue (VAT) measured in cm² by computerized tomography (CT) scan from a single 5 mm slice obtained at the level of L4-L5 inter-vertebral disc space evaluated at baseline (last measurement prior to randomization).

Secondary efficacy endpoints were change from baseline to week 26 in

1. total cholesterol/HDL-cholesterol ratio;
2. triglyceride levels;
3. IGF-1 levels;
4. patient reported outcomes related to Body Image (belly profile, belly size evaluation and belly size distress scales).

The primary endpoints for the extension phase (randomized withdrawal period) were safety endpoints.

The duration of effect endpoints were: change from baseline and change from week 26 in VAT, lipid profile, anthropometric measurements and patient reported outcome questionnaire.

Patient Disposition, Demographic and Baseline Characteristics

Study 10 Main Phase

A total of 570 patients were screened and 412 were randomized; 275 to tesamorelin and 137 to placebo. Two patients (#10030 and #16007) in the tesamorelin group changed their testosterone regimen and were excluded from the study (exclusion criterion). Table 14 displays patient disposition by treatment group. Approximately 20% of patients discontinued from the study. The percentage of AE withdrawals were 10% vs. 3% (TH9507 vs. placebo). The proportion of patients with AE leading to early discontinuation (not necessarily the primary reason for discontinuation) was 34/226 (12.5%) for TH9507 and 5/137 (3.6%) for placebo (p=0.03).

Study 11 Main Phase

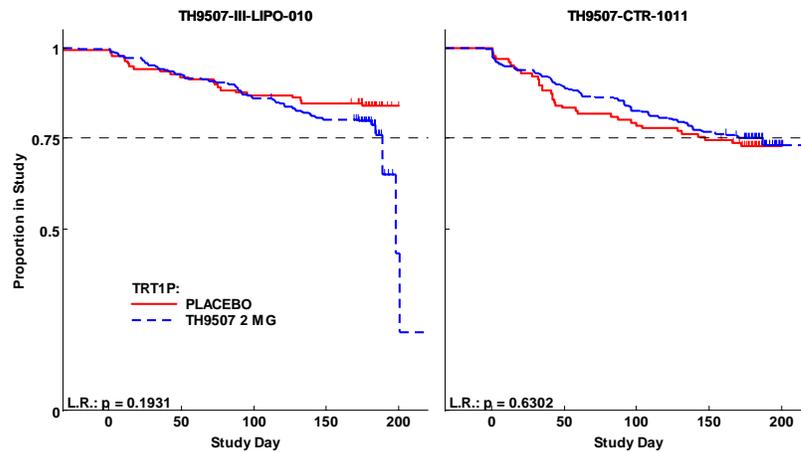
A total of 599 patients were screened and 404 patients were randomized in a 2:1 ratio. Five of the tesamorelin patients and 3 of the placebo patients did not receive the study treatment.

Approximately ¼ of the patients withdrew. The rate of AE withdrawal was 10% for both study groups. Figure 19 display the proportion of patients in study by day on study.

Table 6 Patient disposition – Studies 10 & 11 Main

Frequency Col Pct	Study 10		Study 11	
	TH9507 (2 mg/day)	Placebo	th9 (2 mg/day)	Placebo
Screen	570		599	
Randomized	275	137	275	129
Administered study drug	273	137	270	126
Completed	211 (77%)	115 (84%)	202 (75%)	92 (73%)
Discontinued	62 (23%)	22 (16%)	68 (25%)	34 (27%)
Reason of discontinuation				
Adverse Event	26 (10%)	4 (3%)	26 (10%)	12 (10%)
Withdrawal Of Consent	19 (7.0%)	12 (8.8%)	24 (9%)	7 (6%)
Lack Of Compliance	8 (2.9%)	0 (0.0%)	5 (1.9%)	1 (0.8%)
Other	-	-	8 (3%)	7 (6%)
Lost To Follow-Up	7 (2.6%)	2 (1.5%)	5 (2%)	7 (6%)
Administrative Problem(s)	1 (0.4%)	2 (1.5%)		
Abnormal Laboratory Value(s)	0 (0.0%)	2 (1.5%)		
Unknown	1 (0.4%)	0 (0.0%)		

Figure 3 Proportion of patients in study by day on study



The two treatment groups were similar in patient demographics and baseline characteristics for both studies (Tables 7 and 8).

Table 7 Patient demographics and baseline Characteristics - Main Phase ITT Population

Study	10 N=410	11 N=396
n	Placebo:TH9507 137:273	Placebo:TH9507 126:270
Age (years)		
Mean (SD)	48 (7.4)	48 (7.6)
Median [min, max]	47 [28, 65]	47 [27, 65]
Gender (n %)		
Male	352 (86%)	333 (84%)
Female	58 (14%)	63 (16%)
Ethnic origin (n %)		
White/ Caucasian	308 (75%)	305 (77%)
Black/ African- American	59 (14%)	46 (12%)
Hispanic	34 (8%)	35 (9%)
Asian	2 (0.5%)	3 (0.8%)
Other	7 (2%)	6 (2%)
Country		
USA	94%	73%
Canada	6%	8%
Europe (United, Spain, France, Belgium)	-	19%
Weight (kg)		
Mean (SD)	90 (14)	88 (14)
Median [min, max]	88 [56, 161]	87 [52, 148]
BMI (kg/m ²)		
Mean (SD)	29 (4)	29 (4)
Median	29 [22, 48]	28 [20, 46]
Waist circumference (cm)		
Mean (SD)	104 (10)	105 (9)
Median	101 [90, 154]	103 [94, 151]
Hip circumference (cm)		
Mean (SD)	100 (9)	100 (9)
Median	98 [83, 152]	99 [83, 159]
Smoking status Yes (n %)	96 (23%)	92 (23%)
Testosterone use (n %)	Placebo:TH9507 18%:18%	Placebo:TH9507 17%:25%
	Male:Female 18%:12%	Male:Female 27%:0%
Lipid lowering treatment	Placebo:Th9507 42%:51%	Placebo:Th9507 48%:41%
Diabetes		
IGT/Diabetes condition	Placebo:Th9507	Placebo:Th9507

Study	10 N=410	11 N=396
n	Placebo:TH9507 137:273	Placebo:TH9507 126:270
FBG>108 mg/dL	19%:18%	11%: 17%
IGT≥140 mg/dL	19%:19%	15%:23%
	2%:2%	26%:21%

Table 8 HIV- and Lipodystrophy Syndrome-related Characteristics at Baseline -
Main Phase ITT Population

Study	10 N=410	11 N=396
	Placebo:TH9507 137:273	Placebo:TH9507 126:270
Time since HIV diagnosis (months)	n	
	137:272	126:270
Mean (SD)	156 (64):162 (63)	164 (68):170 (67)
Median [min, max]	157 [8, 288]: 166 [13, 311]	164 [27, 308]:174 [11, 326]
Viral load (%)		
Undetectable	71%:68%	86%:82%
50-400 copies/mL	20%:22%	10%:11%
>400 copies/mL	9%:9%	4%:7%
CD4 cell count (cells/mm ³)		
N	137:271	125:270
Mean (SD)	585 (284):617 (299)	600 (278):588 (290)
Median [min, max]	531 [103, 1623]:569 [93, 2021]	561 [104, 1553]:551 [110, 1749]
CD8 cell count (cells/mm ³)		
N	136:267	125:268
Mean (SD)	1024 (470):940 (423)	930 (375):972 (441)
Median [min, max]	935 [10, 3680]:883 [238, 4247]	862 [247, 2020]:890 [187, 3848]
Duration of ART (mon)		
N	136:272	126:270
Mean (SD)	48 (31):57 (37)	53 (36):53 (36)
Median	43 [5, 154]:49 [7, 231]	46 [4, 147]: 43 [4, 179]
Prior Medications		
ART therapy	Placebo: TH9507	Placebo:TH9507
NRTI-PI	48%:42%	48%:46%
NRTI-NNRTI	27%:41%	31%:29%
NRTI-NNRTI-PI	14%:11%	4%:9%
NRTI alone	9%:4%	3%:3%
Other	2%:3%	13%:10%
Time since lipodystrophy syndrome diagnosis (mon)		
N	135:261	123:261
Mean (SD)	51 (40):50 (40)	70 (43):65 (43)
Median [min, max]	47 [0, 192]:45[0, 224]	66 [1, 259]: 60 [-5, 211]

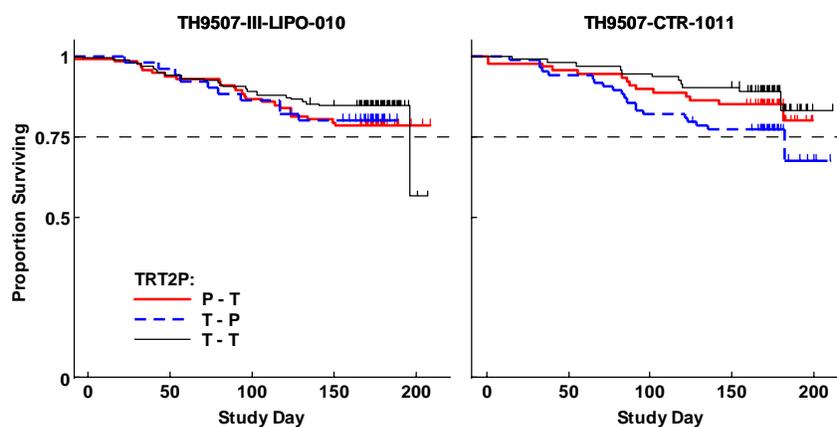
Disposition – Extension Phase

Of the 211 patients completed the TH9507 treatment in the main phase, 207 patients were re-randomized. Of the 207 patients, 3 declined to participate later and were excluded from the study. Of the 204 patients in the extension, 154 were in the TH9507 group and 50 were in the placebo group. 111 of the 115 patients who completed placebo in the main phase switched to 2 mg TH9507 in the extension phase. Similar to the main phase, the completion rate was approximately 80% (Table 9 and Fig. 4).

Table 9 Patient disposition

	Study 10			Study 11		
	TH9507 N=211	Placebo N=115		TH9507 N=202	Placebo N=92	
Completed Main study						
Excluded from extension	7	4				
Included in Extension	204		111		86	
Treatment sequence	TH9507 – TH9507	TH9507 – Placebo	Placebo TH9507	TH9507 – TH9507	TH9507 – Placebo	Placebo TH9507
n	154	50	111	92	85	86
Completed Extension	129	40 (80%)	87	80 (87%)	63 (74%)	72
Withdrawal Of Consent	12 (8%)	4 (8%)	6 (5%)	8 (9%)	11 (13%)	7 (8%)
Adverse Event	5 (3%)	3 (6%)	12	1 (1%)	4 (5%)	5 (6%)
Lack Of Compliance	7 (5%)	1 (2%)	2 (2%)	1 (1%)	3 (4%)	1 (1%)
Lost To Follow-Up	1 (.7%)	2 (4%)	3 (3%)	2 (2%)	2 (2%)	1 (1%)
Other	-	-	-	0	2 (2%)	0
Abnormal Laboratory	0	0	1 (0.9%)	-	-	-

Figure 4 Percentage of patients in study – Extension ITT



VAT

Baseline VAT was carried forward (VAT % change=0) in approximately 10% of the ITT patients in study 10 and 14% of the ITT patients in study 11 (Table 10).

Table 10 Number (%) of patients within VAT % change categories at Week 26 – ITT

		VAT % change			
Study 10		<0	=0	>0	Total
	Placebo	50 (37%)	14 (10%)	72 (53%)	136
	TH9507 (2 mg)	193 (71%)	28 (10%)	51 (19%)	272
Study 11		<0	=0	>0	Total
	Placebo	56 (44%)	18 (14%)	52 (41%)	126
	TH9507 (2 mg)	171 (64%)	38 (14%)	60 (22%)	269

Table 11 displays the descriptive statistics for percent VAT change from baseline. The median percent changes from baseline for treatment TH9507 were -12% (week 13) and -15% (week 26) for Study 10 and -3% (week 13) and -11% (week 26) for Study 11. Figure 5 displays boxplot for VAT by visit from baseline to week 26 and Figure 22 displays the percent VAT change from baseline by visit.

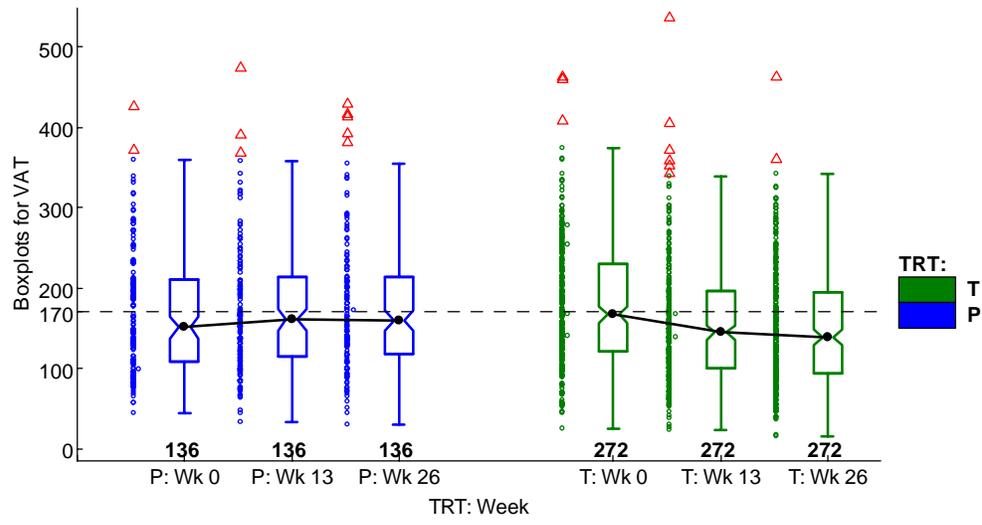
Table 11 Descriptive statistics of VAT % change from baseline – main phase. ITT, LOCF

Study	Trt	Week	N		Mean	SD	Median	Min	Max		
10	P	Baseline	136	VAT	171.0	76.9	151.3	45.1	425.6		
				13	136	VAT	172.7	78.3	160.7	33.9	473.4
						CHG	1.7	30.0	0.0	-90.6	84.3
						PCHG	3.0	21.9	0.0	-51.6	87.9
			26	136	VAT	176.0	81.7	159.0	30.3	428.2	
		CHG			5.0	36.4	3.2	-92.6	106.9		
					PCHG	5.0	23.4	2.1	-58.7	89.1	
		T	Baseline	272	VAT	178.3	76.9	167.3	25.3	461.5	
	13				272	VAT	156.7	76.9	144.6	24.1	534.8
						CHG	-21.6	33.6	-16.3	-133.0	106.5
						PCHG	-12.1	17.5	-11.7	-60.3	73.1
			26	272	VAT	150.5	74.1	138.5	15.4	461.9	
CHG	-27.8				38.7	-21.9	-183.3	97.1			
				PCHG	-15.1	20.8	-14.7	-69.9	73.9		
11	P	0	126	VAT	194.9	95.5	176.1	29.9	447.4		
				13	126	VAT	191.5	95.3	170.8	33.0	505.8
						CHG	-3.4	35.4	0.0	-171.1	133.9
						PCHG	-0.4	19.7	0.0	-59.8	121.9
			26	126	VAT	194.1	100.2	178.2	33.5	461.1	
		CHG			-0.8	32.4	0.0	-70.8	107.5		
					PCHG	-0.6	18.9	0.0	-48.8	94.6	
		T	0	268	VAT	186.5	86.6	176.9	28.1	427.3	
	13				268	VAT	169.9	83.5	155.4	27.4	411.8
						CHG	-16.6	32.8	-5.8	-172.1	79.9
						PCHG	-8.6	15.9	-3.3	-59.6	40.0
			26	268	VAT	165.7	87.0	150.9	20.6	446.5	
CHG	-20.8				42.1	-17.8	-167.9	92.2			

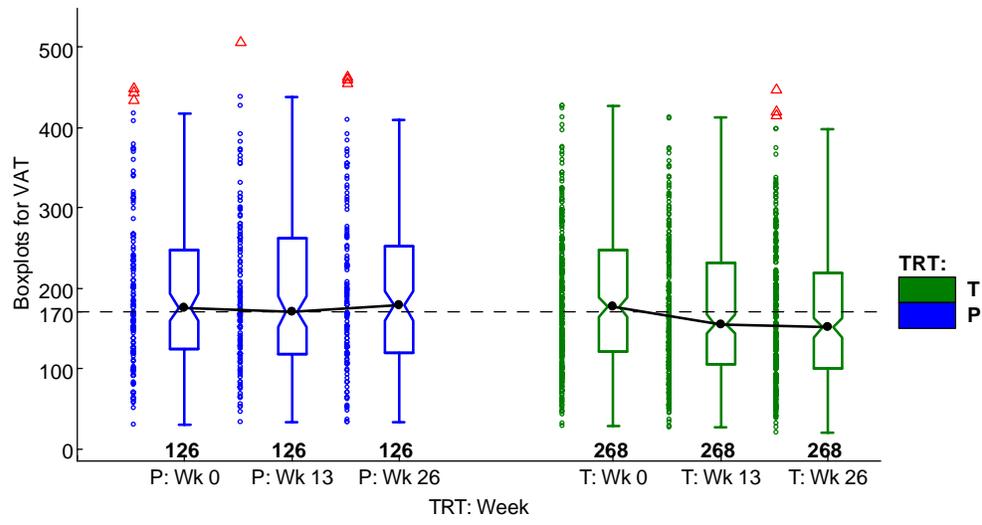
PCHG	-11.1	21.3	-10.6	-76.4	48.6
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Figure 5 Box plot* for VAT over time by treatment – Main phase ITT

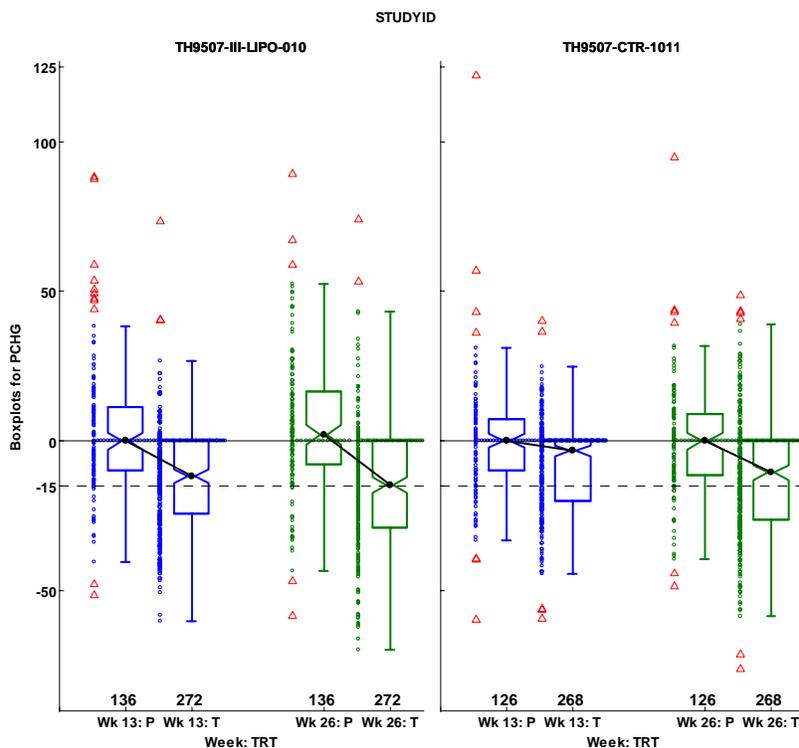
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TH9507-CTR-1011



**Figure 6 Box plot for VAT % change from baseline by treatment at Weeks 13 and 26
Main phase ITT, LOCF**



Tables 12 and 13 display the ANCOVA results of VAT percent change from baseline to week 26 for the ITT and completers, respectively. The analyses were consistent in the 2 patient populations.

Table 12 ANCOVA* results for VAT % change from baseline to Week 26 – ITT, LOCF

Study		TH9507 (2 mg)		Placebo		Treatment difference at Week 26
		n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	Baseline (SD)	272	178.3 (76.9)	136	171.0 (76.9)	
	% change (SE)	272	-17.8% (1.6)	136	+2.2% (2.2)	-19.6 (2.7) [-23.7, -15.3] p<0.01
11	Baseline (SD)	268	186.5 (86.6)	126	194.9 (95.5)	
	% change (SE)	268	-13.8% (1.5)	126	-2.4% (2.2)	-11.7 (2.7) [-16.2, -7.1] p<0.01

* Analysis of covariance: treatment as fixed effect and baseline VAT as covariate

Table 13 ANCOVA* results for VAT % change from baseline to Week 26 – Completers

Study		TH9507 (2 mg)		Placebo		Treatment difference at Week 26
		n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	Baseline (SD)	210	180.0 (77.0)	114	173.0 (78.2)	
	% change (SE)	210	-21.3% (1.9)	114	+2.3% (2.5)	-23.1 (3.2) [-27.7, -18.3] p<0.01
11	Baseline (SD)	201	186.5 (86.6)	92	194.9 (95.5)	
	% change (SE)	201	-16.6% (1.9)	92	-3.8% (2.8)	-13.4 (3.3) [-18.8, -7.6] p<0.01

* Analysis of covariance included treatment as fixed effect and baseline as covariate

Figure 7 displays the cumulative percentage of patients (y-axis) having a VAT percent change that is equal to or less than that shown on the x-axis. Fig 8 shows boxplots for VAT percent change.

Figure 7 Cumulative distribution of VAT % change from baseline to Week 26 by main phase treatment – ITT excluding patients with baseline carried forward

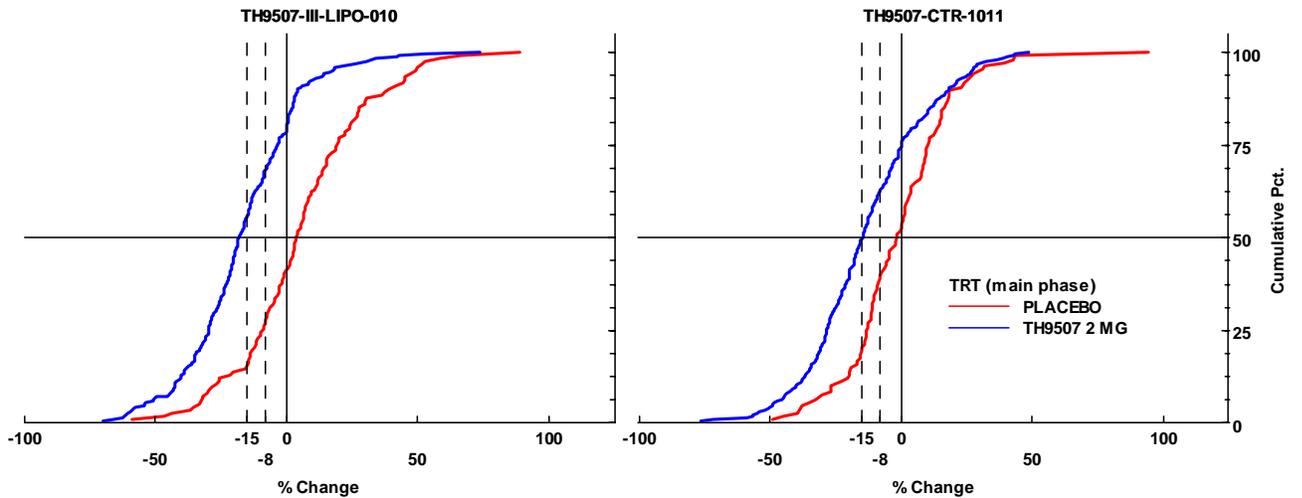
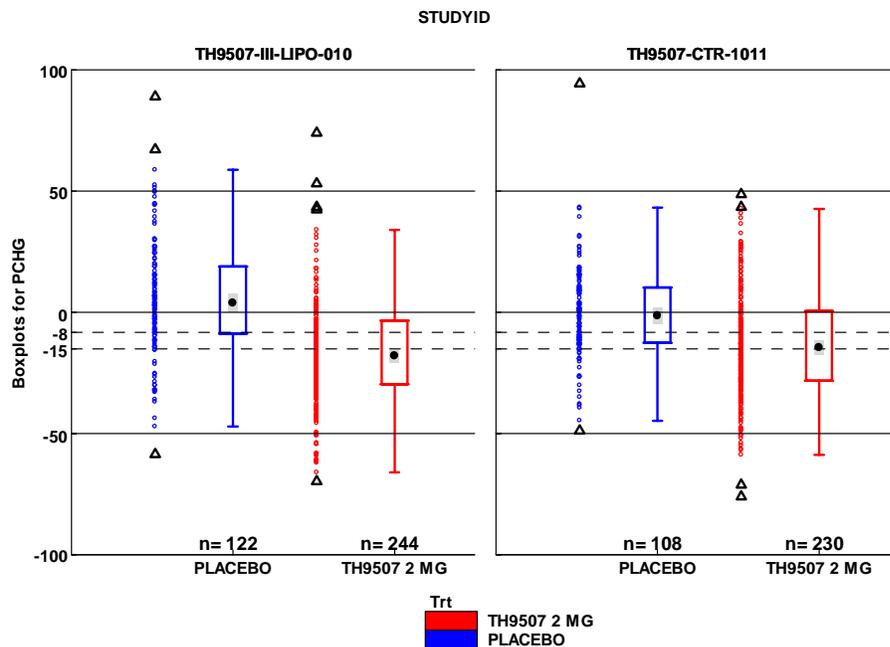


Figure 8 Boxplots of VAT % change from baseline to Week 26 – ITT excluding patients with baseline carried forward

VAT



The box displays the interquartile range (IQR, the middle 50% of the distribution). The whiskers extend from the box to 1.5 times the IQR (75% value +1.5*IQR and 25% value-1.5*IQR). The triangles are outliers

Trt
■ TH9507 2 MG
■ PLACEBO

Secondary efficacy variables were change from baseline in TG, IGF-1 and patient reported outcomes (PROs) related to body image (specifically, belly appearance distress (BAD), belly size evaluation (BSE) and patient’s belly profile assessment (BPA)). There was a prespecified gatekeeper strategy to control the type 1 error. The testing order for Study 10 was: 1. VAT change from baseline to week 26, 2. BAD change score, 3. Total cholesterol:HDL-C ratio and 4. Triglycerides change from baseline to week 26. For Study 11, the testing order was 1. VAT change from baseline to week 26, 2. BAD change score and TG change from baseline to week 26 (using Hochberg’s adjustment) 3. total cholesterol/HDL cholesterol ratio.

Triglycerides (TG)

Table 14 displays descriptive statistics for TG change and percent change from baseline to week 26. Both TG percent change from baseline and change from baseline were statistically different between TH9507 and placebo in Study 10 but not in Study 11 (Table 15). Fig 9 displays the cumulative distribution for TG percent change. Fig 10 shows boxplots for TG change and percent change with outliers.

In study 10, treatment-by-baseline interaction was significant for TG change from baseline ($p<0.0001$) but not for TG percent change ($p=0.96$) (Fig. 11). For this reason, the % change endpoint is more readily interpretable than change from baseline.

Forty-four percent of patients were on lipid lowering therapy at baseline. TG levels were significantly higher in patients on lipid-lowering therapy (median 220) than without therapy (median 177). The treatment-by-lipid lowering therapy interaction for TG percent change from baseline was not significant ($p=0.2$). Figure 12 displays boxplots of TG levels at baseline and week 26 by treatment for lipid-lowering therapy (yes or no).

Table 14 Descriptive statistics for triglyceride (TG) change from baseline to week 26 - ITT

	Study 10		Study 11	
	TH9507 N=273	Placebo N=137	TH9507 N=270	Placebo N=126
Baseline				
mean (SD)	252 (188)	234 (145)	239 (261)	223 (144)
Median	206	194	168	182
[min, max]	[43, 1009]	[56, 896]	[38, 3276]	[54, 795]
Mean change (SD)	-51 (145)	9 (118)	-22 (131)	3 (106)
Median change	-25	0	-2	-2
[min, max]	[-855, 357]	[-293, 455]	[-1060, 435]	[-337, 540]
Mean % change (SD)	-8% (40)	12%(57)	3% (45)	8%(46)
Median % change	-13%	0%	-1.6%	-1.5%
[min, max]	[-85, 183]	[-71, 333]	[-81, 226]	[-62, 174]

Table 15 Analysis results for triglyceride (TG) (mg/dL) change from baseline to week 26

	Study 10			Study 11		
	Treatment		Trt Difference from placebo*	Treatment		Trt Difference from placebo*
	TH9507 N=273	PLACEBO n=137	LSM (SE) [95% CI] p-value	TH9507 N=270	PLACEBO n=126	(SE) [95% CI] p-value
LSM % Change (SE)	-8% (3)	11% (4)	-19% (5) [-29%, -10%] P<0.0001	4% (3)	8% (4)	-4% (5) [-14%, +6%] P=0.4
LSM Change (SE)	-48.0 (6.6)	4.8 (9.3)	-53 (11) [-75, -30] P<0.0001	-18.5 (6.9)	1.3 (10.0)	-20 (12) [-44, 4] P=0.10

*ANCOVA model with treatment, lipid lowering treatment (Y/N) as fixed effects and baseline TG as covariate
LSM=Least-square mean

Figure 9 Cumulative distribution of TG % change from baseline to Week 26 – ITT excluding patients with baseline carried forward

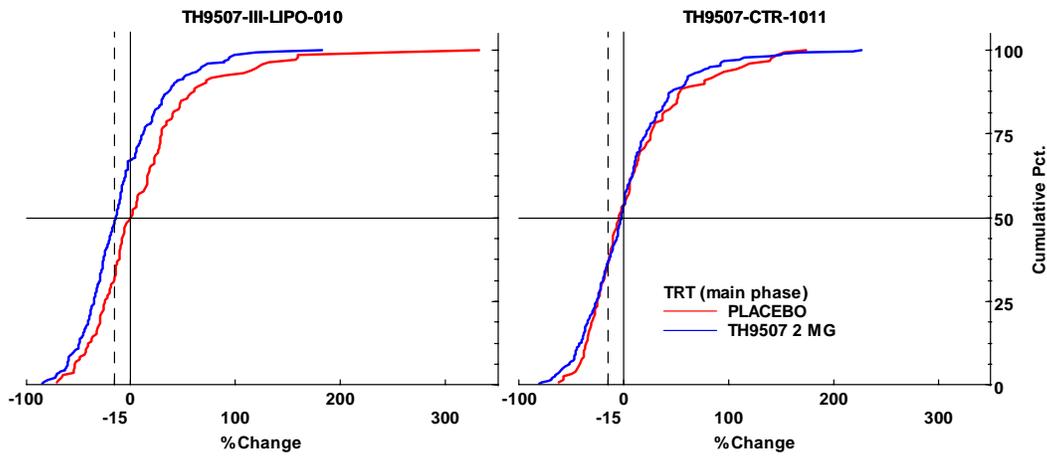


Figure 10 Boxplots for TG change from baseline and % change from baseline to Week 26 – ITT excluding patients with baseline carried forward

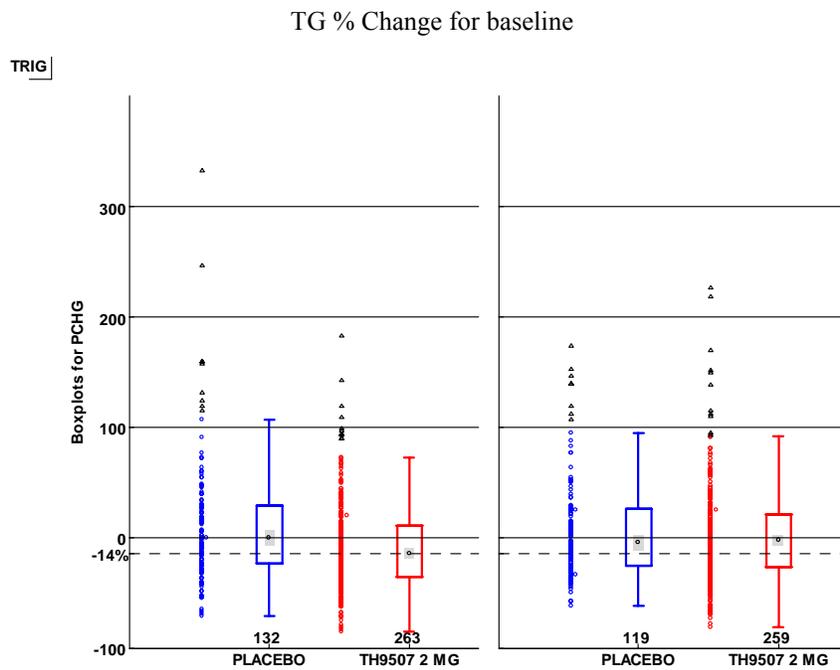
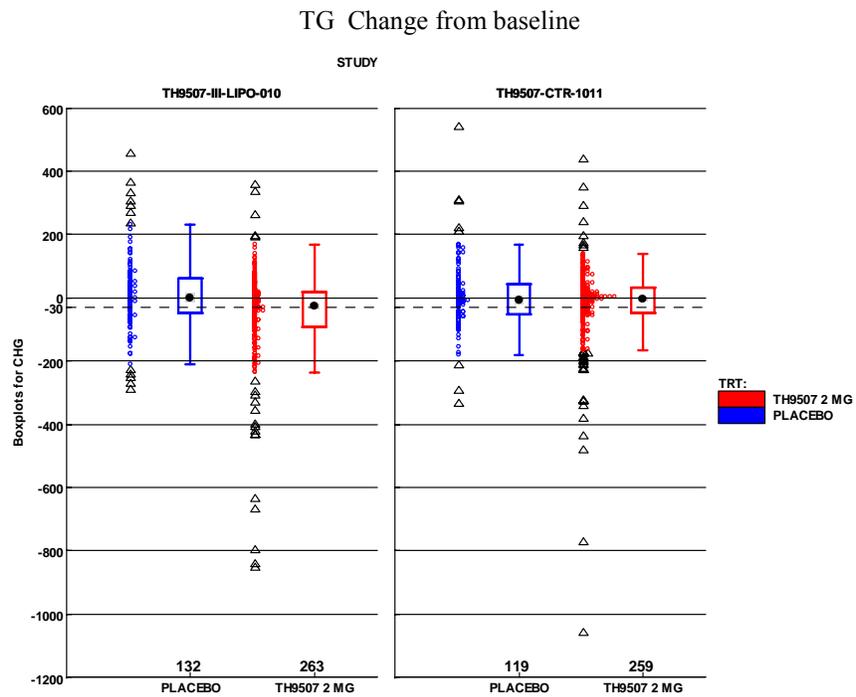
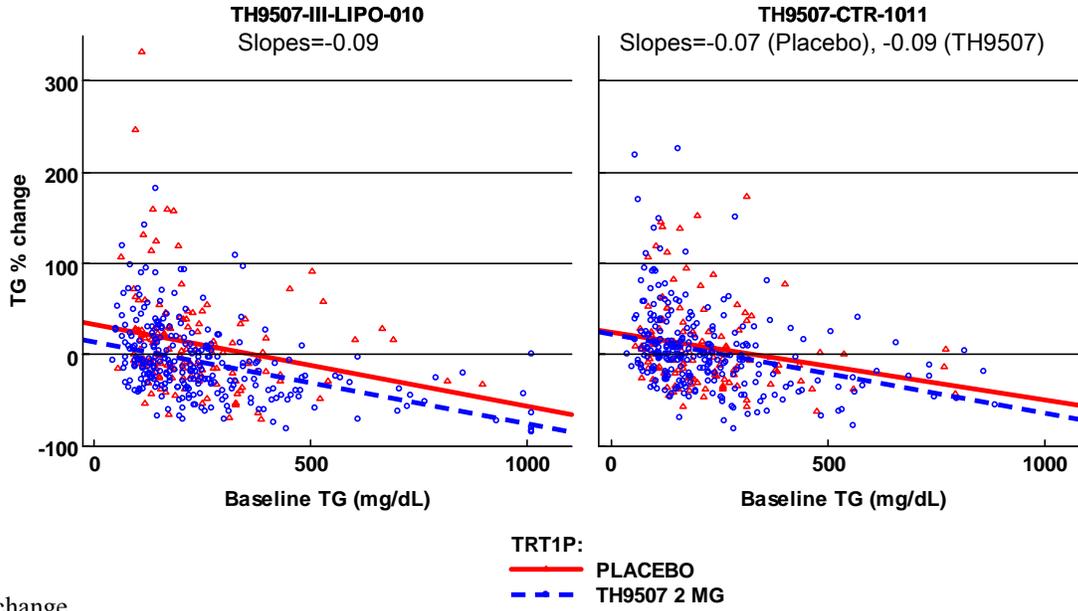


Figure 11 % change and change of TG from baseline to Week 26 by baseline TG – ITT excluding patients with baseline carried forward

TG % change



TG change

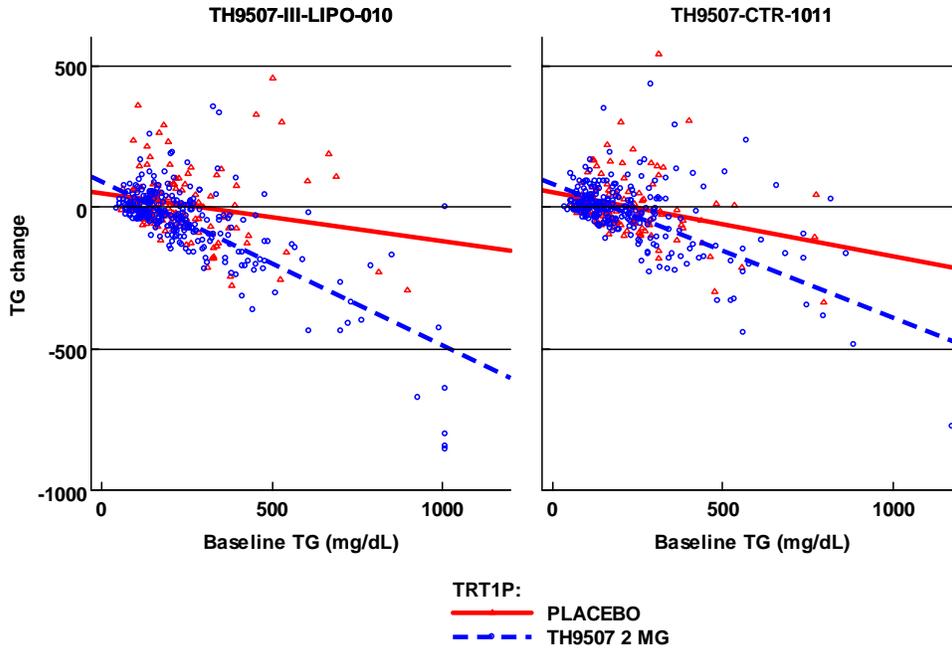
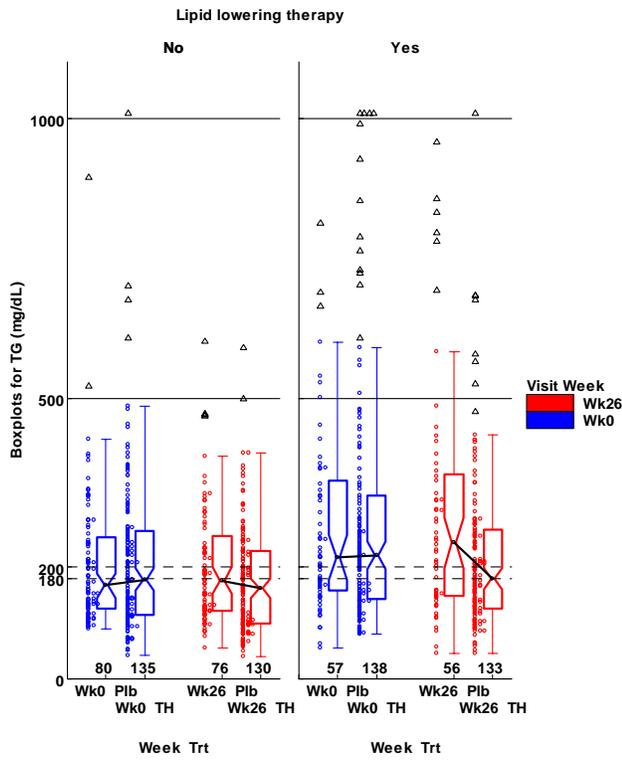


Figure 12 TG levels at baseline and Week 26 by lipid lowering therapy – ITT excluding patients with baseline carried forward

STUDYID
TH9507-III-LIPO-010



IGF-1

IGF-1 change from baseline to week 26 for TH9507 was statistically significantly different from placebo ($p < 0.001$) (Table 16). Figures 13 and 14 show cumulative distributions and boxplots for IGF-1 change from baseline to week 26, respectively.

Table 16 ANCOVA* results for IGF-1 (mg/dL) change from baseline to week 26

	Study 10			Study 11		
	Treatment		Difference	Treatment		Difference
	TH9507 N=269	PLACEBO n=136	From placebo	TH9507 N=265	PLACEBO n=125	From placebo
	LSM (SE)	LSM (SE)	LSM (SE) [95% CI]	LSM (SE)	LSM (SE)	LSM (SE) [95% CI]
Baseline	146.2 (65.9)	149.1(59.4)		161.1 (59)	168.1 (75)	
Change from baseline	106.5 (5.9)	-14.7 (8.3)	121.1 (10.2) [101.1, 141.3]	108.4 (5.9)	2.6 (8.6)	105.7(10.5) [85.1, 126.3]

*ANCOVA included treatment as effect and baseline IGF-1 as covariate
LSM=least-square mean

Figure 13 Cumulative distributions for IGF-1 change from baseline to Week 26 – ITT excluding patients with baseline carried forward

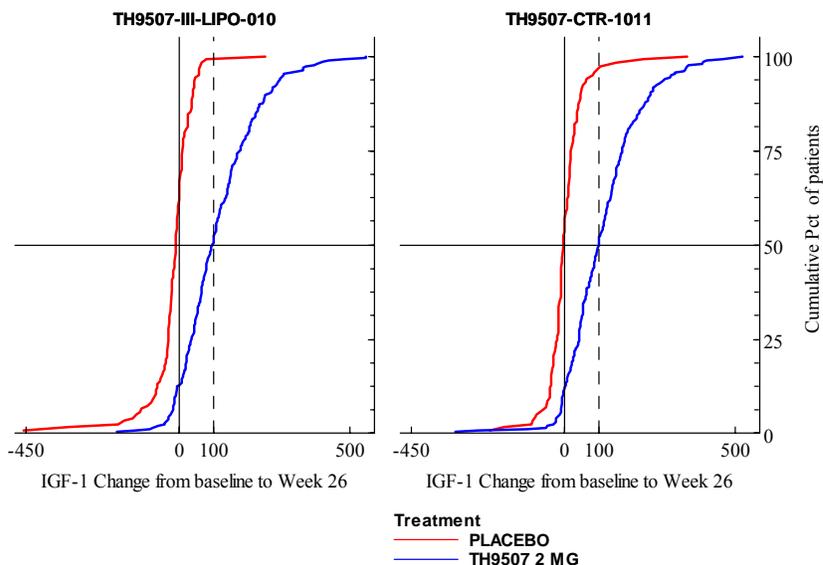
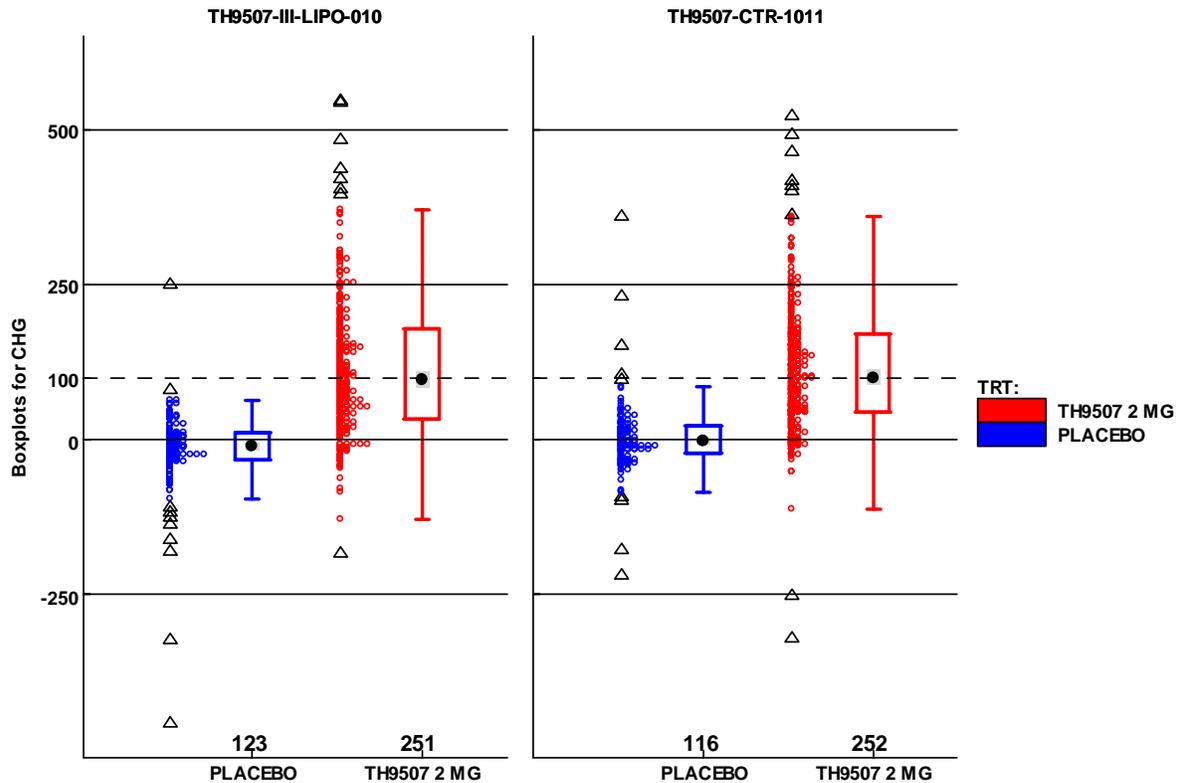


Figure 14 Boxplots for IGF-1 change from baseline to Week 26 – ITT excluding patients with baseline carried forward



Other Secondary Efficacy Variables:

Trunk Fat, Lean Body Mass (LBM) and Total Body Fat were statistically significantly different between TH9507-treated patients and placebo-treated patients (Table 17-19 and Fig 15).

Table 17 ANCOVA* results for trunk fat change (kg) from baseline to Week 26 – ITT, LOCF

Study	TH9507 (2 mg)		Placebo		Treatment difference
	n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	261	14.9 (5.6)	130	15.3 (5.8)	
		-1.0 (0.1)		+0.4 (0.16)	-1.4 (0.19) [-1.8, -1.0] p<0.001
11	264	15.3 (5.3)	123	15.2 (5.1)	
		-0.8 (0.12)		+0.2 (0.17)	-1.0 (0.21) [-1.4, -0.6] p<0.001

*Analysis of covariance model with treatment as fixed effect and baseline trunk fat as covariate. LSM=least-square mean

Figure 15 Cumulative distributions of trunk fat % change from baseline to Week 26 – ITT excluding patients with baseline carried forward

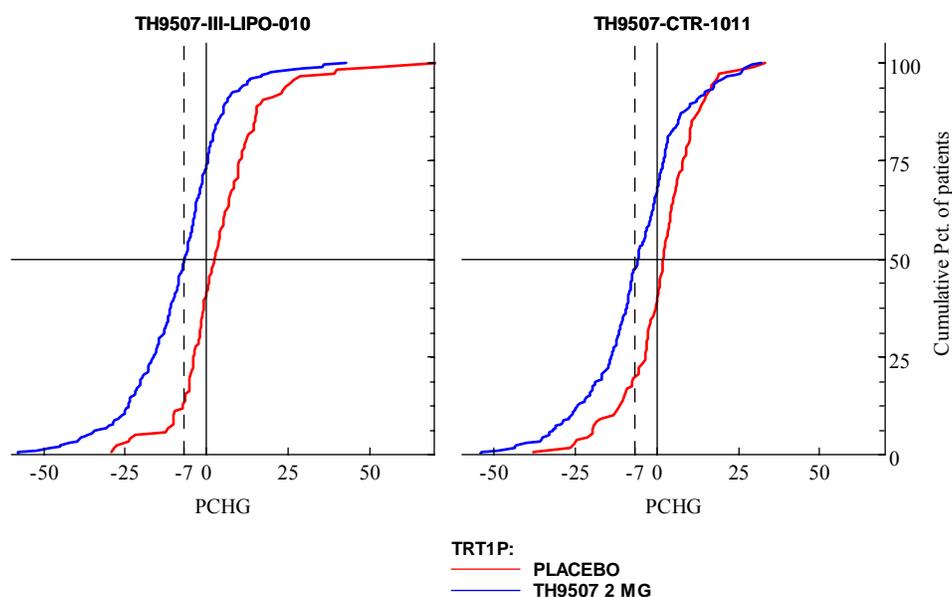


Table 18 ANCOVA* results for Lean Body Mass change (kg) from baseline to Week 26 – ITT, LOCF

Study	TH9507 (2 mg)		Placebo		Treatment difference LSM, (SE), [95% CI], p-value
	n	Mean	n	Mean	
10	Baseline (SD)	261 62.0 (10.1)	130	61.4 (9.6)	
	Change (SE)	1.3 (0.1)		-0.2 (0.2)	1.6 (0.2) [1.1, 2.0] p<0.0001
11	Baseline (SD)	264 62.4 (10.3)	123	60.5 (11.2)	
	Change (SE)	1.2 (0.1)		-0.1 (0.2)	1.3 (0.2) [0.8, 1.8] p<0.0001

*Analysis of covariance model with treatment as fixed effect and baseline LBM as covariate
LSM=least-square mean

Table 19 ANCOVA* results for Total Body Fat change (kg) from baseline to Week 26 – ITT, LOCF

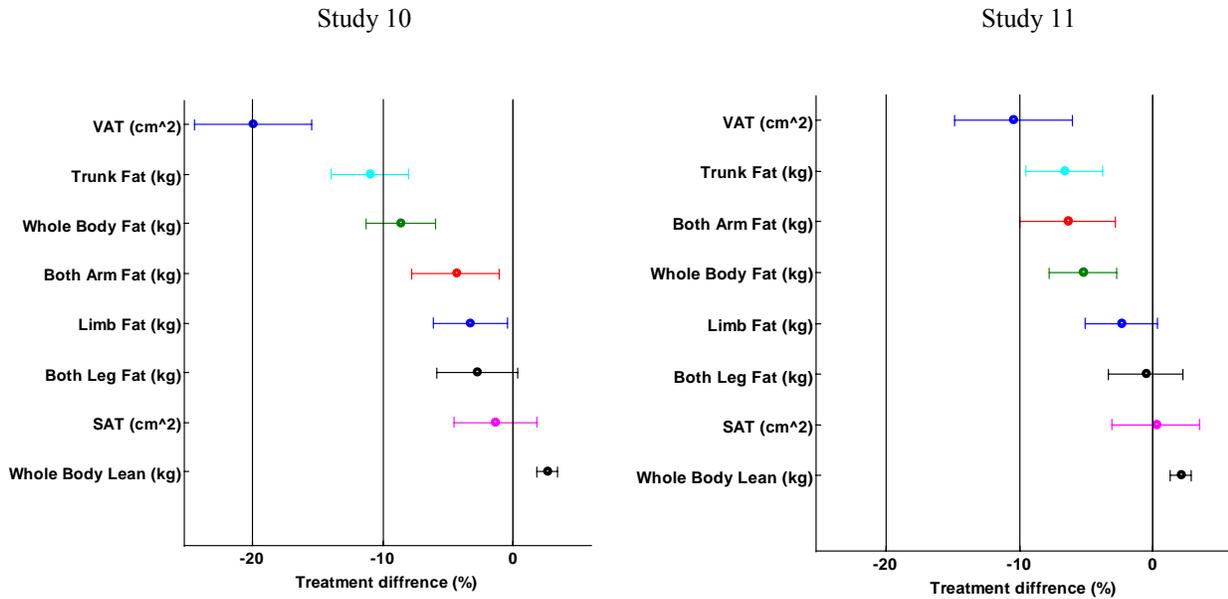
Study	TH9507 (2 mg)		Placebo		Treatment difference LSM, (SE), [95% CI], p-value
	n	Mean	n	Mean	
10	Baseline (SD)	261 22.9 (9.5)	130	23.9 (9.9)	
	Change (SE)	-1.1 (0.2)		0.6 (0.2)	-1.7 (0.3) [-2.2, -1.2] p<0.0001
11	Baseline (SD)	264 23.6 (9.4)	123	23.3 (8.4)	
	Change (SE)	-0.9 (0.2)		0.3 (0.2)	-1.2 (0.3) [-1.8, -0.6] p<0.0001

*Analysis of covariance model with treatment as fixed effect and baseline total body fat as covariate
LSM=least-square mean

Imaging and laboratory variables

Figure 16 summarizes the least-squared-mean treatment differences between TH9507 2 mg and placebo for percent change from baseline to week 26 in all image variables. Figure 17 shows the treatment differences for selected laboratory variables.

Figure 16 LS Mean treatment differences [95% CI] for % change from baseline to Week 26 for all image variables – ITT, LOCF



Treatment effects for lipid and glucose variables were neutral (Fig. 17).

Figure 17 LS Mean treatment differences [95% CI] for % change from baseline to Week 26 for laboratory variables – ITT, LOCF

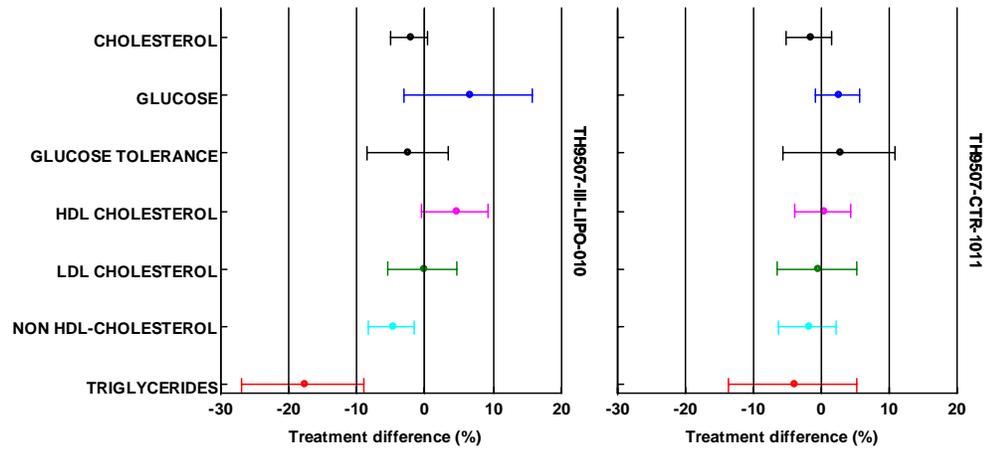


Figure 18 showed the mean SAT percent change from baseline (dotted lines) was not different between treatment groups for studies 10 (FKK000260) and study 11 (RDA17350).

Figure 18 VAT % change and SAT % change from baseline by treatment group

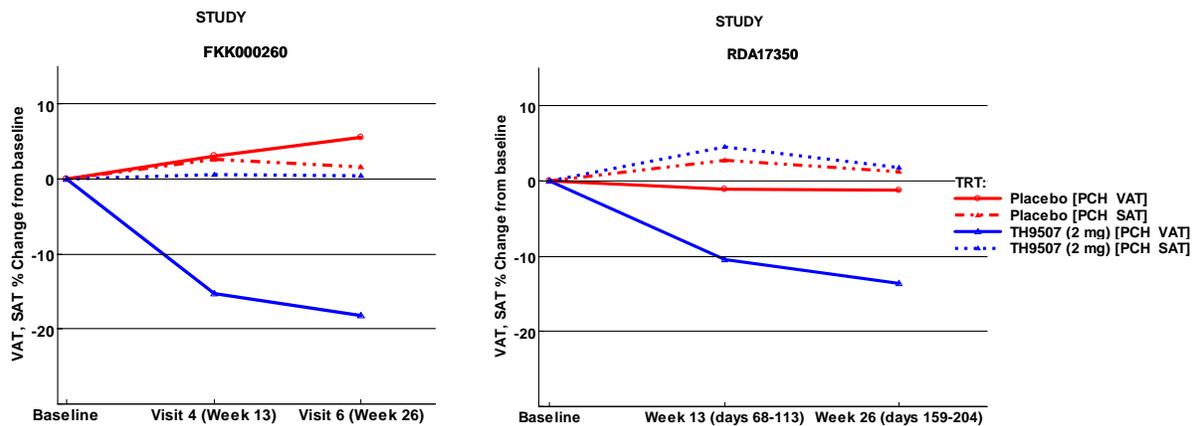
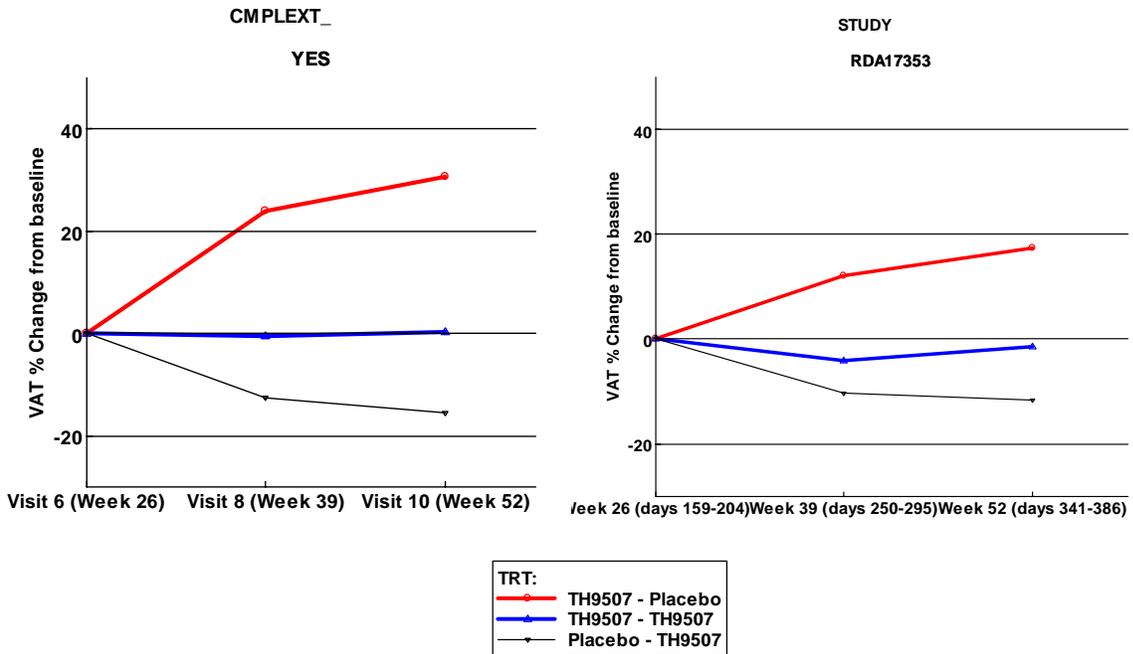


Figure 19 displays mean VAT percent change from re randomization to Week 52 by treatment sequence.

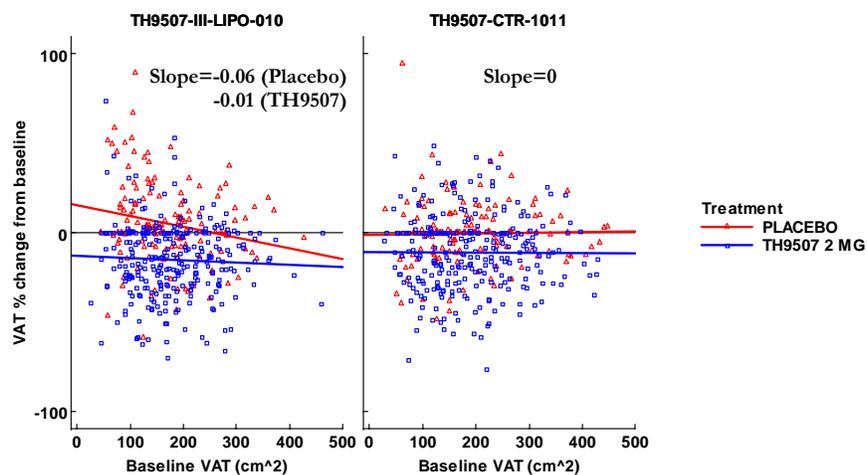
Figure 19 VAT % Change from re-randomization (Week 26) to Week 52 by treatment group

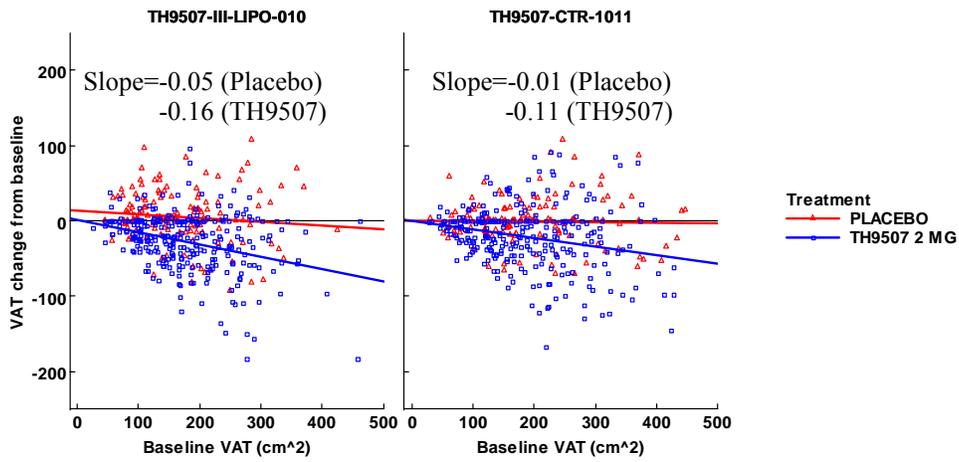


Treatment-by-baseline interaction:

For VAT percent change from baseline, the interaction was not significant for Study 11 (p=0.7) and it was borderline significant for Study 10 (p=0.1). For VAT change from baseline to Week 26, treatment-by-baseline interaction was significant (p=0.02) for both studies (Figs. 20).

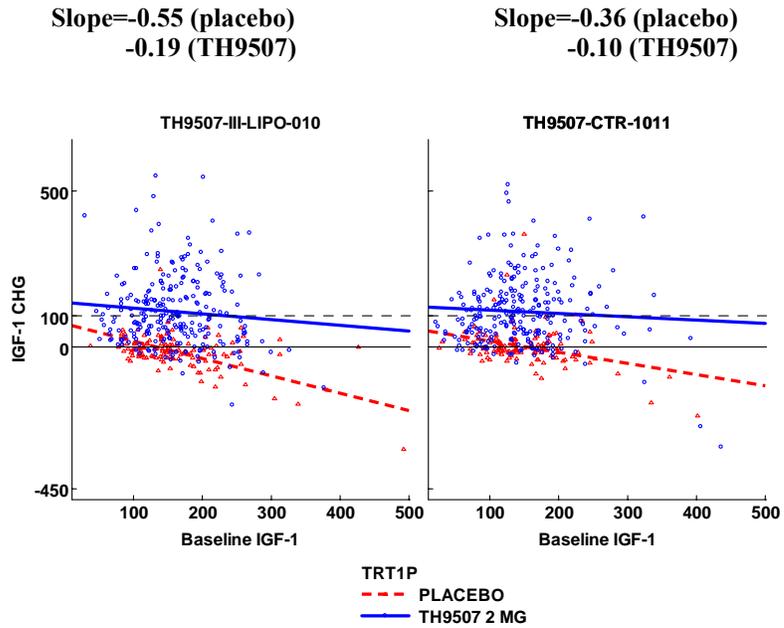
Figure 20 VAT % change and change from baseline to week 26 by baseline VAT





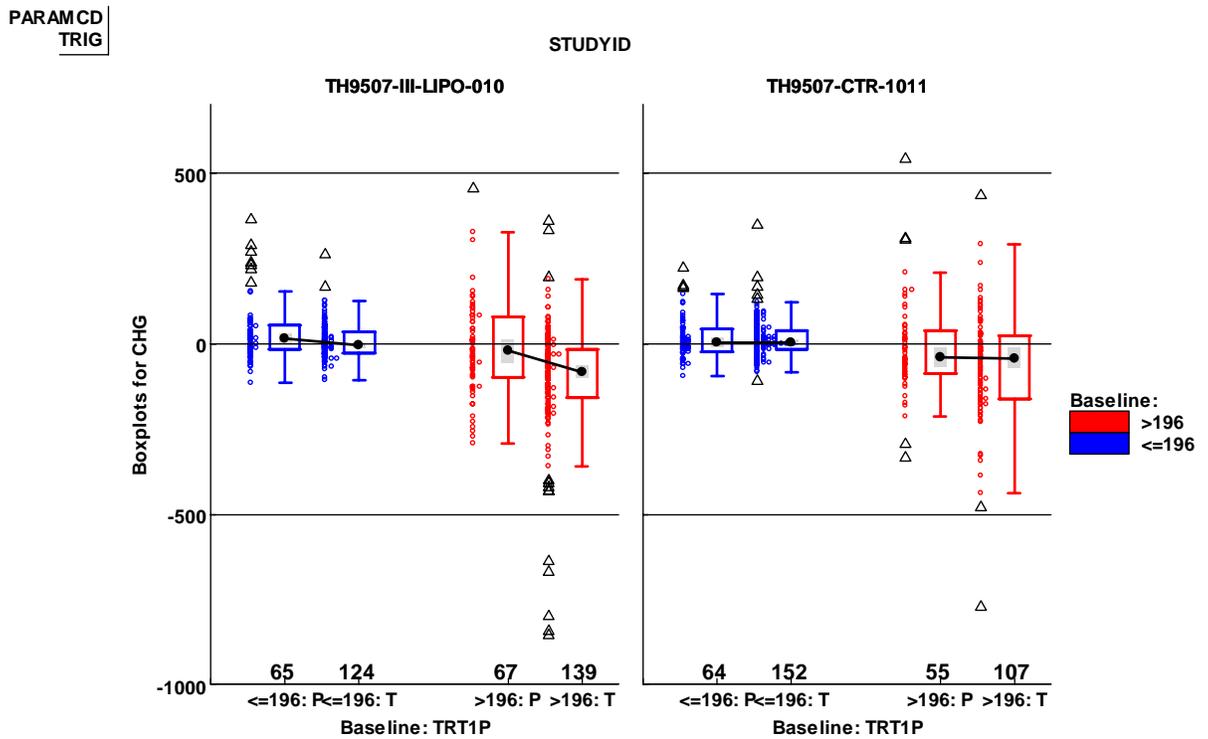
Treatment-by-baseline IGF-1 was significant for IGF-1 change from baseline to week 26 (Fig. 21).

Figure 21 IGF-1 change from baseline to Week 26 by baseline IGF-1



For TG change from baseline, treatment-by-baseline TG was significant ($p < 0.001$) for Study 10. The treatment difference was greater in patients whose baseline TG was greater than the median (>196 mg/dL) for Study 10 (Fig. 32). The TG change from baseline to week 26 was not significant for Study 11.

Figure 22 TG change from baseline to Week 26 by baseline TG median ≤ 196 or >196 – ITT (no baseline carried forward)



Extension Phase

In both studies, the initial randomized phases of 26 weeks were followed by an extension phase consisting of a randomized withdrawal period of 26 weeks. Completers in the TH9507 treatment group at Week 26 were re-randomized to TH9507 or placebo for another 26 weeks. The purpose of the extension was to collect long-term safety data and to explore the duration of the effect after the main study. The treatment comparisons between placebo and TH9507 during the extension period were exploratory. Patients originally randomized to placebo were switched to TH9507 after Week 26.

For the TH9507–TH9507 treatment sequence, VAT percent changes from Week 26 to Week 52 were +4.5% and -0.4%, respectively, for Studies 10 and 11/12. For the TH9507–placebo treatment sequence, VAT percent changes were +25% and +23.5%, respectively.

For patients switching from placebo to TH9507 at week 26, VAT percent changes from week 26 to week 52 were -15% and -12%, respectively, for studies 10 and 11/12.

Table 20 displays the ANCOVA results for the re randomized groups. The difference between the T-T and T-P treatment sequences was statistically significant. Figure 23 displays cumulative distributions for VAT % change from week 26 to week 52 in the ITT population of the extension phase. Figure 24 displays boxplots for VAT % change in the extension phase.

Table 20 ANCOVA* results for VAT % change from Week 26 baseline to Week 52 – ITTE, LOCF

Study	T - T		T - P		Treatment difference LSM, (SE), [95% CI], p-value
	n	LSM (SE)	n	LSM (SE)	
10	154	+4.5% (2.4)	50	+24.9% (4.1)	-20.4% (4.8) [-29.8, -11.0] P<0.0001
12	92	-1.4% (5.2)	85	+24.5% (5.4)	-25.8% (7.6) [-40.7, -10.9] P=0.0008

*ANCOVA included treatment as fixed effect and Week 26 baseline VAT as covariate
LSM=least-square mean

Figure 23 Cumulative distribution of VAT % change from Week 26 to week 52 – ITTE, LOCF

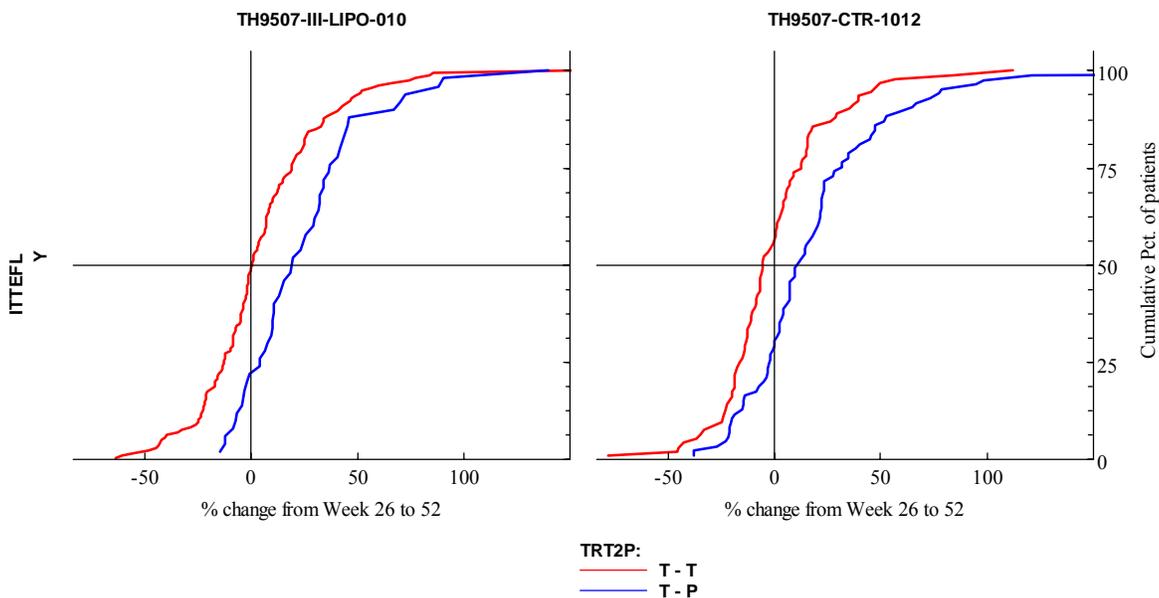


Figure 24 Boxplots for VAT % change from Week 26 baseline to Week 52 – ITTE, LOCF

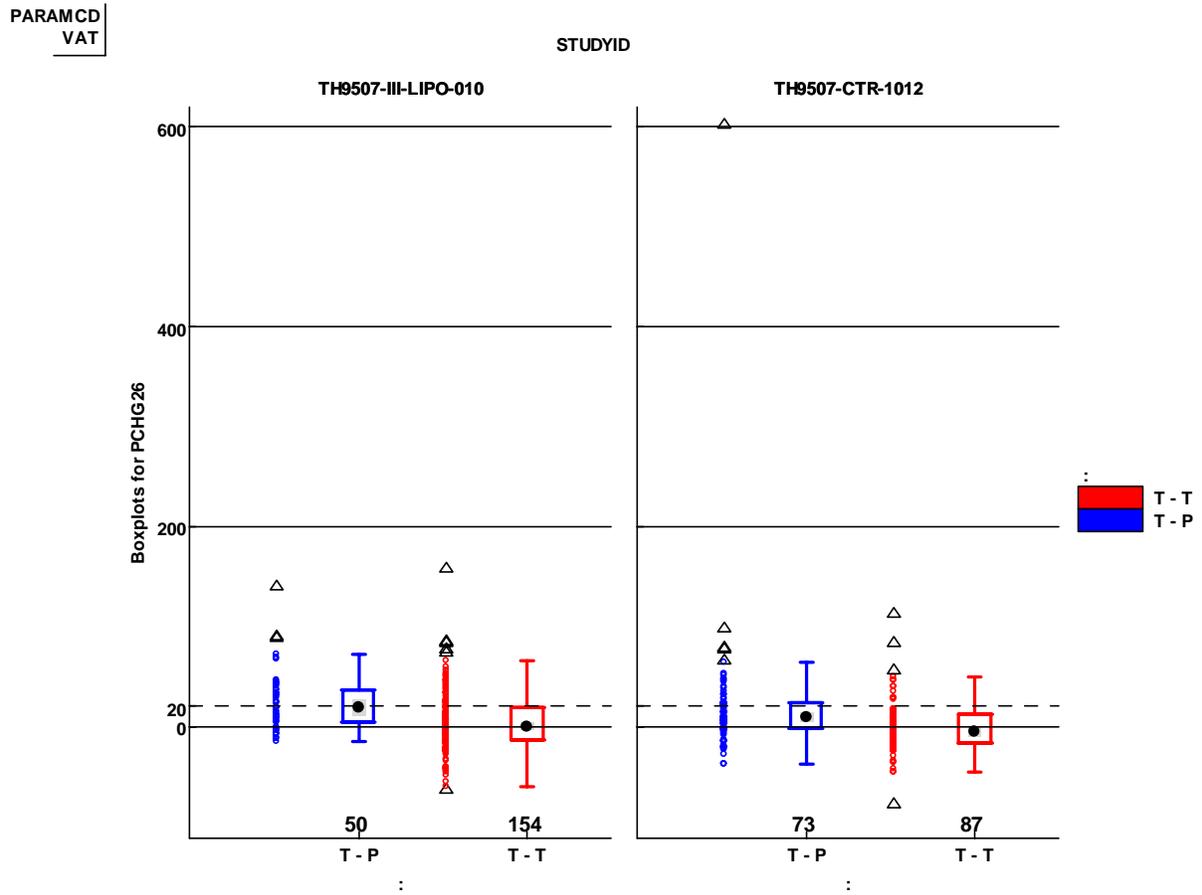


Figure 25 displays VAT (cm²) levels over time by treatment sequence during the main phase and the extension phase for patients who completed 52 weeks of treatment. Figure 16 displays VAT percent changes over time with sample sizes for each treatment group in the main phase and in the extension phase for the completers at week 52. The efficacy of TH9507 was clearly reversed within 13 weeks after drug discontinuation.

Figure 25 VAT levels over time by treatment sequence (main and extension) in 52-week completers

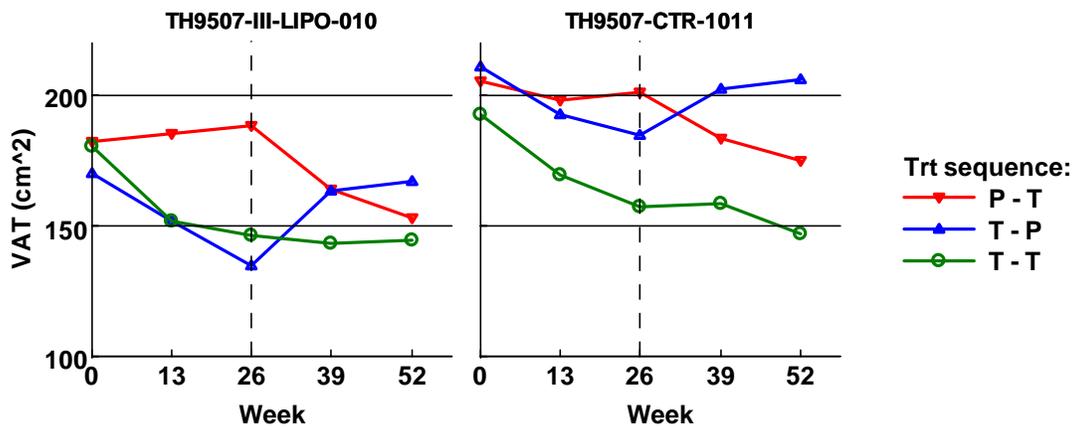
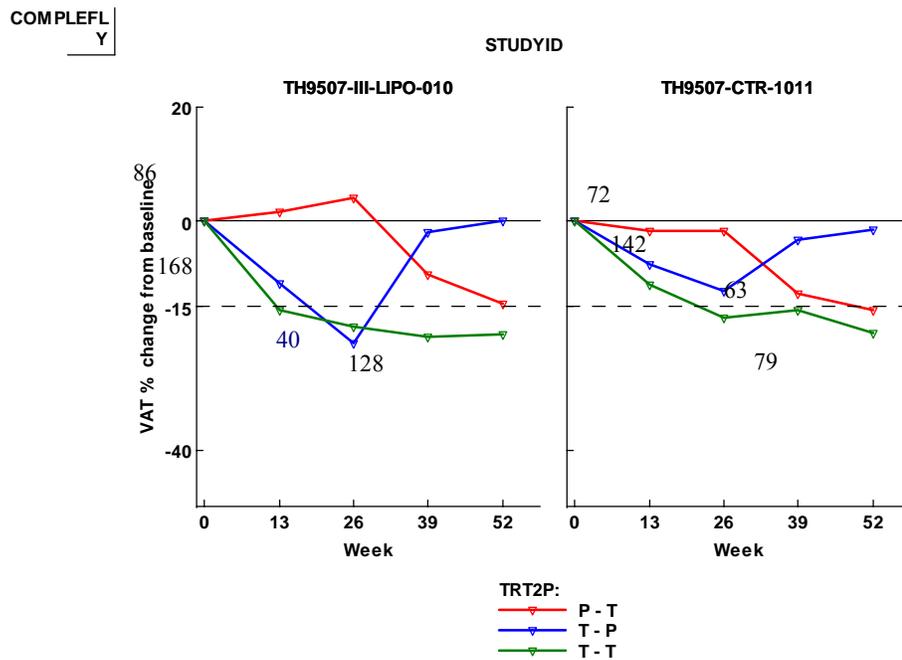
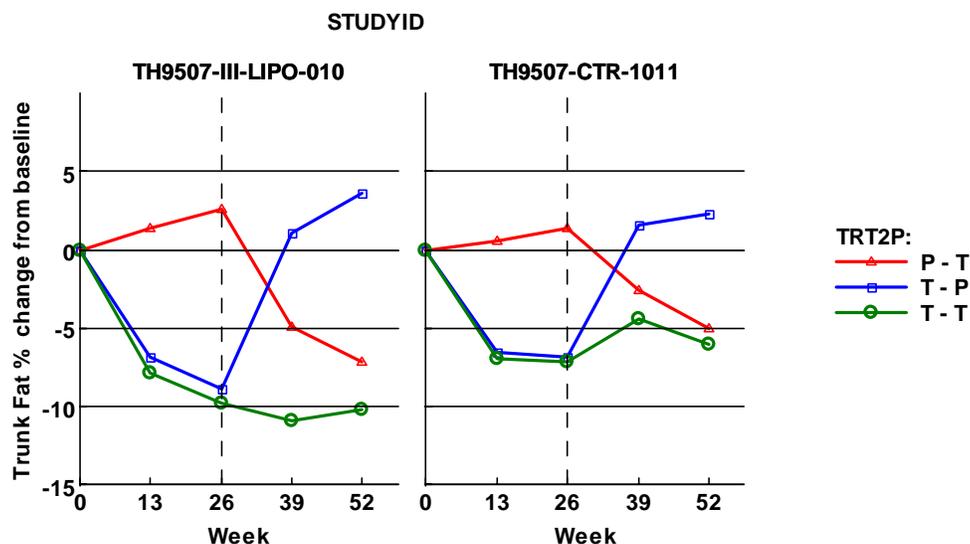


Figure 26 Mean VAT % change by treatment sequence (main and extension) - Week 52 completers



Similar to VAT, the efficacy of TH9507 with respect to trunk fat was reversed within 13 weeks of study drug discontinuation (Fig. 27 blue).

Figure 27 Mean Trunk Fat % change by treatment sequence (main and extension) in Week 52 completers



TG

TG change from baseline 0 to week 26 was statistically significant favoring TH9507 in the main phase of study 10 but not in study 11. In the extension, the difference between the T – T and T – P treatment sequence was not significant in TG change from baseline 26 to week 52 for either of the studies ($p > 0.6$).

Figure 28 Cumulative distribution of TG (mg/dL) change from Week 26 to Week 52 - ITTE

IGF-1

Difference between the re randomized groups were statistically significant in IGF-1 change from week 26 baseline to week 52 (Table 21). The T – P treatment sequence in Figure 31 shows at week 39, IGF-1 reversed to week 0 level after discontinuation at week 26.

Table 21 ANCOVA* results for IGF-1 change from week 26 to week 52– ITT, LOCF

Study		T - T		T - P		Treatment difference at Week 26 LSM, (SE), [95% CI], p-value
		n	Mean	n	Mean	
10	Week 26 (SD)	154	291 (124)	50	281 (105)	78 (14.3) [50, 106] p<0.0001
	change (SE)	154	-59 (7.1)	50	-137 (12.4)	
11	Week 26 (SD)	92	280 (134)	85	269 (110)	110 (11.9) [87, 134] p<0.0001
	change (SE)	92	-25 (8.2)	85	-135 (8.5)	

* Analysis of covariance: treatment as fixed effect and baseline VAT as covariate

Figure 29 Cumulative distribution of TG (mg/dL) change from Week 26 to Week 52 - ITTE

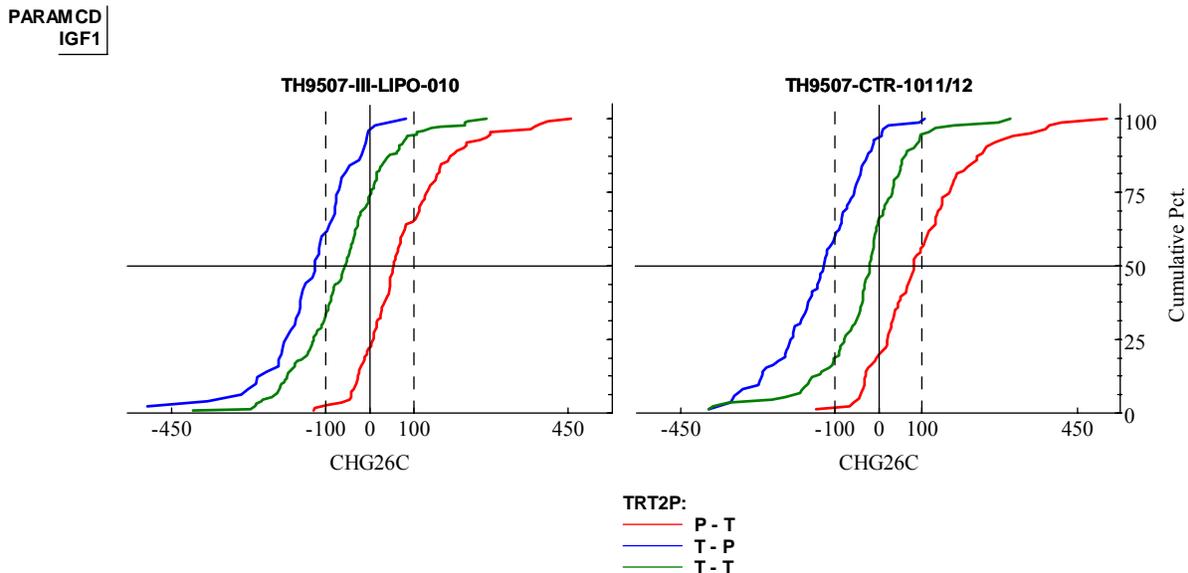


Figure 30 Mean IGF-1 change from Week 26 by visit week and treatment sequence – Week 52 Completers

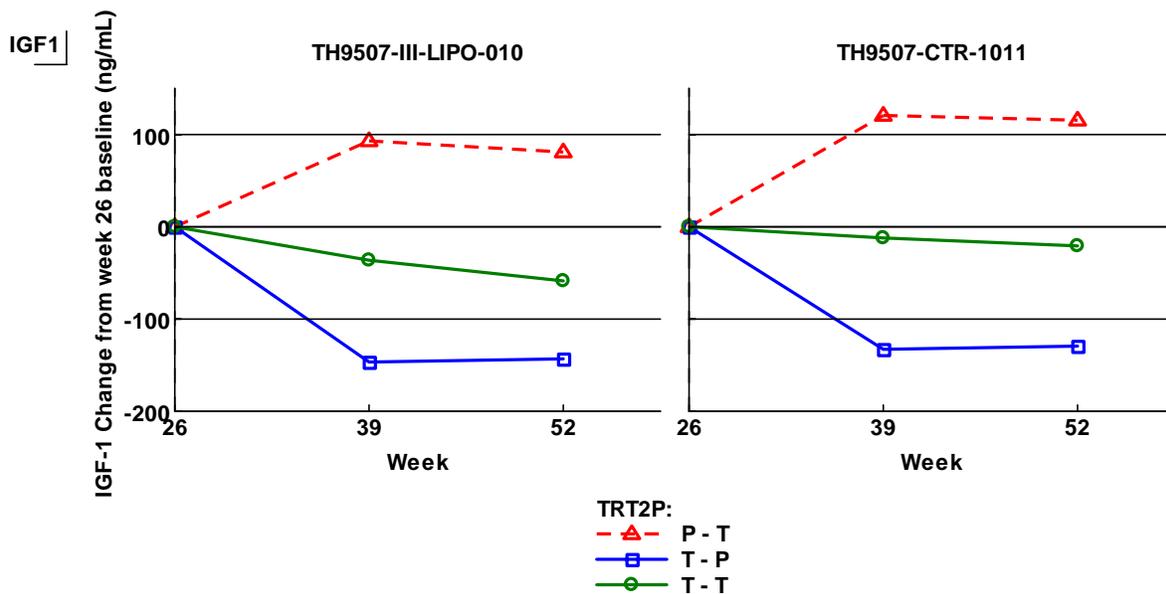
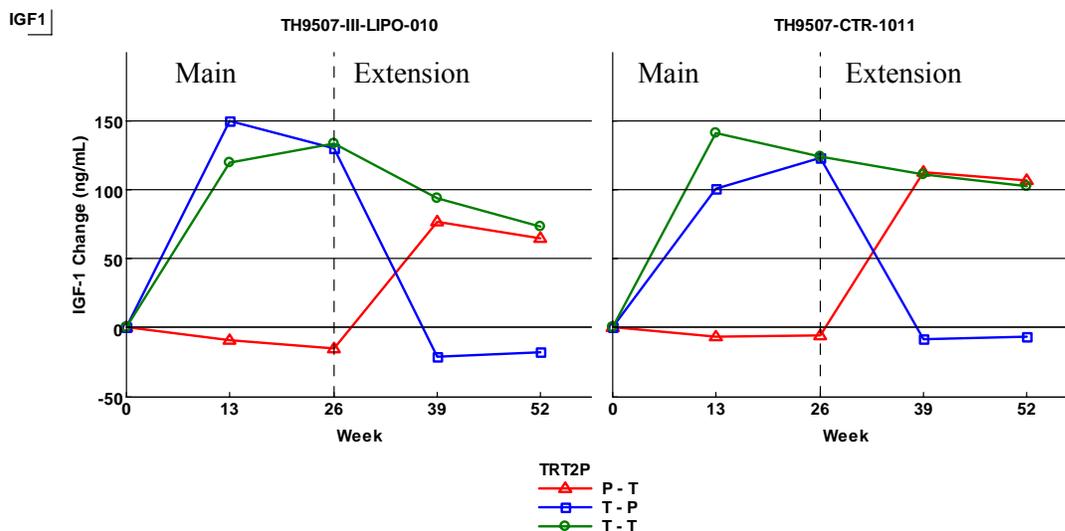


Figure 31 Mean IGF-1 change from baseline (week 0) by visit week – Week 52 Completers



3.2 Evaluation of Safety

This section addresses specific safety issues identified by the FDA medical reviewer.

Issues:

1. IGF-1 levels over time for different treatment sequences.
2. Correlation of IGF-1 and VAT
3. The effect of TH9507 on the development of diabetes.

Conclusions:

Results for the two studies, 10 and 11 were consistent. The statistical conclusions are:

1. IGF-1 behaved in a predictable manner in all group sequences, T-T, T-P and P-T from Week 0 to Week 52 (Fig 1). That is, IGF levels during a particular treatment phase did not appear to exhibit carryover effects from previous treatment exposure.
2. The correlation of IGF-1 SDS change and VAT percent change from baseline to week 26 was approximately -0.2. The percentage of the variation in VAT % change accounted for by IGF-1 was approximately 5%. As a result, the 95% confidence intervals were wide for the VAT % change (Fig 5).
3. Compared to the placebo group, the percent of patients with diabetes was statistically significantly greater in the TH9507 2 mg group at Week 26 (Table 4)

Analysis:

IGF-1 SDS (standard deviation score):

The MO asked this reviewer to evaluate IGF-SDS change over time including the extension. In particular, the MO noticed that observed levels appeared to decrease from Weeks 0 to 52 for the treatment sequence T-T.

Table 22 presents the descriptive statistics of IGF-SDS change from baseline by treatment sequence and visit week.

Table 22 Descriptive statistics of IGF-SDS change from baseline by treatment sequence and week – Extension completers

Trt	Week	n	Study 10				Study 11				
			Mean	(SD)	Min	Max	n	Mean	(SD)	Min	Max
P - T	13	84	-0.2	(1.4)	-8.0	3.0	71	-0.2	(1.2)	-3.7	4.8
	26	83	-0.3	(1.2)	-7.7	1.5	71	-0.1	(1.1)	-4.5	3.7
	39	80	1.8	(2.1)	-4.4	8.1	69	2.4	(2.1)	-1.5	9.9
	52	80	1.5	(2.1)	-3.5	6.9	65	2.2	(2.9)	-4.7	13.8
T - P	13	39	3.2	(2.0)	0.4	7.5	59	2.2	(1.8)	-2	6.9
	26	39	2.7	(2.4)	-1.1	13.0	61	2.6	(2.6)	-6	8.5
	39	36	-0.5	(0.8)	-2.4	1.4	60	-0.2	(1.1)	-5.6	2.2
	52	38	-0.3	(1.1)	-3.8	2.1	54	0	(1.0)	-4.4	2.2
T - T	13	124	2.7	(2.5)	-2.7	13.4	77	3.1	(2.7)	-4	14.1
	26	124	2.9	(2.6)	-2.1	13.0	78	2.8	(2.7)	-5.1	12.4
	39	118	2.2	(2.2)	-2.5	10.8	78	2.4	(2.2)	-3	8.8
	52	118	1.6	(2.2)	-3.5	10.5	70	2.3	(2.8)	-3.1	11.6

Figure 32 displays IGF-1 SDS change from Week 0 baseline to Week 52 by treatment sequence for those patients who completed the extension. Fig 32 demonstrated predictable changes in IGF-SDS during sequential periods of exposure to drug and/or placebo.

Figure 32 Mean IGF-1 standard deviation score (SDS) over time by treatment sequence – Extension-phase completers

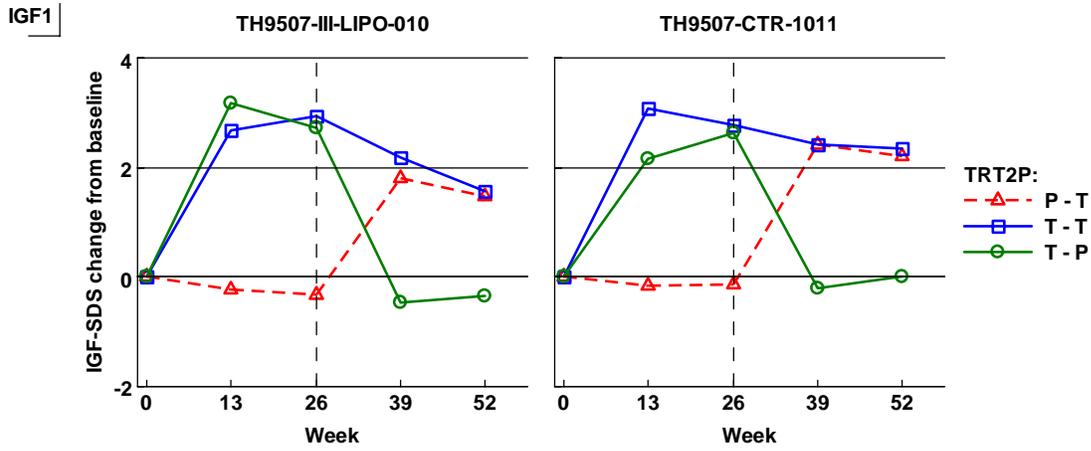


Figure 33 shows similar predictable changes by gender. Tables 24 displays the descriptive statistics of IGF-SDS change from baseline by treatment sequence, gender and week. The treatment-by-gender interaction was not statistically significant ($p=0.3$). Similar predictability was observed in mean IGF percent change from baseline over time (Fig 34 and Table 25). Figure 35 displays boxplots of IGF-SDS change from baseline by treatment sequence at Week 52.

Table 23 Descriptive statistics of IGF-SDS change from baseline by treatment sequence, gender and week – Extension completers

Trt	Gender	Week	Study 10				Study 11						
			n	Mean	(SD)	Min	Max	Week	n	Mean	(SD)	Min	Max
P - T	F	13	10	-0.1	(0.7)	-1.6	0.7	13	9	-0.5	(1.1)	-3.3	0.3
		26	10	-0.5	(0.8)	-2.5	0.8	26	9	-0.4	(1.2)	-3.2	0.9
		39	9	1.2	(1.4)	-1.5	2.9	39	9	1.3	(1.0)	-0.4	2.7
		52	10	1.6	(1.6)	-0.8	4.2	52	9	1.1	(1.5)	-1.8	2.9
	M	13	74	-0.2	(1.5)	-8	3	13	62	-0.1	(1.2)	-3.7	4.8
		26	73	-0.3	(1.3)	-7.7	1.5	26	62	-0.1	(1.1)	-4.5	3.7
		39	71	1.9	(2.2)	-4.4	8.1	39	60	2.6	(2.2)	-1.5	9.9
		52	70	1.4	(2.2)	-3.5	6.9	52	56	2.4	(3.1)	-4.7	13.8
T - P	F	13	5	2	(1.6)	1.2	4.9	13	5	2	(1.6)	1.2	4.9
		26	5	2	(1.9)	0.1	4.9	26	5	2	(1.9)	0.1	4.9
		39	5	-0.4	(0.5)	-1.1	0	39	5	-0.4	(0.5)	-1.1	0
		52	5	-0.2	(0.7)	-1.4	0.3	52	5	-0.2	(0.7)	-1.4	0.3
	M	13	34	3.3	(2.0)	0.4	7.5	13	34	3.3	(2.0)	0.4	7.5
		26	34	2.8	(2.5)	-1.1	13	26	34	2.8	(2.5)	-1.1	13
		39	31	-0.5	(0.9)	-2.4	1.4	39	31	-0.5	(0.9)	-2.4	1.4
		52	33	-0.4	(1.2)	-3.8	2.1	52	33	-0.4	(1.2)	-3.8	2.1
T - T	F	13	16	1.8	(1.7)	-0.2	6	13	8	2.4	(2.0)	0	6.2
		26	15	1.6	(1.5)	-0.6	5.1	26	8	1.5	(2.0)	-0.4	5.4
		39	14	1.5	(1.5)	-1.1	4.7	39	8	2.1	(2.1)	0.2	5.4
		52	15	0.7	(1.3)	-1.4	3	52	7	1.3	(1.1)	0.2	2.9
	M	13	108	2.8	(2.6)	-2.7	13.4	13	69	3.2	(2.8)	-4	14.1
		26	109	3.1	(2.7)	-2.1	13	26	70	2.9	(2.8)	-5.1	12.4
		39	104	2.3	(2.3)	-2.5	10.8	39	70	2.4	(2.3)	-3	8.8
		52	103	1.7	(2.3)	-3.5	10.5	52	63	2.5	(2.9)	-3.1	11.6

Figure 33 Mean IGF-1 standard deviation score (SDS) over time by gender and treatment sequence – Extension-phase completers

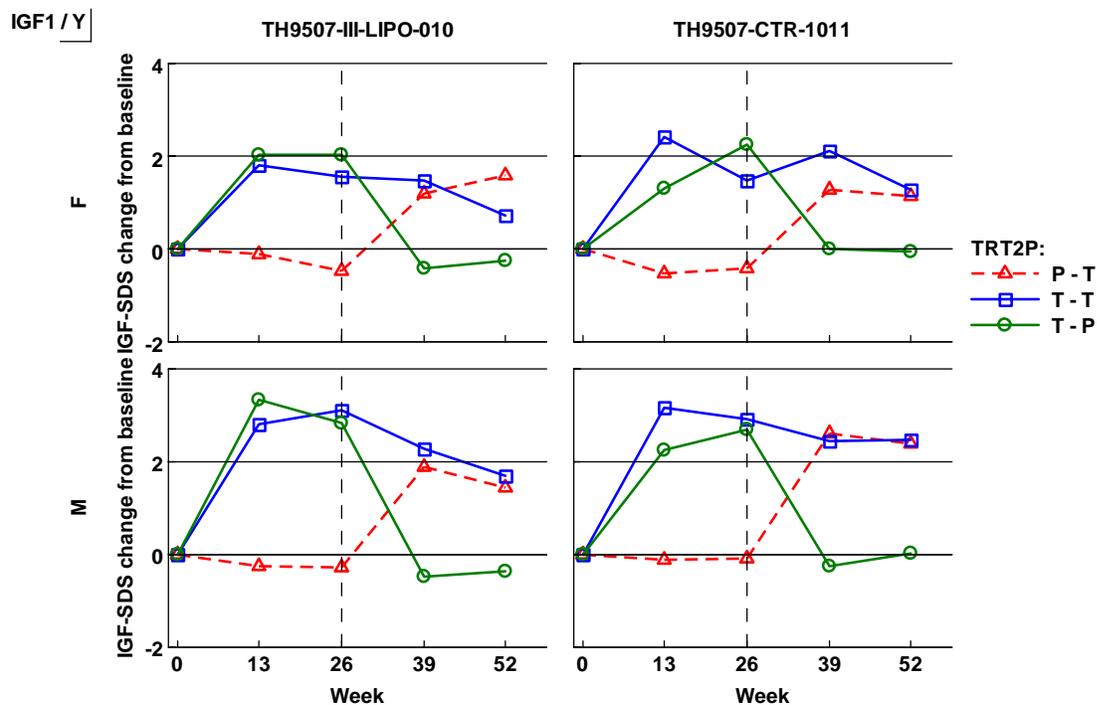


Table 24 Descriptive statistics of IGF-1 % change from baseline by treatment sequence and visit week – Extension completers

Trt	Week	Study 10					Study 11				
		n	Mean	(SD)	Min	Max	n	Mean	(SD)	Min	Max
P - T	13	84	1	(34)	-68	137	71	-1	(39)	-55	239
	26	83	-5	(25)	-66	67	71	2	(36)	-55	187
	39	80	59	(63)	-50	297	69	82	(70)	-50	309
	52	80	51	(75)	-68	310	65	81	(96)	-56	430
T - P	13	39	102	(68)	6	238	59	85	(68)	-38	343
	26	39	92	(82)	-23	411	61	106	(95)	-62	405
	39	36	-11	(21)	-41	57	60	1	(32)	-67	126
	52	38	-7	(29)	-55	57	54	7	(35)	-78	126
T - T	13	124	85	(70)	-50	309	77	100	(85)	-58	470
	26	124	92	(77)	-49	374	78	89	(87)	-73	413
	39	118	69	(70)	-45	398	78	81	(75)	-43	318

Study 10							Study 11				
Trt	Week	n	Mean	(SD)	Min	Max	n	Mean	(SD)	Min	Max
	52	118	50	(65)	-57	329	70	81	(90)	-44	387

Figure 34 Mean IGF-1($\mu\text{g/L}$) % change over time by treatment sequence – Extension-phase completers

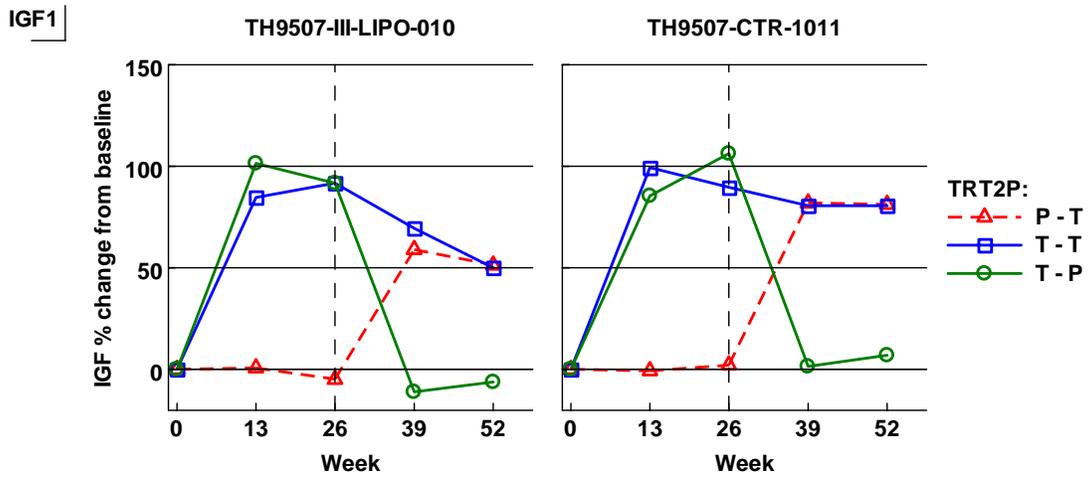
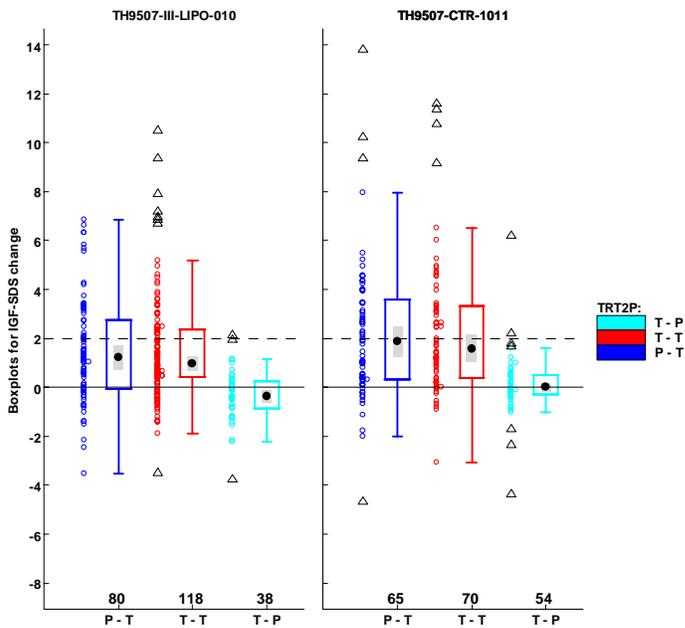


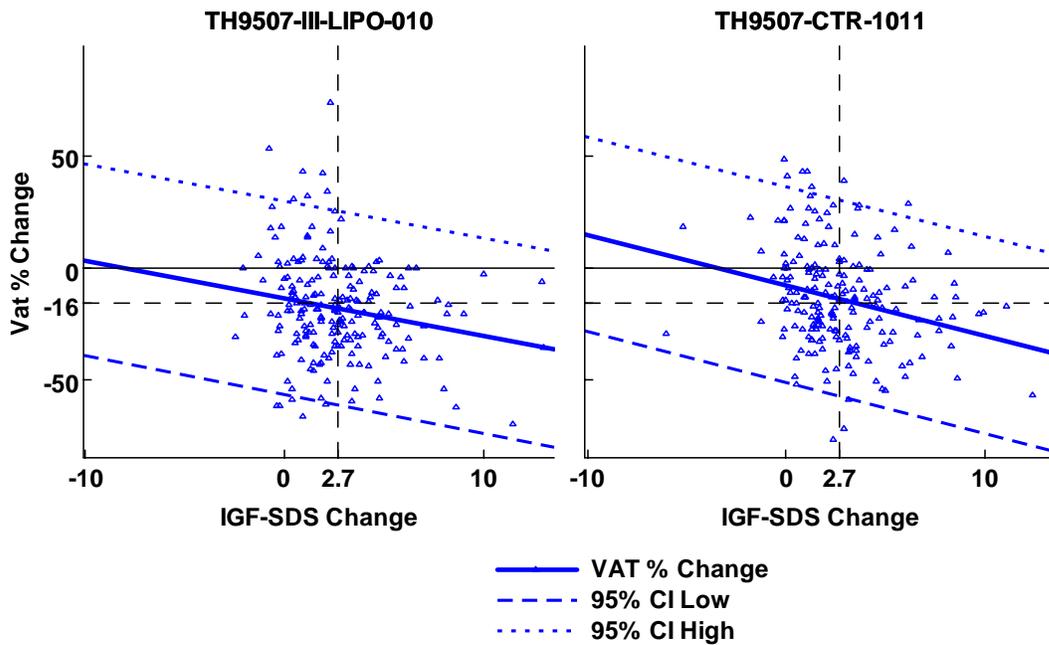
Figure 35 Boxplot of IGF-SDS change from baseline at Week 52 by treatment sequence – Extension completers



Correlation between IGF-SDS change and VAT percent change at Week 26

The correlation coefficient was -0.19 for Study 10 and -0.25 for Study 11 (-0.22 pooled). R^2 was 0.04 and 0.06 (0.05, pooled), respectively. Consequently, the variability of the VAT % change from baseline that could be explained by the IGF-SDS change from baseline was only 4% to 6% (wide 95% CI in Figure 36).

Figure 36 Correlation between IGF-SDS change and VAT % change from baseline with 95% confidence interval



Diabetes:

Diabetes was defined by the Medical Officer, Ali Mohamadi, M.D., as an HbA_{1c} level $\geq 6.5\%$. We performed Exact tests on the safety population of the main phase to evaluate the percentage of patients with HbA_{1c} $\geq 6.5\%$ at Week 26 using last-observation-carried-forward data.

The analysis stratified by study showed that TH9507 was statistically significantly different than placebo in the percentage of patients with diabetes ($p=0.004$) after 26 weeks of treatment (Table 25). The homogeneity test for odds ratios was not significant ($p=0.6$) which means the two study results were consistent. The results were similar when excluding patients with baseline HbA_{1c} $\geq 6.5\%$ (Table 26). In addition, the Log Rank test on time to first event of HbA_{1c} $\geq 6.5\%$ was also significant (Fig 37).

Table 25 Analysis of percentage of patients with diabetes – Safety population, Main Phase

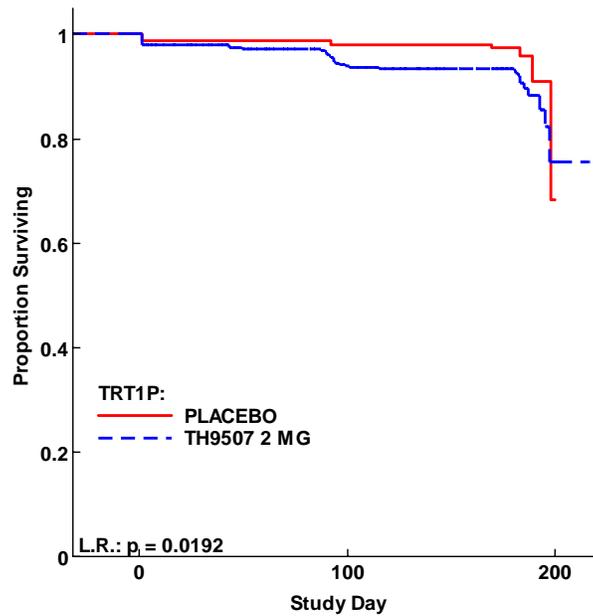
Study	Placebo	TH9507	risk difference	Odds Ratio (95% CI)	2-sided p-value Fisher's Exact test
10	1/137 (1%)	15/273 (5%)	5% (2%, 8%)	7.9 (1.2, 335)	0.016
11	4/126 (3%)	21/270 (8%)	5% (0%, 9%)	2.6 (0.8, 10.5)	0.118
Integrated analysis stratified by Study				3.6 (1.5, 12.0)	0.004

Table 26 Analysis of percentage of patients with diabetes – Safety population excluding baseline diabetics, Main Phase

Study	Placebo	TH9507	risk difference	Odds Ratio (95% CI)	2-sided p-value Fisher's Exact test
10	0/135 (0%)	10/267 (4%)	4% (1%, 6%)	undef (1.2, undef)*	0.03
11	4/125 (3%)	17/265 (6%)	3% (-0%, 7%)	2.1 (0.7, 8.6)	0.28
Integrated analysis stratified by Study				3.4 (1.3, 11.5)	0.017

* undefined due to 0 event in placebo

Figure 37 Kaplan-Meier curves of time to first HbA_{1c} ≥ 6.5%



The pre-post plot of HbA_{1c} (Week 26 vs. baseline) (Fig. 38) showed that TH9507 patients with HbA_{1c} above 5.6 (prediabetes defined by MO) at baseline (x-axis) had a greater risk than did placebo patients to become diabetes (above 6.5, y-axis).

Figure 38 Pre-Post plot of HbA_{1c}

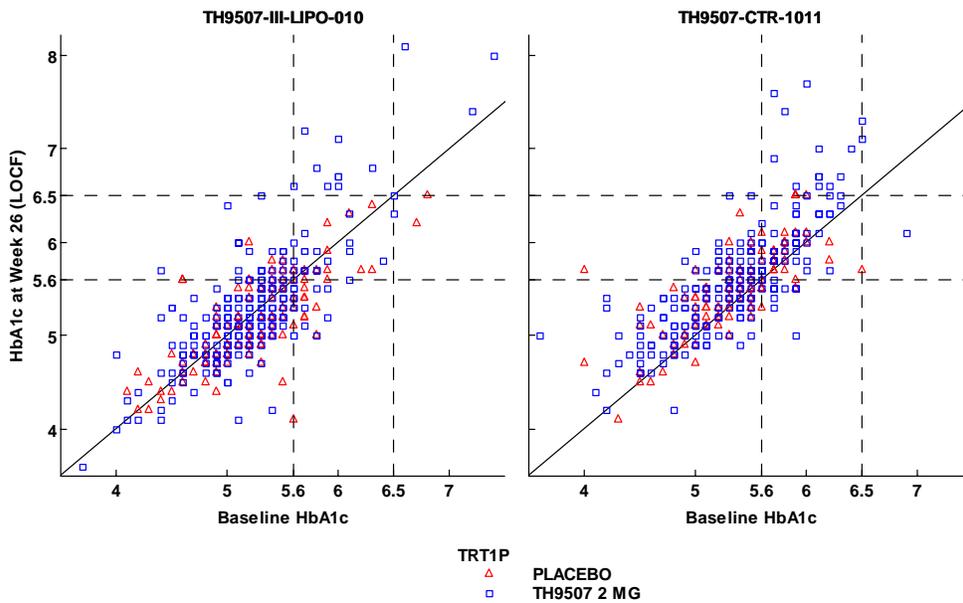
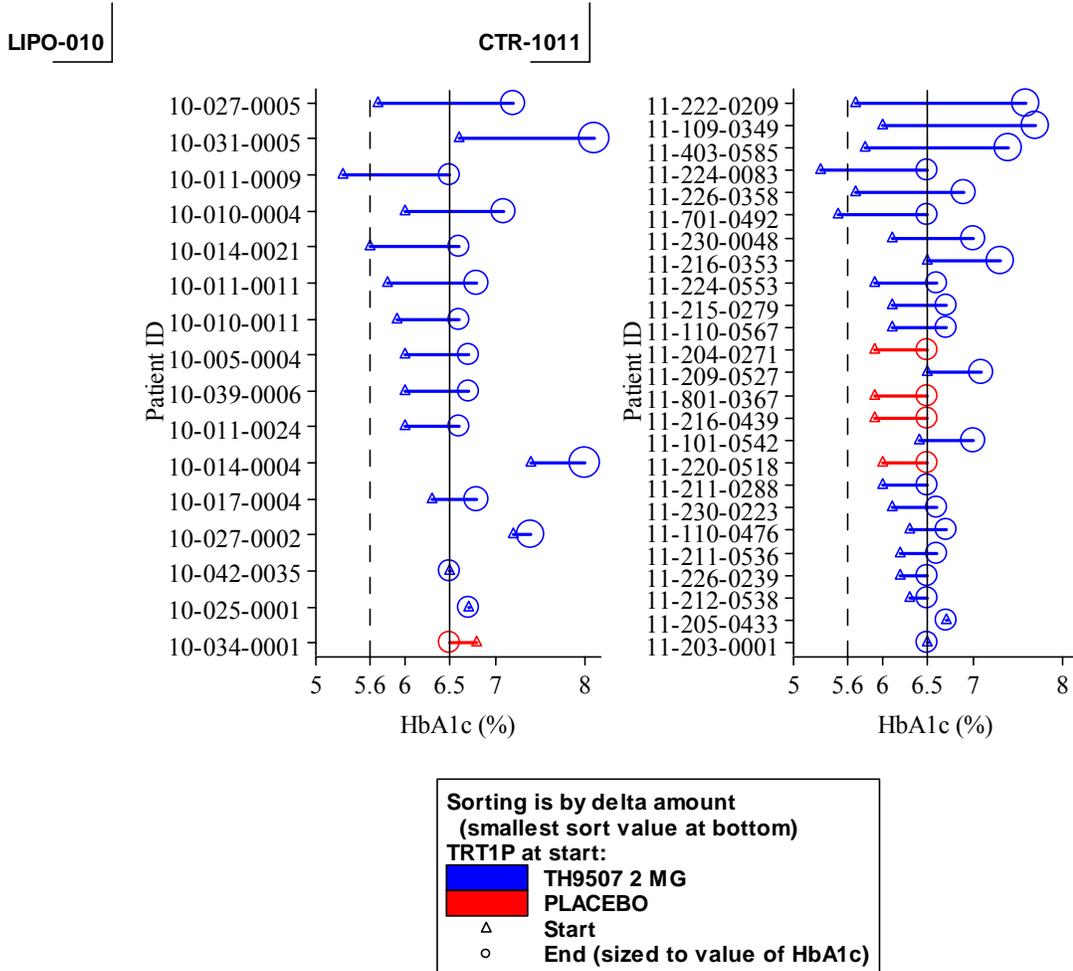


Figure 39 displays HbA_{1c} change from baseline to Week 26 (LOCF) in patients with Week 26 HbA_{1c} ≥ 6.5%. As noted previously, the patients were predominately pre-diabetics at baseline (triangle) (5.6% > HbA_{1c} < 6.5%). Most patients with a larger HbA_{1c} change were treated with TH9507 (blue).

Figure 39 Delta graph of HbA_{1c} change from baseline to Week 26 by patient with Week 26 HbA_{1c} ≥ 6.5%



4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Gender:

The majority of patients were males (85%). To increase the sample size for females, the 2 studies were combined. Baseline VAT was significantly less in females than males (Fig 40) (median, 112 cm² vs. 187 cm²). Treatment-by-gender interaction was not significant but treatment-by-gender-baseline interaction was significant. Figure 41 displays the regression of VAT percent change on baseline VAT by treatment group by gender. Treatment difference increased as baseline VAT increased in females whereas treatment difference decreased as baseline VAT increased in males. Similarly, Fig 42 displays boxplot by gender and baseline VAT ≤ 120 cm² and >120 cm².

Figure 40 Box plot for baseline VAT by gender

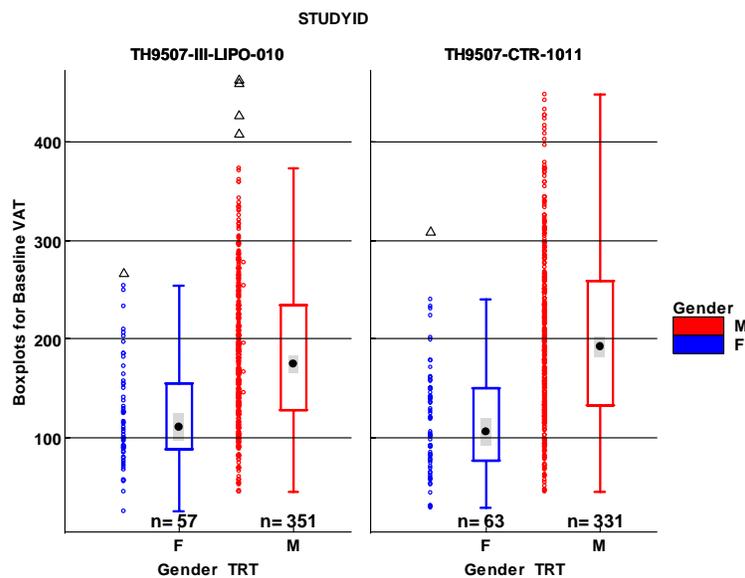


Figure 41 VAT % change by baseline VAT by gender

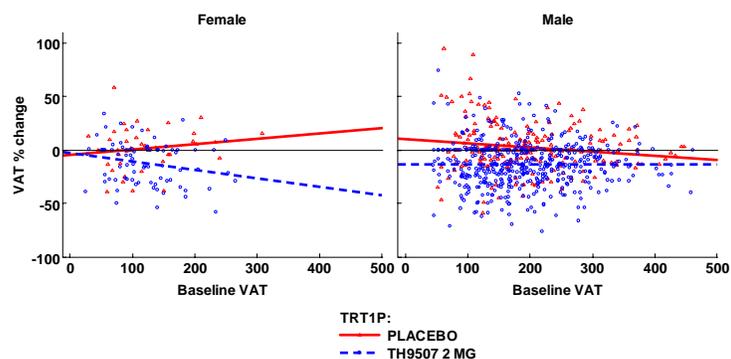
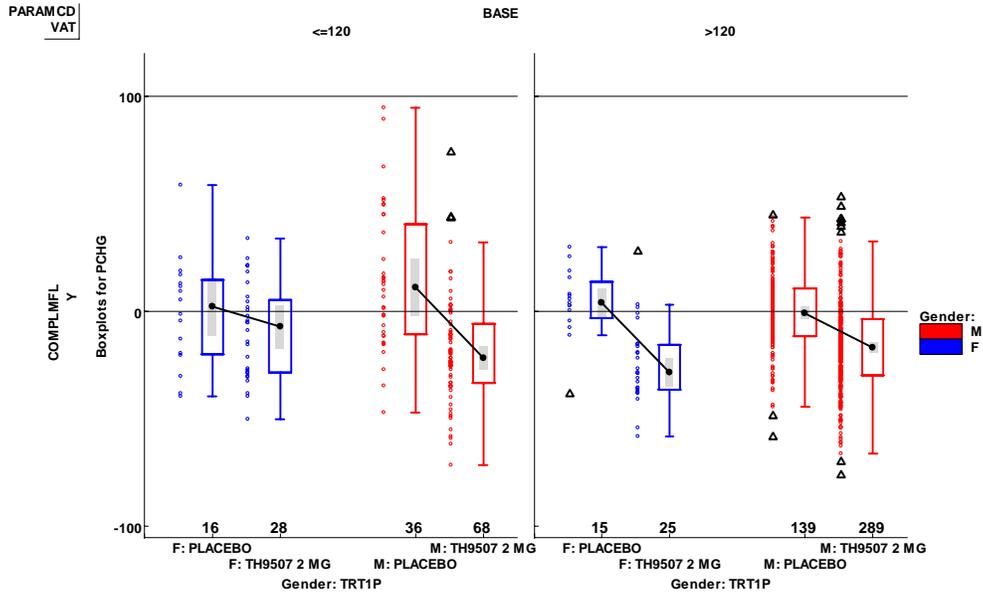


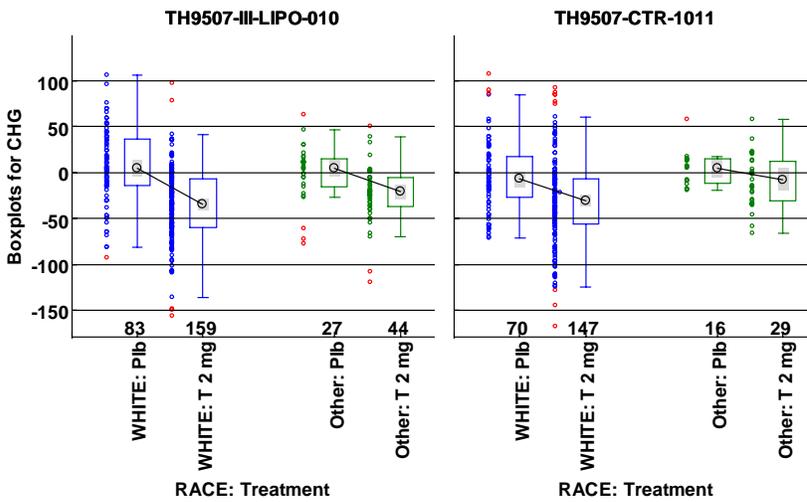
Figure 42 Boxplot for VAT % change by baseline VAT ≤120 or >120 and gender



Race

P-value for treatment-by-race interaction was 0.1 when race was classified as Caucasians and ‘Others’ (Fig 43).

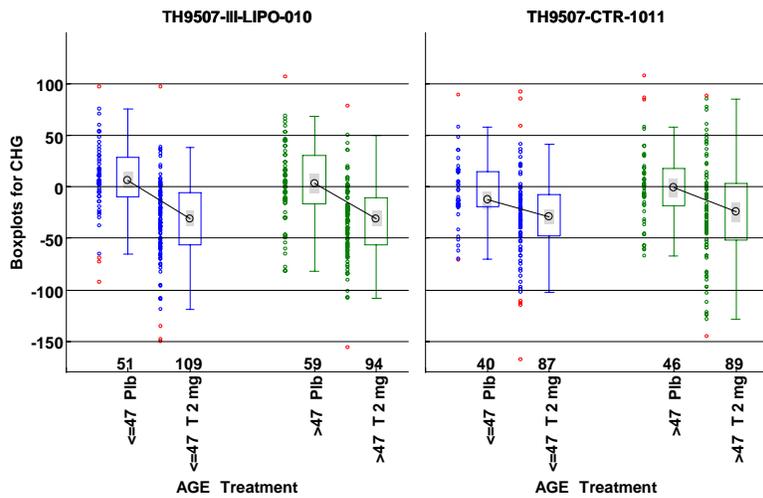
Figure 43 Boxplot of VAT % change from baseline to week 26 by race and treatment group



Age group

Treatment-by-age group using median age of 47 was not significant (Fig. 44).

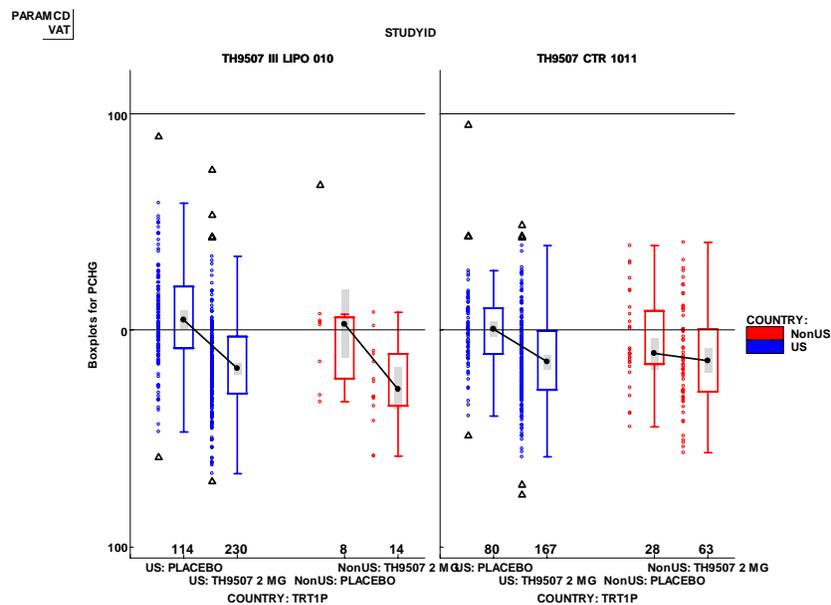
Figure 44 Boxplot of VAT % change from baseline to week 26 by age and treatment group



4.2 Other Special/Subgroup Populations

Majority of patients were in US sites (94% study 10, and 73% study 11). Figure 45 displays the boxplot by US or non-US sites. The p value for treatment-by-site (US and non-US) interaction was 0.1 using pooled data.

Figure 45 Boxplot of VAT % change from baseline to week 26 by site and treatment group



5. SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

Based on results from studies 10 and 11, the 2 mg TH9507 was statistically significantly different from placebo for the primary efficacy variable, VAT percent change from baseline to week 26. The efficacy of TH9507 for triglycerides change was not consistent between studies. The PRO change from baseline to week 26 was not consistent in method of analysis and study. The two studies were powered for both the VAT change and the PRO changes. The 2 studies should not be pooled to show significance of PRO endpoints.

Appendix

Patient Reported Outcomes (PRO)

Secondary efficacy PRO variables were belly size evaluation (BSE), belly appearance distress (BAD) and belly profile assessment (BPA) scales. The primary analysis was parametric ANCOVA for BAD and BSE and the Mann-Whitney test for (BPA) for study 10 and ranked ANCOVA for study 11 for all 3 PRO endpoints, BSE, BAD and BPA. This reviewer reported p-values from these agreed-upon, prespecified analyses. A summary of p-values are found at the end of this section following descriptive data for each endpoint.

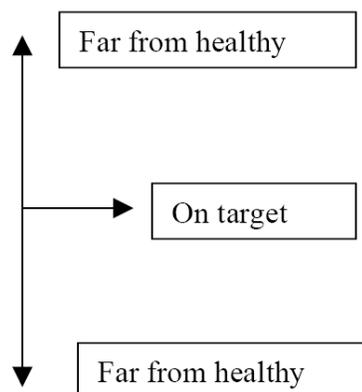
1. Belly Size Evaluation (BSE)

The Body Size Scale below consists of bi-directional responses which measure deviation from a healthy look. Patients compared their ‘current appearance’ to their perceived ‘healthy look’.

Compared to my “healthy look”, my current amount or size is....

Scored Patient Selects Phrase

-100	A great deal less/very smaller or thinner
-75	A lot less/much smaller or thinner
-50	Somewhat less, smaller or thinner
-25	A little less, smaller or thinner
0	About right
+25	A little more or bigger
+50	Somewhat more or bigger
+75	A lot more or much bigger
+100	A great deal more or very much bigger



The bi-directional response used a corrected change score, negative of the (absolute (final) - absolute(baseline)) to yield consistently positive scores for improvement and negative scores for worsening and 0 for staying the same distance from ‘about right’ (Table 27) .

Table 27 BSE bi-directional

	1	2	3
Possible Score Category	Baseline and final values>0 (bigger than ‘about right’)	Baseline and final values<0 (smaller than ‘about right’)	Values fall on opposite sides of 0 (smaller than ‘about right’ at one time and bigger than ‘about right’ at another time)
Change from baseline: Final – baseline	+ = worsening - = improvement	+ = improvement - = worsening	NA
Corrected change from baseline: - (absolute(final)-absolute(baseline))	+ = improvement - = worsening	+ = improvement - = worsening	+ = improvement - = worsening 0 = staying the same distance

Table 28 displays the descriptive statistics for BSE. At baseline, the median BSE score was 75 (belly size ‘much bigger’ than the ‘healthy look’) (Fig 46). At week 26, both groups improved toward the target look. The difference between treatment groups was not statistically significant. P-values were p=0.75 for study 10 and p=0.21 for study 11. Figure 47 displays the cumulative distribution for BSE change from baseline to week 26 and Figure 48 the percentage of patients by BSE change.

Table 28 Descriptive statistics for Belly Size Evaluation – ITT, LOCF

Protocol	TRT	N	Label	Mean	Std Dev	Median	Min	Max
LIPO-010	Placebo	137	BL	55.8	52	75	-100	100
			Wk 26	35.4	55	50	-100	100
			Change*	13.1	31.4	0	-100	100
LIPO-010	Th9507	272	BL	59.8	47.7	75	-100	100
			Wk 26	35.3	54.9	50	-100	100
			Change*	14.6	30.1	0	-75	100
CTR-1011	Placebo	126	BL	56.9	57.2	75	-100	100
			Wk 26	47.6	53.7	75	-100	100
			Change*	11.7	25.2	0	-75	100
CTR-1011	Th9507	268	BL	56	54.2	75	-100	100
			Wk 26	33.4	58	50	-100	100
			Change*	14.6	27.6	0	-75	100

*Corrected changed score = -(absolute(week 26)-absolute(baseline)) with positive score= improving and negative score=worsening

Figure 46 Percentage of patients by BSE score at baseline - ITT

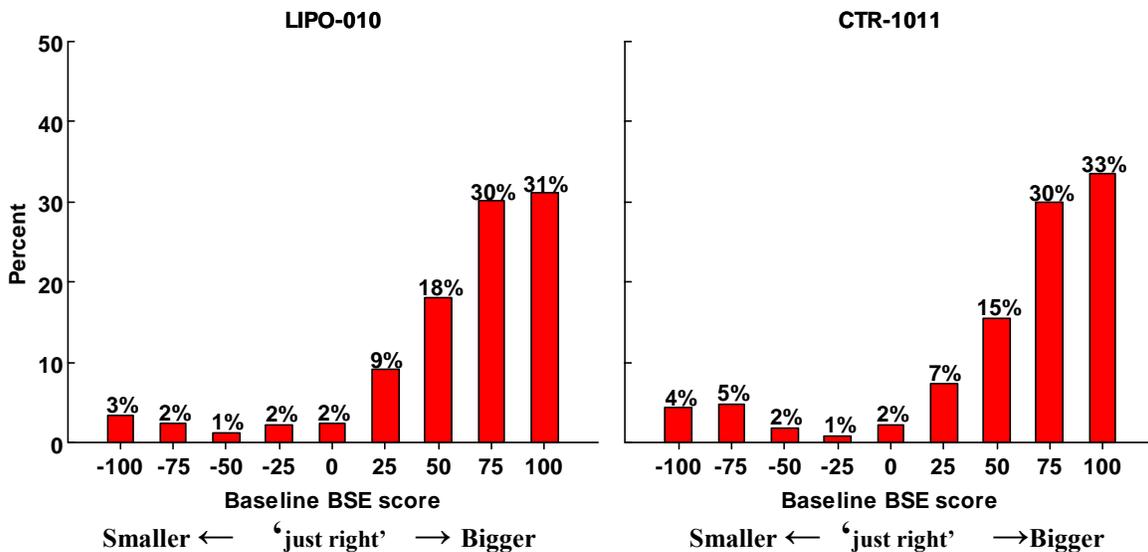


Figure 47 Cumulative distribution of Belly Size Evaluation change from baseline to Week 26 – ITT, LOCF

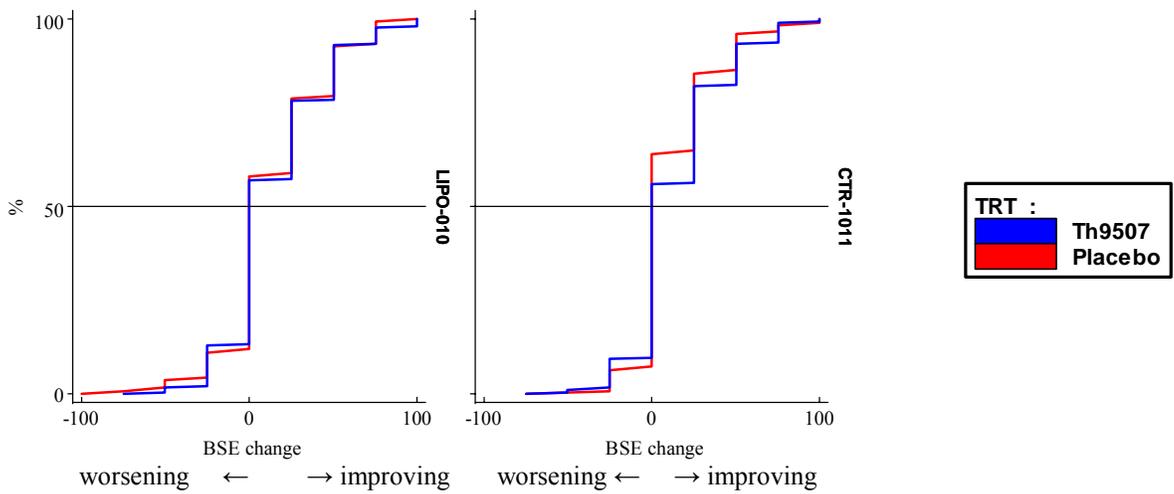
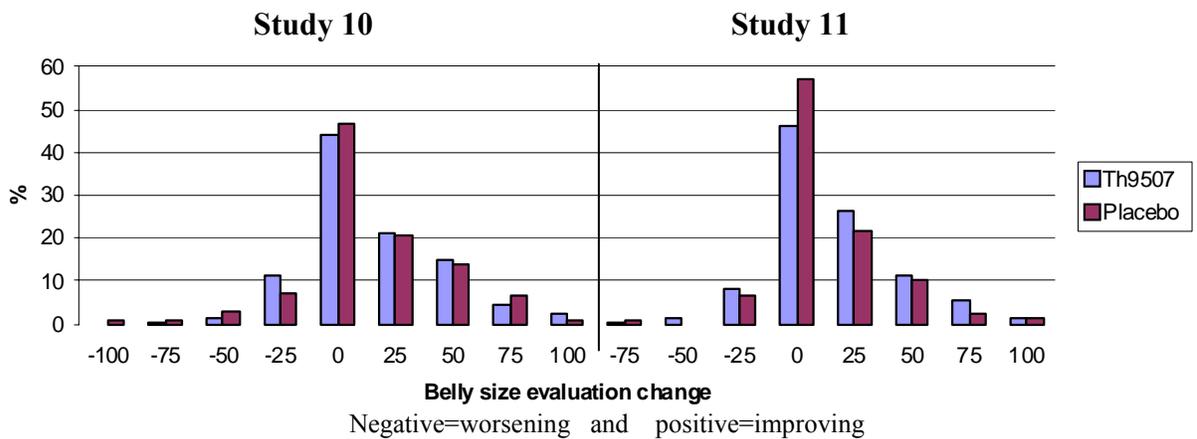


Figure 48 Percentage of patients by BSE change from baseline to Week 26 – ITT LOCF



2. Belly Appearance Distress

The 0 to 100 scale ranged from extremely upsetting and distressing to extremely encouraging with a score of 50 being neutral. A positive change indicated improvement.

Think about your “current appearance”. The following statements are about how you feel about certain aspects of your current appearance.

Score	Patient Selects Phrase
0.0	Extremely upsetting and Distressing
12.5	Very Upsetting and Distressing
25.0	Quite Upsetting and Distressing
32.5	A little Upsetting
50.0	No feeling either way
62.5	A little encouraging
75.0	Quite encouraging
87.5	Very Encouraging
100.0	Extremely Encouraging

Table 29 displays the descriptive statistics for BAD. More than 50% of patients reported ‘extremely upsetting and distressing (30%)’ or ‘very upsetting and distressing (24%)’ at baseline for belly appearance distress (Fig 49). At week 26, the scores in both groups improved (Figs 50, 51). The treatment difference was not statistically significant for study 10 ($p=0.076$) and was significant for study 11 (0.022).

Table 29 Descriptive statistics of Belly Appearance Distress – ITT, LOCF

Protocol	TRT	N	Label	Mean	Std Dev	Median	Min	Max
LIPO-010	Placebo	137	BL	24	25.7	12.5	0	100
			Wk 26	30.2	27.3	25	0	100
			Change	6.2	25.8	0	-87.5	100
	Th9507	273	BL	22.1	22.2	12.5	0	100
			Wk 26	33.8	25.9	25	0	100
			Change	11.6	26.9	0	-87.5	87.5
CTR-1011	Placebo	126	BL	20.2	22.1	12.5	0	100
			Wk 26	25.4	25.1	25	0	87.5
			Change	5.2	26.6	0	-87.5	87.5
	Th9507	268	BL	22.4	24.2	12.5	0	100
			Wk 26	30.6	25.4	25	0	100
			Change	8.3	29	0	-100	100

Figure 49 Percentage of patients by BAD score at baseline – ITT, LOCF

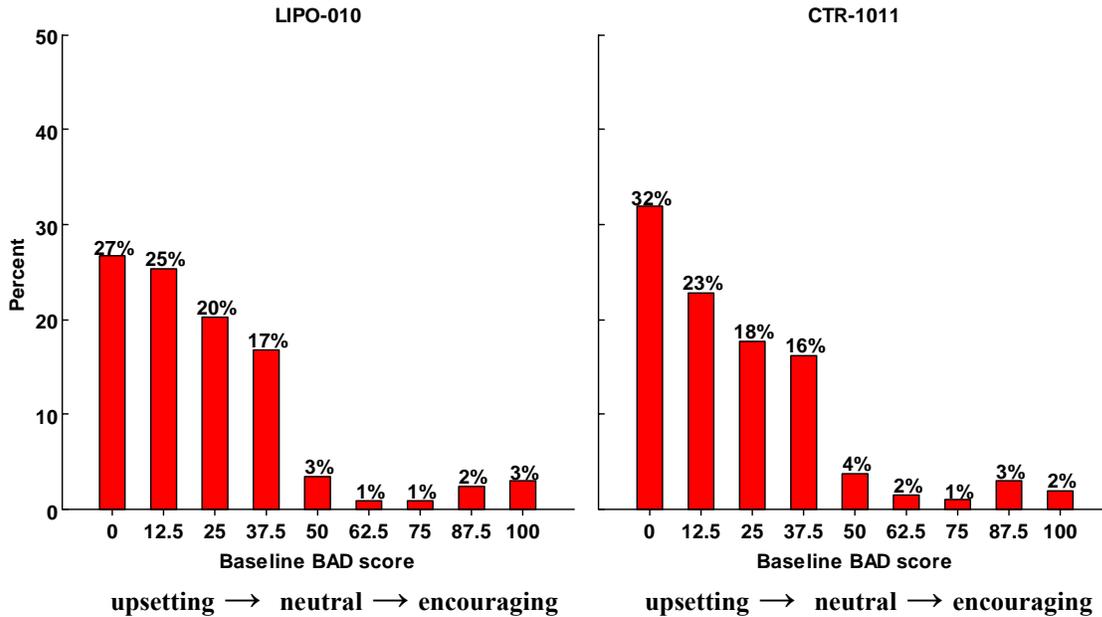


Figure 50 Cumulative distribution of Belly Appearance Distress change from baseline to Week 26 – ITT, LOCF

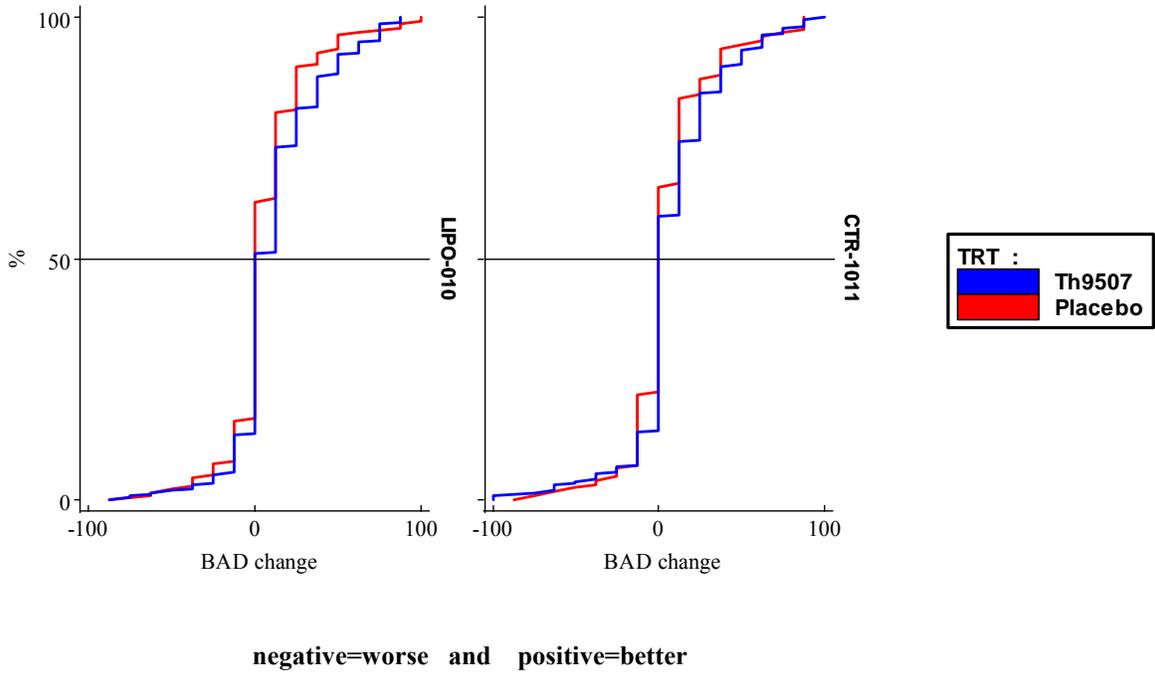
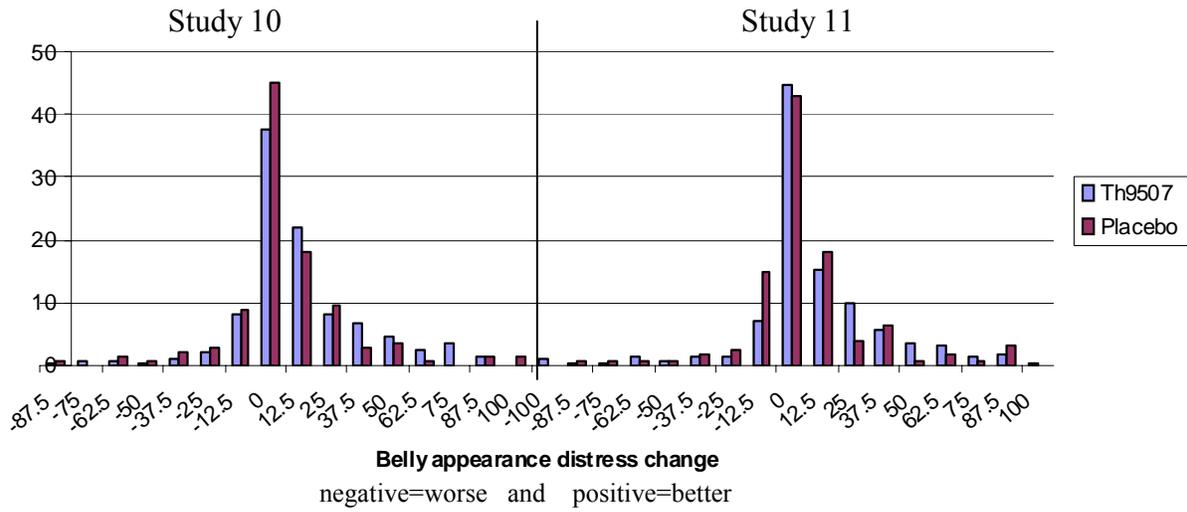


Figure 51 Percentage of patients by BAD change from baseline – ITT, LOCF



1. Patient rated Belly Profiles Scales

Patients and Physicians selected from 6 body profile images using a scale from 0 (normal) to 5 (the most dysmorphic) that reflected an increasing belly or hump.

Patients chose an image in response to each of three questions:

- Most how you think you look today?
- You would most like to look?
- Smallest amount of improvement that you consider beneficial to your health and well being?

Physician profile evaluations provided a clinical perspective to establish a standard for a ‘minimally clinically important change.’

- Most how you think your patient looks today
- You would most like your patient to look
- Smallest amount of improvement that you consider beneficial to your patient’s health and well being?

Table 30 displays the descriptive statistics for belly profiles today. Median current Belly Profile for baseline and week 26 was 3 (Fig 52). P-values from the nonparametric Mann-Whitney test were p=0.031 for Study 10. The p-value from ranked ANCOVA was 0.075 for study 11.

Table 30 Descriptive statistics of Belly Profiles Today – ITT, LOCF

Protocol	TRT	N	Label	Mean	Std Dev	Median	Min	Max
LIPO-010	Placebo	137	BL	3.2	1.5	3	0	5
			Wk 26	2.8	1.5	3	0	5
			Change	-0.3	1.3	0	-4	5
	Th9507	273	BL	3.3	1.3	3	0	5
			Wk 26	2.6	1.4	3	0	5
			Change	-0.7	1.2	0	-5	4
CTR-1011	Placebo	126	BL	3.3	1.2	3	1	5
			Wk 26	3.1	1.4	3	0	5
			Change	-0.3	1	0	-4	2
	Th9507	268	BL	3.2	1.4	3	0	5
			Wk 26	2.7	1.6	3	0	5
			Change	-0.5	1.3	0	-5	4

Figure 52 Percentage of patients by BPA Today score at baseline – ITT, LOCF

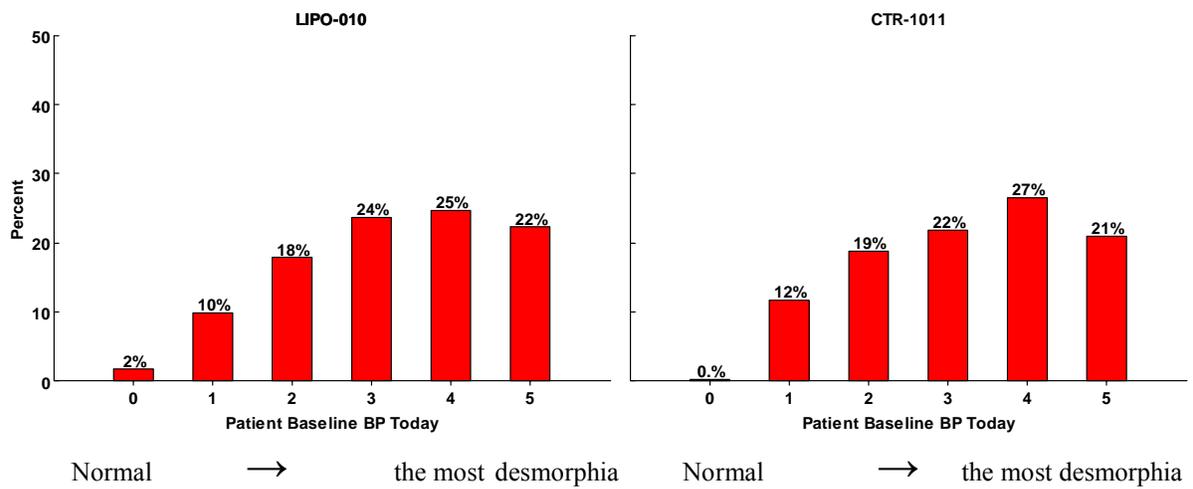
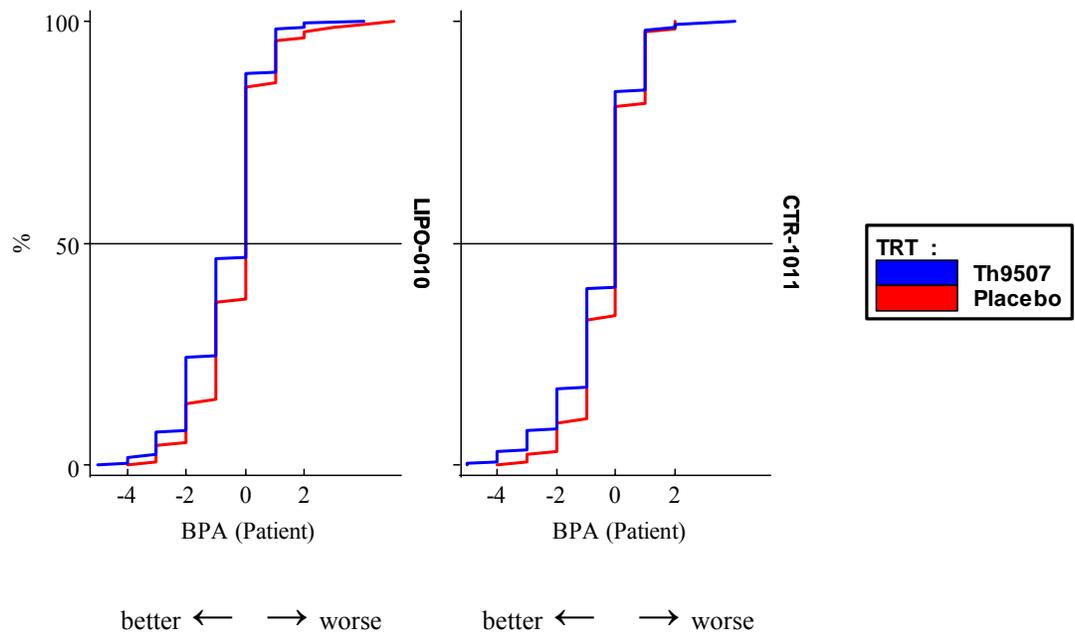
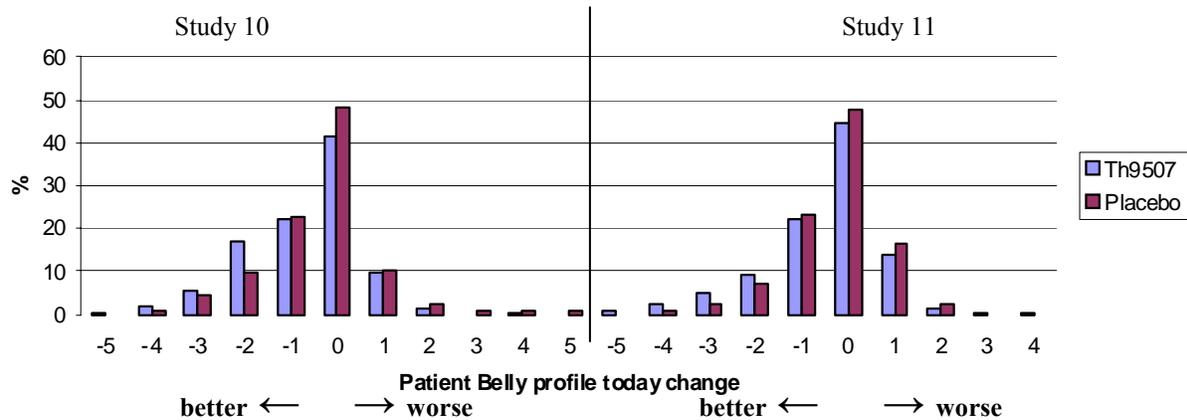


Figure 53 Cumulative distribution of Patient's Belly Profile Today change from baseline to Week 26 – ITT, LOCF



**Figure 54 Percent of patients by patient BP change from baseline to week 26
– ITT, LOCF**



In conclusion, statistical evidence of TH9507 on PRO endpoints was not robust. More than 40% of patients perceived no change from baseline after 26 weeks of treatment for all 3 endpoints. Table 13 displays the p-values from the primary analyses, ANCOVA for BAD and BSE, and Mann-Whitney for BPA in study 10. Ranked ANCOVA was used to analyze all 3 endpoints in Study 11. There were no consistent significant results between studies.

Table 31 Summary of PRO p-values

PRO endpoint	Study 10	Study 11 Ranked ANCOVA
BAD	0.076*	0.022
BSE	0.750*	0.211
BPA	0.031**	0.075

*ANCOVA

**Mann-Whitney

Relationship between Anti-TH9507 antibodies and VAT percent change

Approximately half of the TH9507-treated patients developed anti-TH9507 antibody (Table 14). Figure 27 displays the scatter plot for VAT percent change from baseline at Week 26 versus anti-TH9507 antibody titer using a log scale in TH9507-treated patients with the antibody. Figure 28 presents boxplot of VAT % change by titer category.

Table 32 % of patients with anti-TH9507 antibody and by titer category

Treatment	Study 10						Study 11					
	TH9507			Placebo			TH9507			Placebo		
# patients with Anti-TH9507 antibody/total # (%)	104/209 (50%)			3/112 (3%)			96/197 (49%)			3/89 (3%)		
Titer: 0, low (<400), high (≥400)	0	Low	High	0	Low	High	0	Low	High	0	Low	High
% of patients	50%	42%	8%	97%	3%	0%	51%	38%	11%	97%	3%	0%

Figure 55 Scatter plot of VAT % change by anti-TH9507 antibody titer

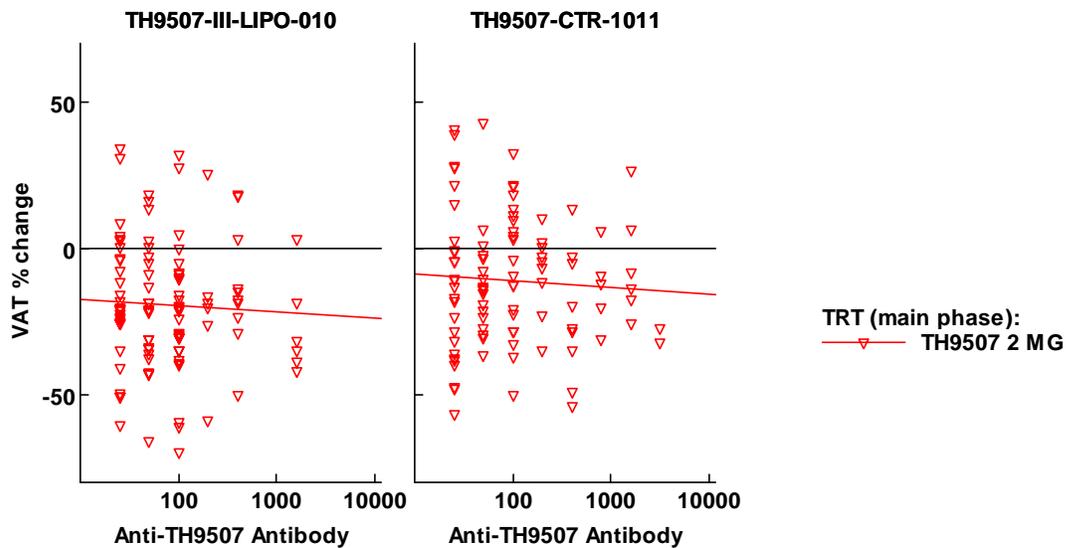
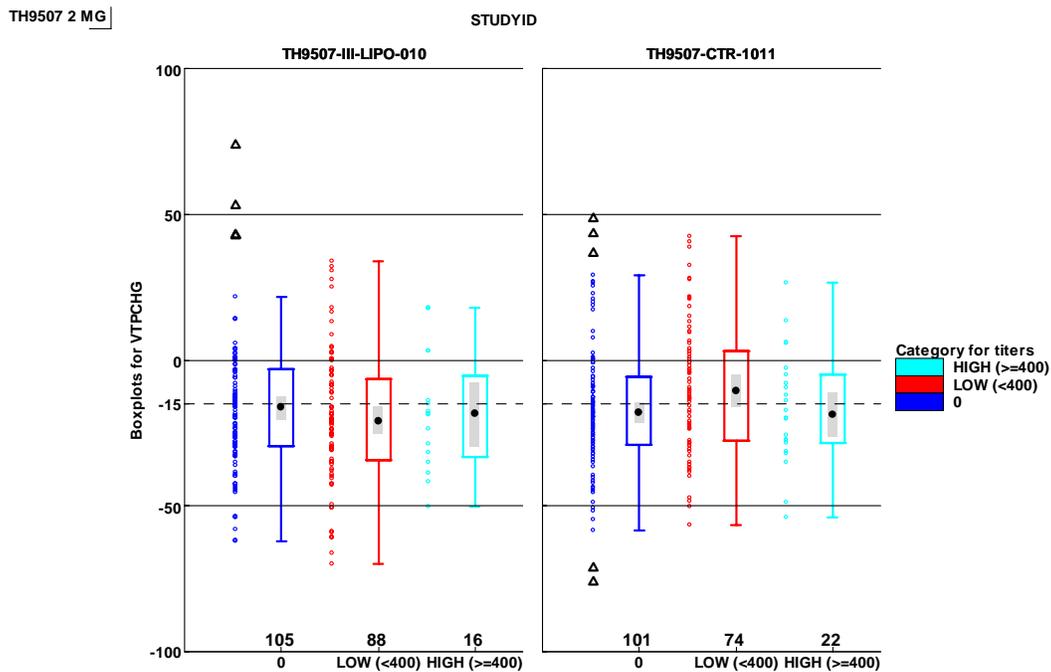


Figure 56 Boxplot of VAT % change by anti-TH9507 antibody titer category



1.3 Waist Circumference

The medical team leader, Dragos Roman, M.D. requested statistical input concerning an epidemiology study of 359,387 participants from nine countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) published in the NEJM by Pishon et. al., 11/13/2008). The authors suggested that ‘both general adiposity and abdominal adiposity are associated with the risk of death and support the use of waist circumference or waist-to-hip ratio in addition to BMI in assessing the risk of death.’

Assigning the mortality rate of participants with waist circumference <86.0 (lowest quintile) as 1, the relative risk was 1.35 (1.26, 1.46) for participants with waist circumference ≥ 102.7 (highest quintile). The RRs of other quintiles were approximately 1.0.

The median waist circumference change from baseline for Egrifta was -1.4 cm when studies 10 and 11 were pooled (Table 33). The median change for patients with baseline waist circumference ≥ 102.7 cm was -0.3 cm (Fig 57). The percentage for patients with waist circumference ≥ 102.7 cm was 49% at baseline and 41% after 26 weeks of TH9507 treatment.

In conclusion, TH9507 2 mg is not very effective in reducing waist circumference, especially for patients with a waist circumference ≥ 102.7 cm. This means that Egrifta most likely has a minimal impact in reducing mortality, or CV death.

Table 33 Quartiles of waist circumference (cm) at baseline and week 26 by treatment and study – ITT

	Study 10				Study 11				Total	
	Waist circumference (cm)								Change from baseline	
	Placebo n=137		TH9507 n=273		Placebo n=126		TH9507 n=270		Placebo n=263	TH9507 n=543
Week	0	26	0	26	0	26	0	26	26	26
100% Max	138	139	154	156	151	168	149	153	16.5	10.8
75% Q3	110	109	108	108	109	109	109	109	1.8	0.3
50% Median	102	102	101	100	102	102	103	101	0.0	-1.4
25% Q1	98	96	97	94	98	97	98	96	-3.1	-5.2
0% Min	92	83	90	84	94	83	94	82	-18	-43.5

Figure 57 Boxplot of waist circumference (cm) change from baseline to week 26 by baseline category and treatment – Main phase ITT

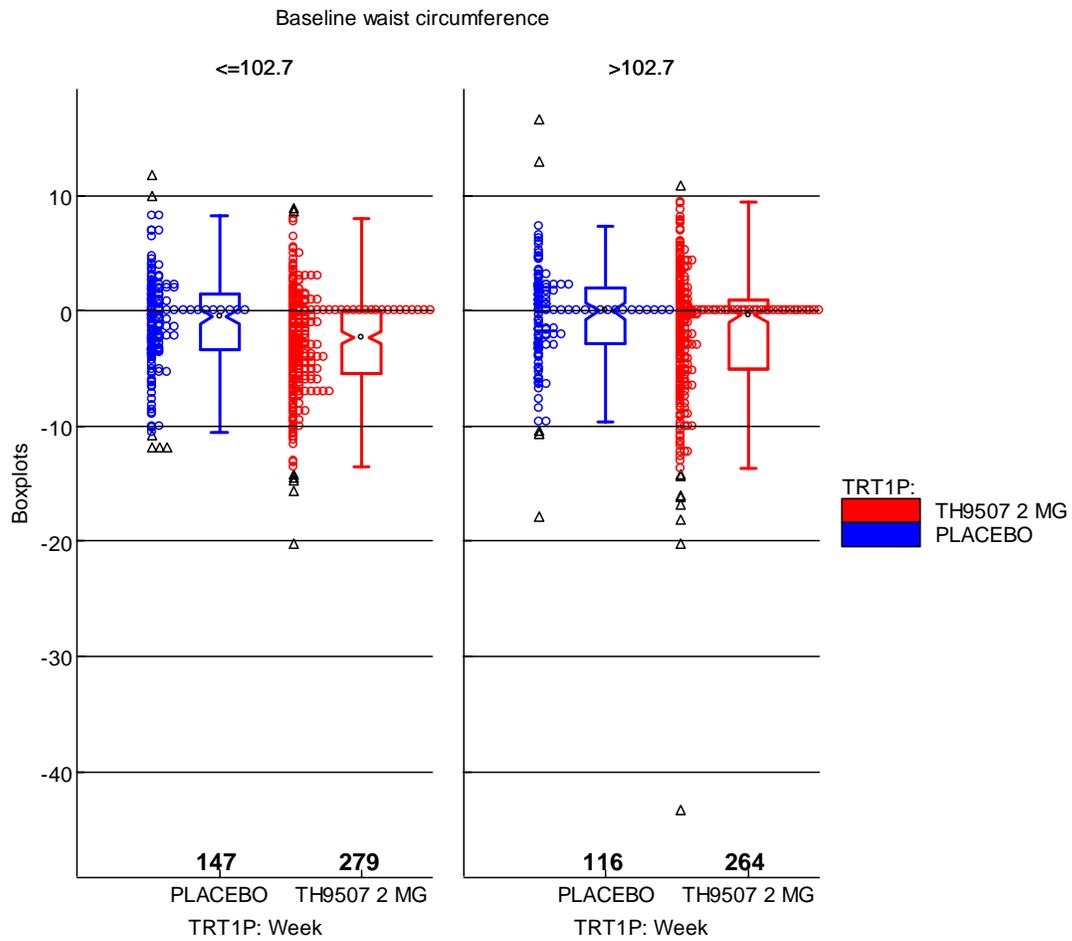


Figure 58 Cumulative distribution of waist circumference (cm) by treatment at Week 26 – Main phase ITT

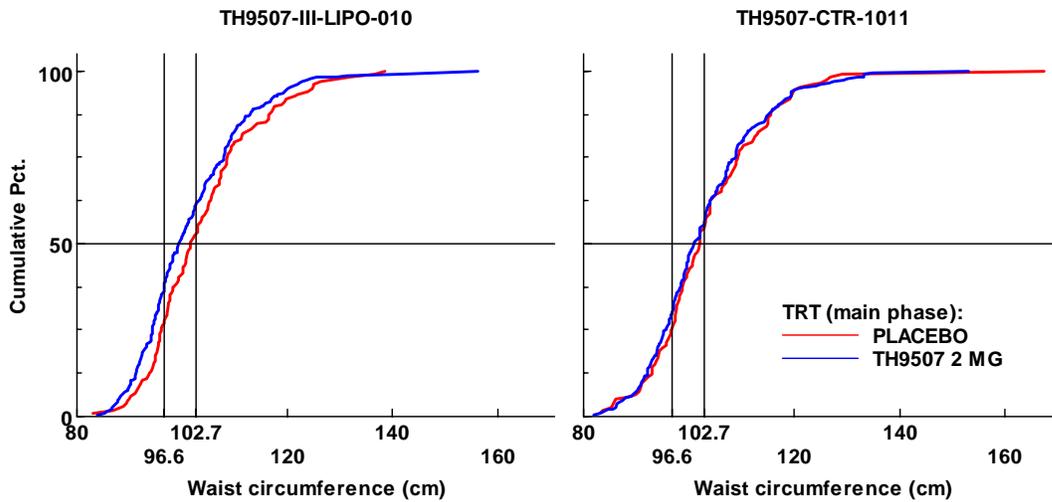


Figure 59 Cumulative distribution of waist circumference (cm) by treatment at Week 52 – Extension phase ITT

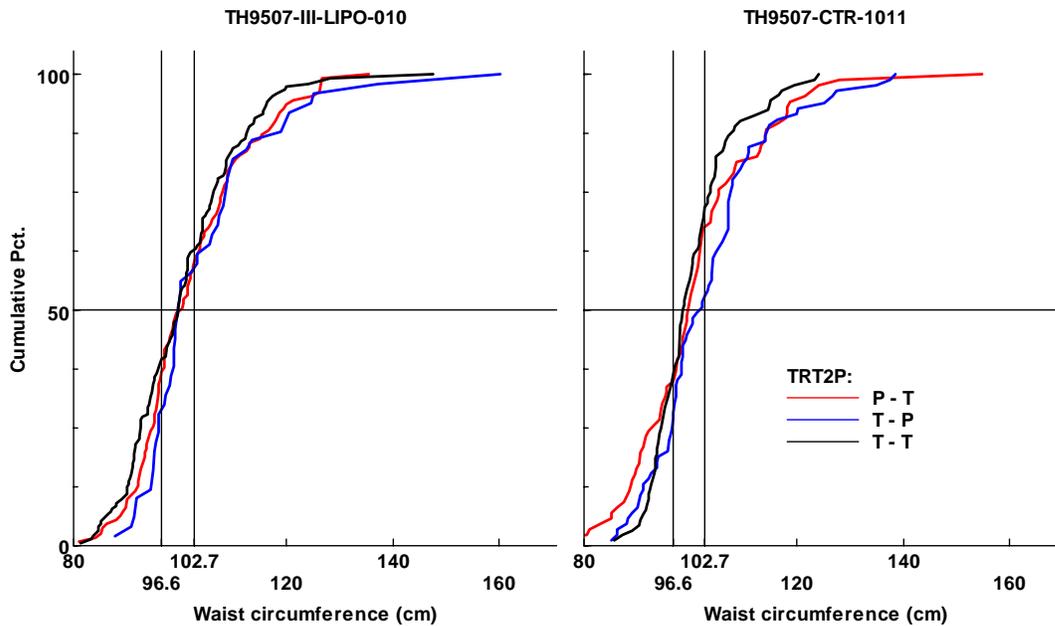


Figure 60 Cumulative distribution of waist circumference (cm) change from baseline by treatment at Week 26 – Main phase ITT

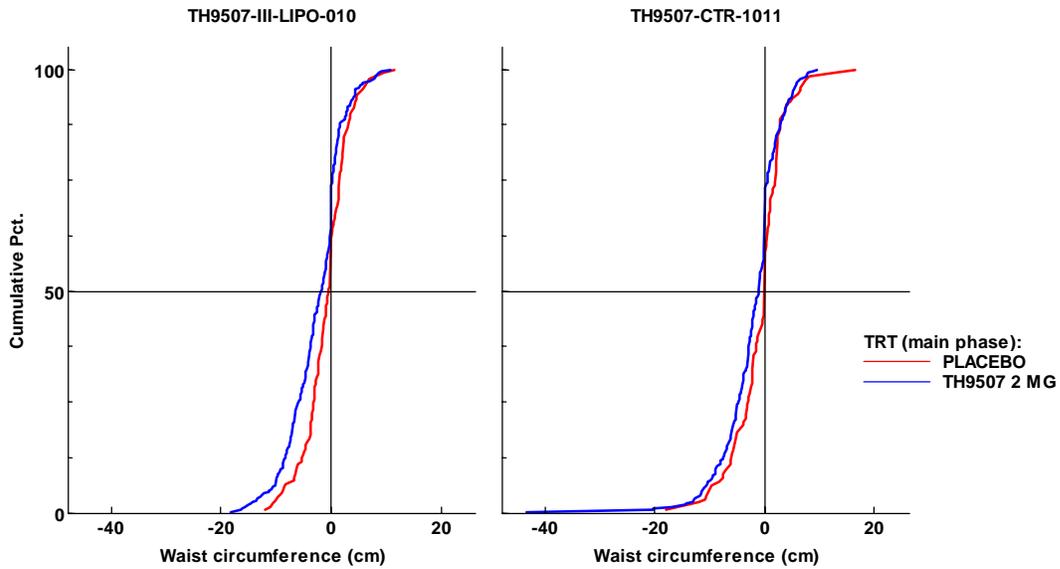


Figure 61 Cumulative distribution of waist circumference (cm) change from baseline by treatment at Week 52 – Extension phase ITT

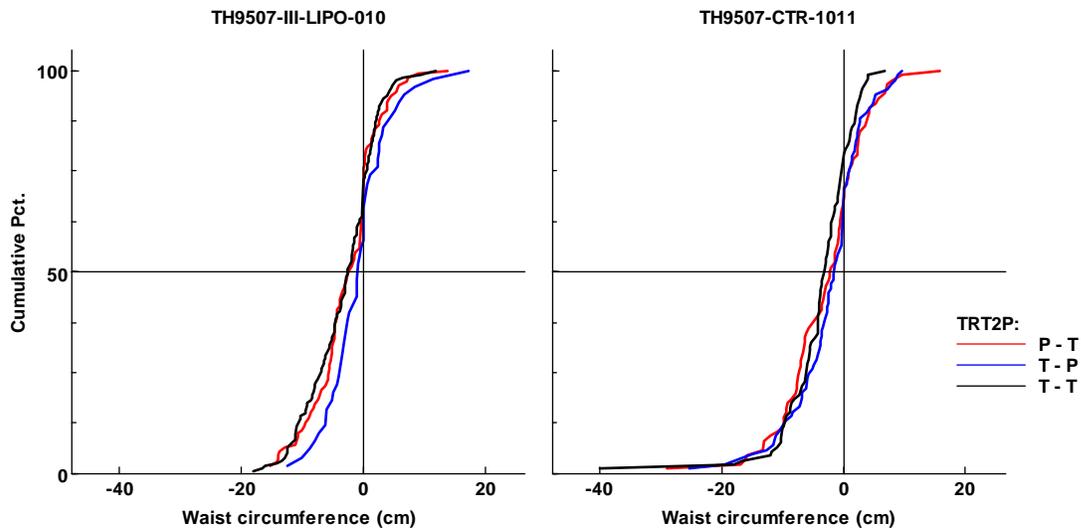


Figure 62 Box plot of waist circumference (cm) by treatment and time – Extension phase, ITT

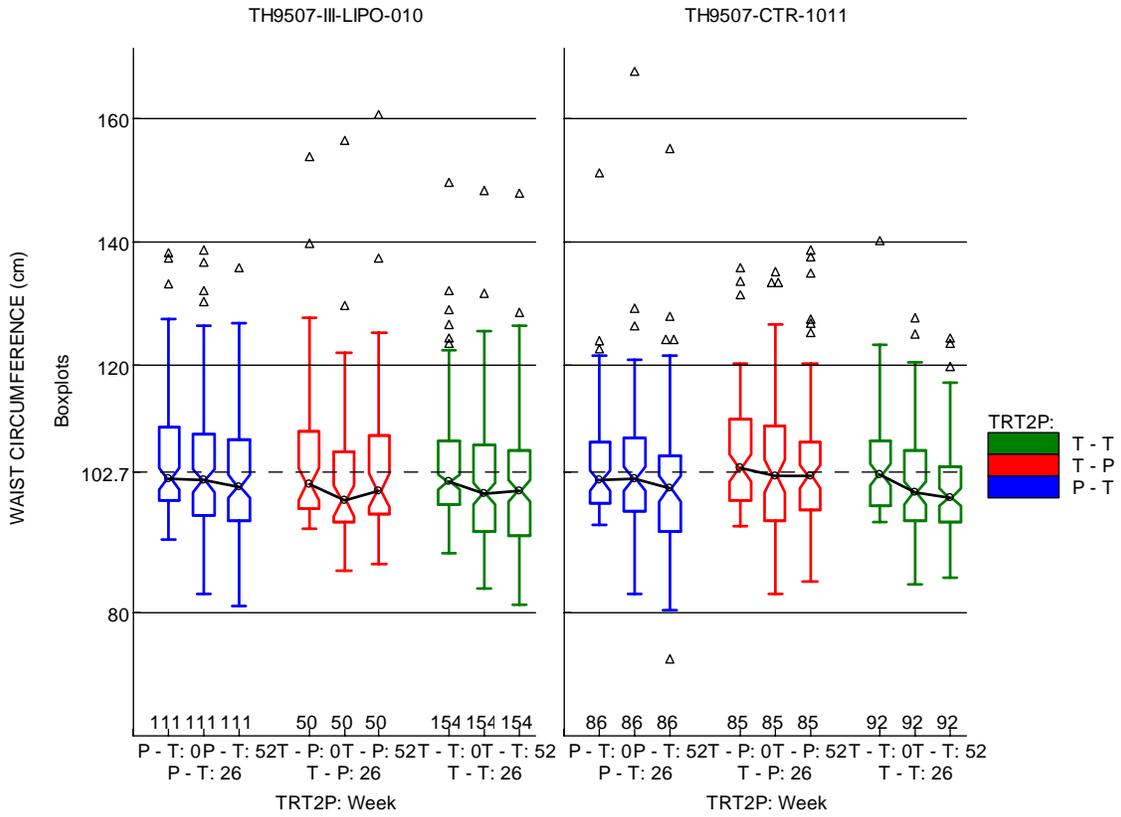


Figure 63 Median waist circumference (cm) over time – Main phase completers

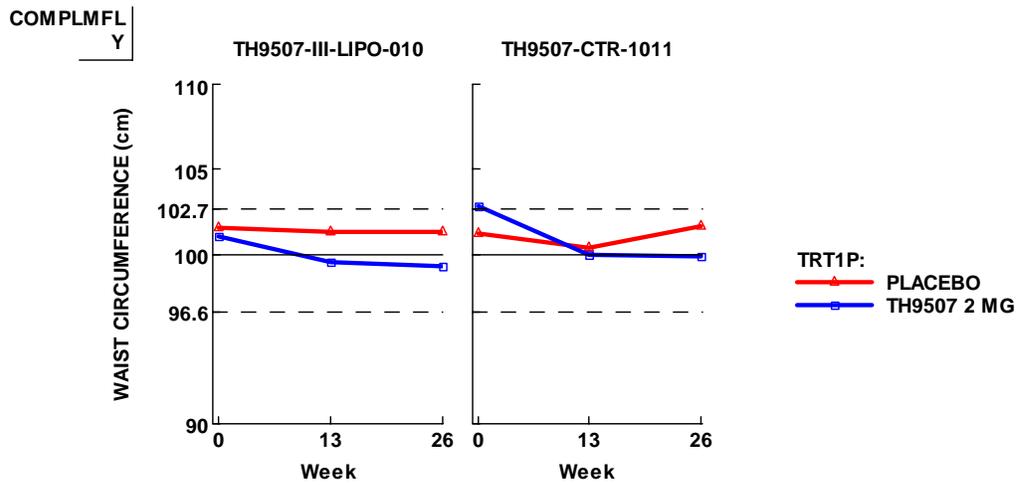


Figure 64 Median waist circumference (cm) over time – Extension phase completers

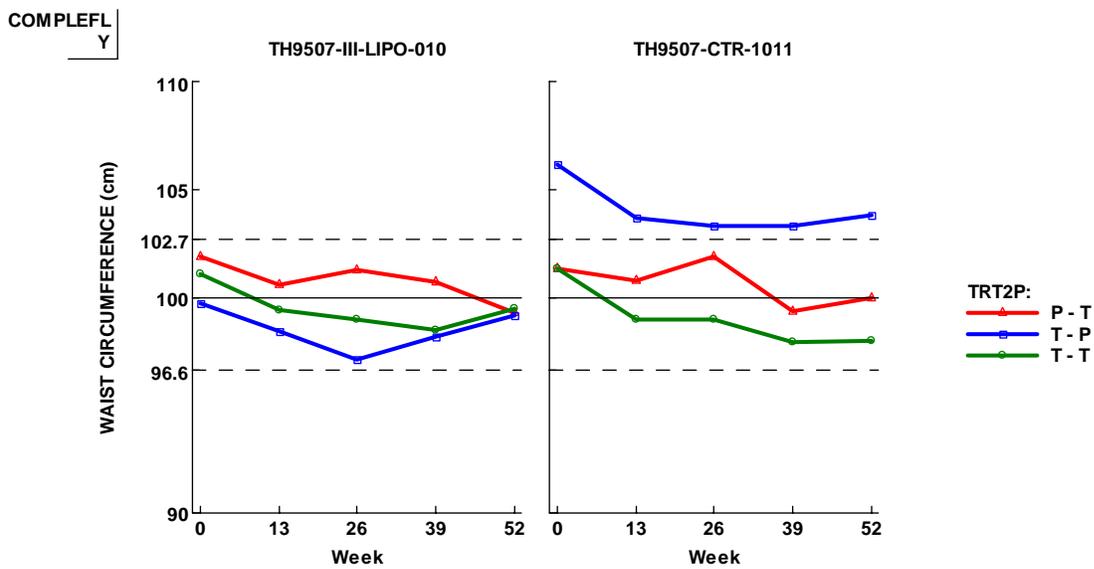
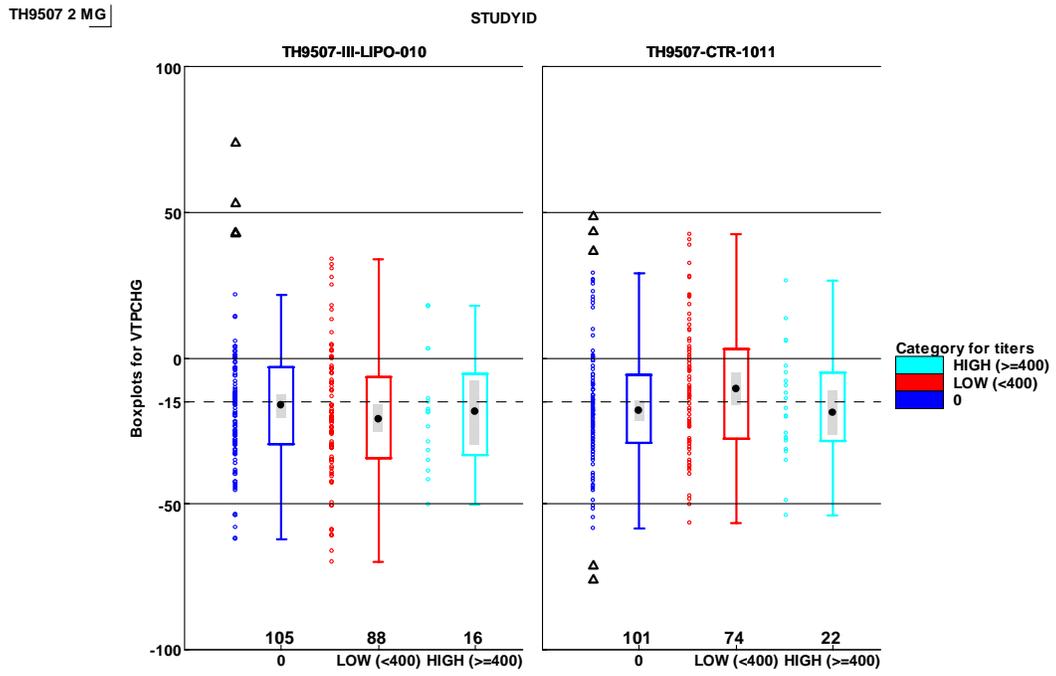


Figure 65 Boxplot of VAT % change by anti-TH9507 antibody titer category



Graphs

Figure 66 VAT % change from baseline to Week 26 stratified by Testosterone use at baseline

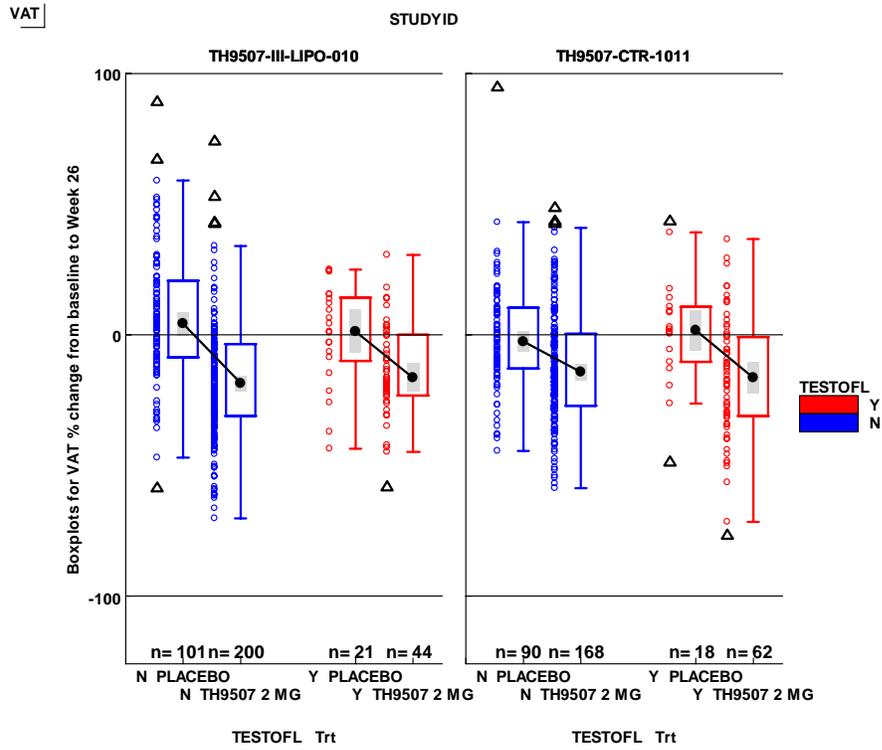


Figure 67 VAT % change from baseline to Week 26 stratified by IGT/Diabetes condition at baseline

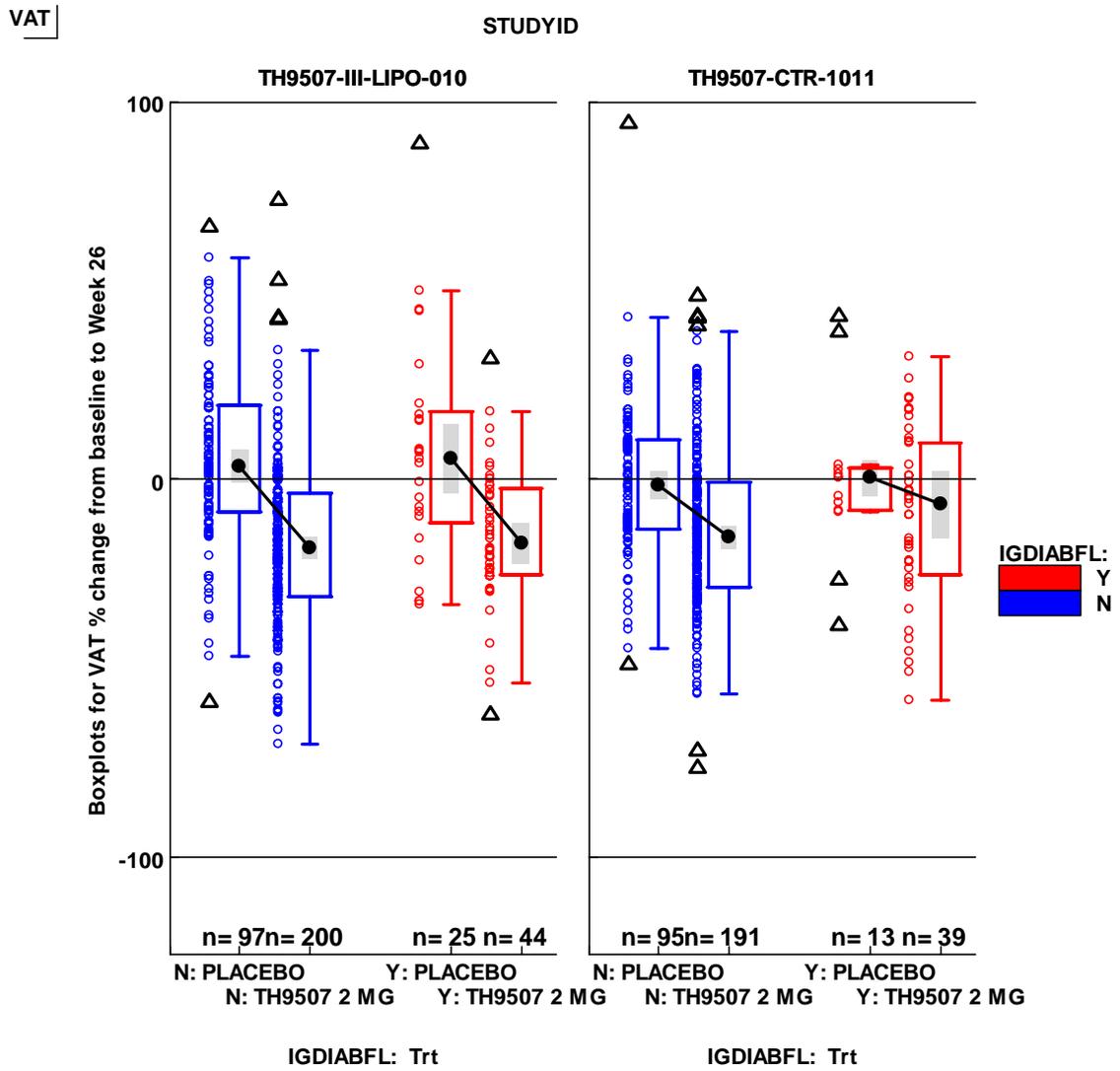


Figure 68 VAT % change over time by patient – Phase 2 study

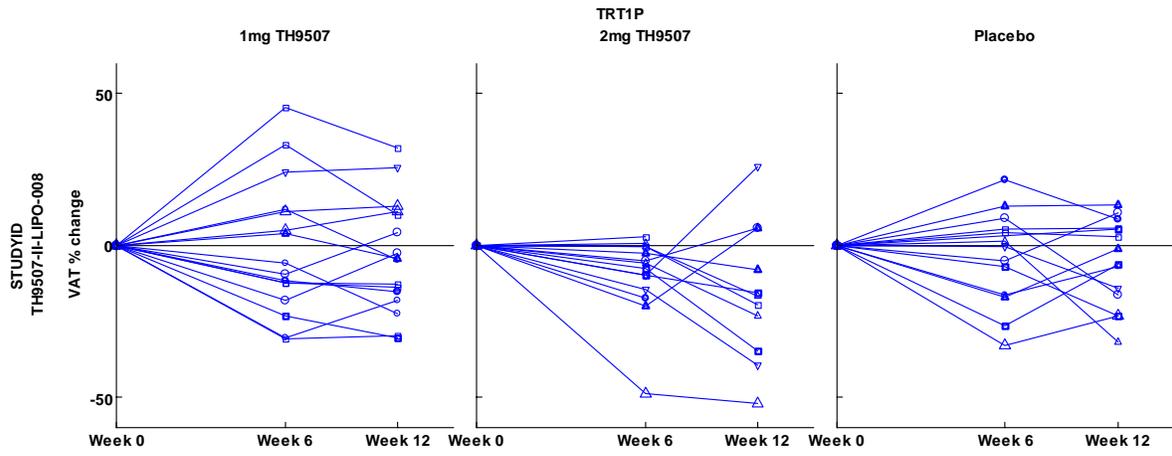


Figure 69 Mean treatment difference (95% C.I.) between 2 mg TH9507 and placebo for % change from baseline to ~Week 12 (sorted by estimate) – ITT, LOCF

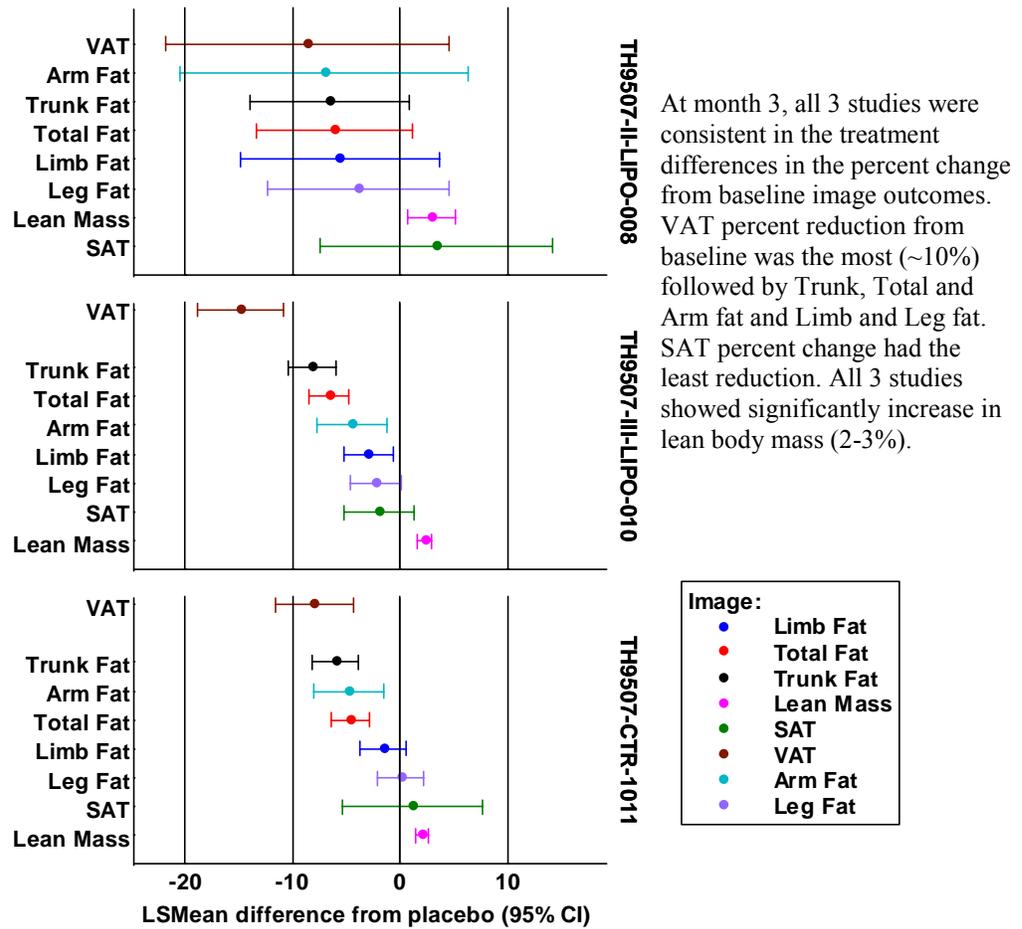


Figure 70 Boxplot of TG % change from baseline (week 0) by treatment sequence and week – ITText

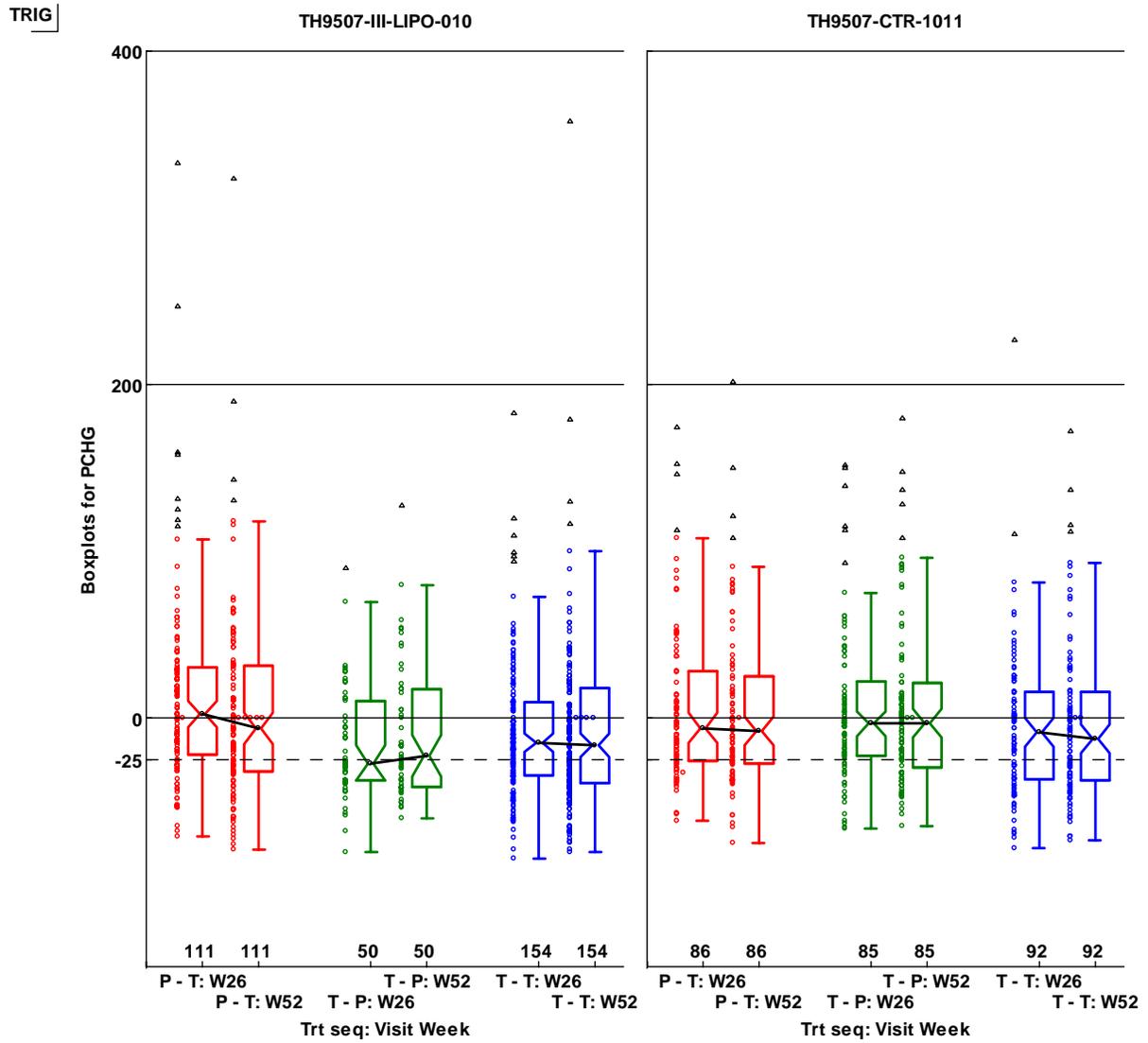


Figure 71 Boxplot of IGF-1 % change from baseline (week 0) by treatment sequence and week – ITTExt

IGF1

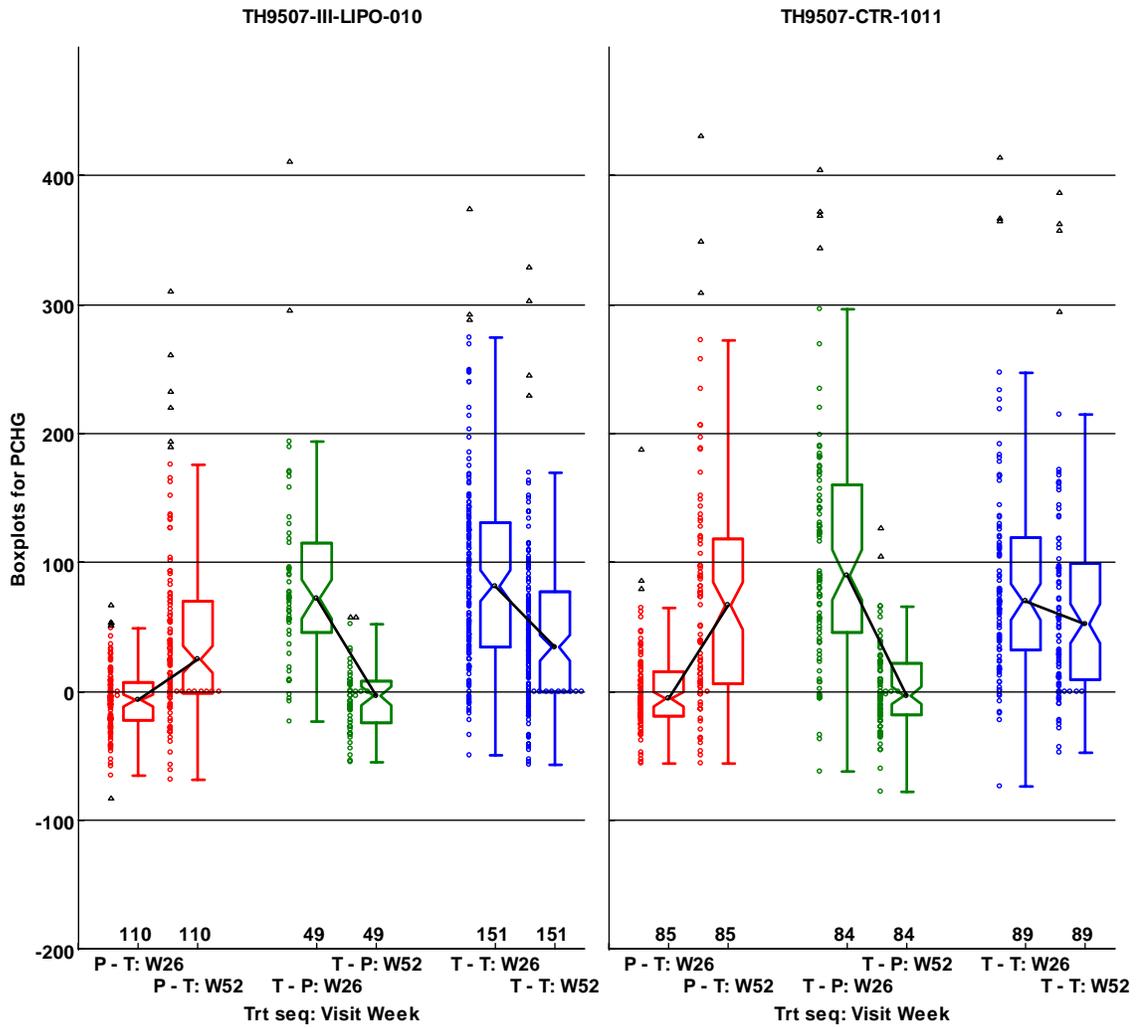
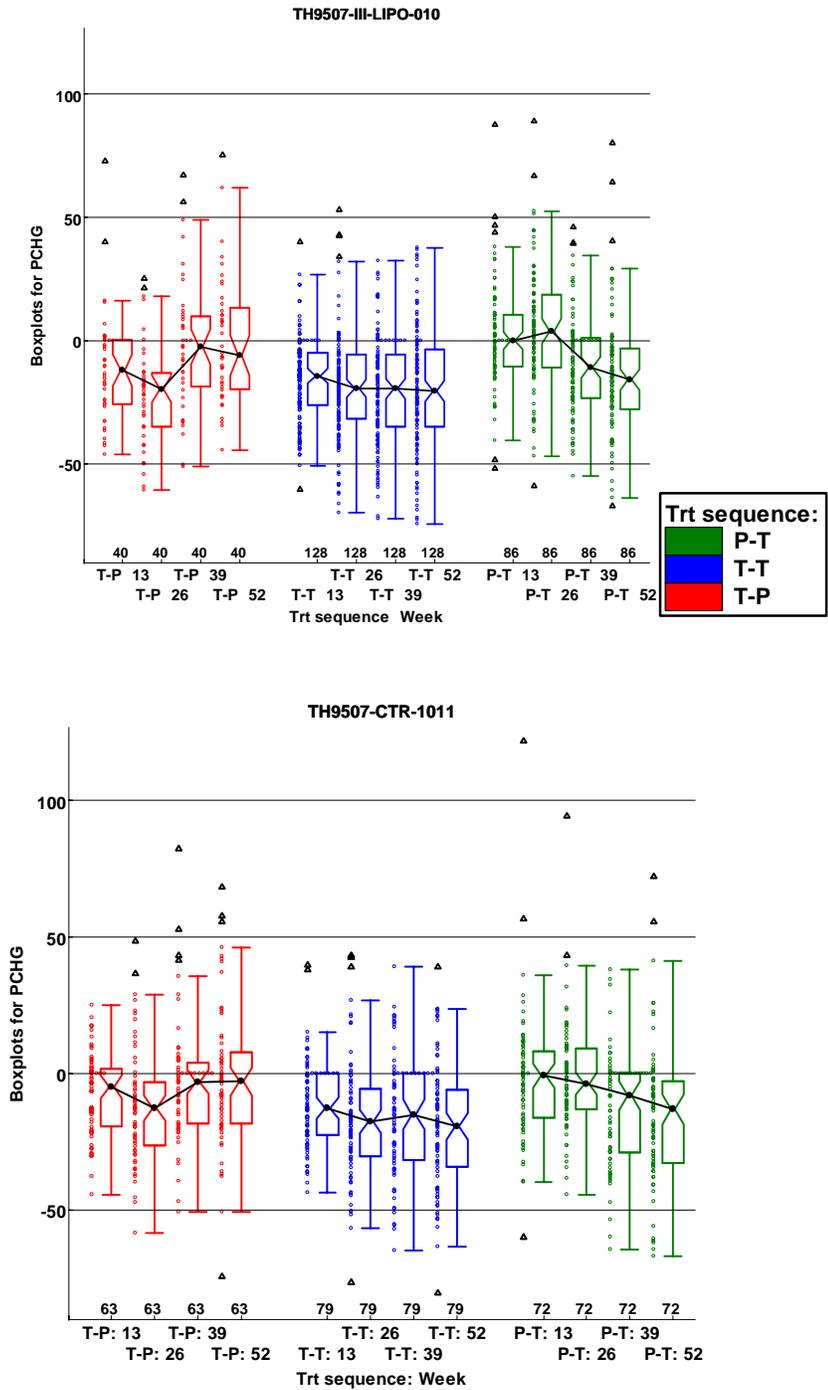


Figure 72 Box plot for median % change from baseline by visit week and treatment sequence – extension completers



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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