Protocol C3711005

A PHASE 2A, 2-PART, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY PLACEBO-CONTROLLED, PARALLEL-GROUP (SPONSOR OPEN) STUDY TO ASSESS PHARMACODYNAMICS AND SAFETY OF PF-06865571 (DGAT2I) COADMINISTERED WITH PF-05221304 (ACCI) IN ADULT PARTICIPANTS WITH PRESUMED NONALCOHOLIC STEATOHEPATITIS (NASH)

Statistical Analysis Plan
(SAP)

Version: **2**

Date: 16-Jun-2021

[redacted]

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 / 11-Aug-2020	Original protocol dated 27-Mar-2020 + associated PACL dated 01-Jul-2020	N/A	N/A
2 / 16-Jun-2021	Original protocol dated 27-Mar-2020 + associated PACL dated 01-Jul-2020 + associated PACL dated 22-Jan-2021	Per request from IRC as part of 1st safety review (May2021) to include derived non-HDL-C	• Sections 2.1, 3.3.4, 6.3.4, and 7.1.1 were modified to include ***derived*** non-HDL-C as endpoint along with summarization, and analysis. • Appendix 4 was modified to include non-HDL-C acronym definition.

2. INTRODUCTION

The current study is to evaluate the effect of coadministration of a range of doses of DGAT2i (ie, PF-06865571) *with 1 (and potentially 2) doses of ACCi* (ie, PF-05221304), *on the primary pharmacology (effect on liver steatosis) and evaluate the ability of a range of doses of DGAT2i to mitigate ACCi-induced elevations in serum triglycerides. This is the first clinical study specifically designed to identify the lowest dose of DGAT2i which, when coadministered with ACCi, results in reduction in hepatic steatosis while mitigating the identified adverse reaction (ie, elevation in serum triglycerides) observed with administration of ACCi alone.*

This study has a 2-part design with sequential conduct of Part 1 and Part 2 with each part conducted in distinct/separate cohorts of participants. While the overall study design, objectives/endpoints, eligibility criteria for both parts are envisioned to remain identical, data from Part 1 will be used to determine whether to conduct Part 2. Observed data from Part 1 will guide the selection of doses and dosing regimens (ie, QD vs BID) of DGAT2i + ACCi coadministration evaluated in optional Part 2.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	***Endpoints***	***Estimands***
Primary:		
*To evaluate **effect on liver fat**, determined by MRI-PDFF, of a range of DGAT2i doses coadministered with a fixed dose of ACCi compared to placebo in participants with presumed NASH.*	*Percent change from baseline in liver fat as assessed via MRI-PDFF, at Week 6.*	Estimand 1
Secondary:		
*To evaluate effect on fasting serum **triglyceride levels** of a range of DGAT2i doses coadministered with a fixed dose of ACCi compared to placebo in participants with presumed NASH.*	*Percent change from baseline in fasting serum triglyceride levels over time.*	Estimand 2
*To assess **safety and tolerability** with a range of DGAT2i doses coadministered with fixed dose of ACCi compared to placebo in participants with presumed NASH.*	*Proportion of participants with treatment-emergent adverse events (TEAEs) and clinically significant, abnormal clinical laboratory tests, vital signs, and 12-lead ECGs.*	Not applicable for safety and tolerability endpoints
Tertiary/Exploratory:		

Objectives	***Endpoints***	***Estimands***
*To evaluate effect on **liver fat** determined by quantitative ultrasound (FibroScan®) of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH.*	*Percent change from baseline in liver fat at Week 6, as assessed by CAP™ via FibroScan®.*	Estimand 1

*To evaluate effect on **liver function tests** of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH*	• *Percent change from baseline, over time, in:*
	  • *ALT*
	  • *AST*
	  • *Alkaline Phosphatase*
	  • *Total Bilirubin and*
	  • *GGT*
		Estimand 2

*To evaluate effect on **metabolic parameters** of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH*	• *Percent change from baseline, over time, in:*
	  • *Total cholesterol*
	  • *Direct LDL*
	  • *HDL-C*
	  • *Direct VLDL*
	  • *Apolipoprotein A1, B_{total}, B_{100}, B_{48}, C3, and E*
	  • Derived non-HDL-C
	• *Change from baseline, overtime, in:*
	  • *HbA1C*
	  • *FPG*
	  • *FPI*
	  • *HOMA-IR*
		Estimand 2
		
		Estimand 3

*To evaluate the effect on mechanism/disease-related **biomarkers** of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH*	• *Percent change over time in:*
	  • *CK 18-M30, -M65*
	  • *Pro-C3, and Pro-C6*
	  • *PCSK9*
	  • *Adiponectin*
	  • *hsCRP*
		Estimand 2

To summarize plasma PK of DGAT2i and ACCi, across the active doses of DGAT2i + ACCi evaluated in participants with presumed NASH	*Predose DGAT2i and ACCi plasma concentrations (ie, C_{trough})*	Not Applicable for this analysis
To enable the exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision	*Biobanking of blood-based specimens (including Prep D1, B1.5, and B2.5 collections to permit retrospective analysis of yet-to-be identified biomarkers)* • *These results may or may not be generated in the context of the present study*	Not Applicable for this analysis

2.1.1. Estimand 1

For a given endpoint, the estimand will be the estimated population based average treatment effect on ***natural log-transformed relative change*** from baseline for DGAT2i + ACCi relative to placebo ***at Week 6*** for all randomized/evaluable participants.

Intercurrent Events:

- Non evaluable baseline – All data collected post-randomization will be excluded.
- Withdrawal from study intervention after randomization – All data collected after a participant stops taking study intervention will be excluded.
- Prohibited medications – All assessments after a participant receives prohibited medications that would modulate the primary endpoint will be omitted from the analysis. The list of concomitant medications would be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.
- Inadequate compliance – All randomized/evaluable participants with compliance <80%, over the ***entire duration of dosing*** with double-blind, double-dummy study intervention, will ***not*** have their endpoint measurement used as recorded in the analysis.

Population level summary:

- The population level summary will be the mean difference in natural log-transformed relative change from baseline between DGAT2i + ACCi groups and placebo groups for the endpoint of interest at Week 6.

2.1.2. Estimand 2

For a given endpoint, the estimand will be the estimated population based average treatment effect on ***natural log-transformed relative change*** from baseline for DGAT2i + ACCi relative to placebo ***over time*** for all randomized/evaluable participants.

Intercurrent Events:

- Non evaluable baseline – All data collected post-randomization will be excluded.
- Withdrawal from study intervention after randomization – All data collected after a participant stops taking study intervention will be included.
- Prohibited medications – All assessments after a participant receives prohibited medications that would modulate the endpoint will be omitted from the analysis. The list of concomitant medications would be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.

- Inadequate compliance – All randomized/evaluable participants, *regardless of the level of compliance*, will have their endpoint measurement used as recorded in the analysis.

Population level summary:

- The population level summary will be the mean difference in natural log-transformed relative change from baseline between DGAT2i + ACCi groups and placebo groups for the endpoint of interest *over time*.

2.1.3. Estimand 3

For a given endpoint, the estimand will be the estimated population based average treatment effect on ***change from baseline*** for DGAT2i + ACCi relative to placebo ***over time*** for all randomized/evaluable participants.

Intercurrent Events:

- Same as Estimand 2.

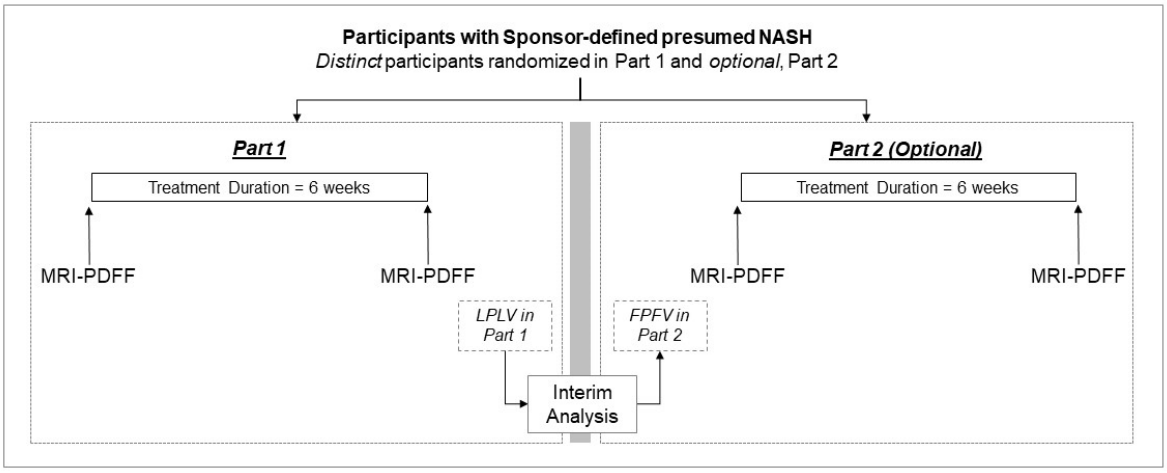
Population level summary:

- Same as Estimand 2 but with the mean difference in change from baseline between DGAT2i + ACCi groups and placebo groups for the endpoint of interest *over time*.

2.2. Study Design

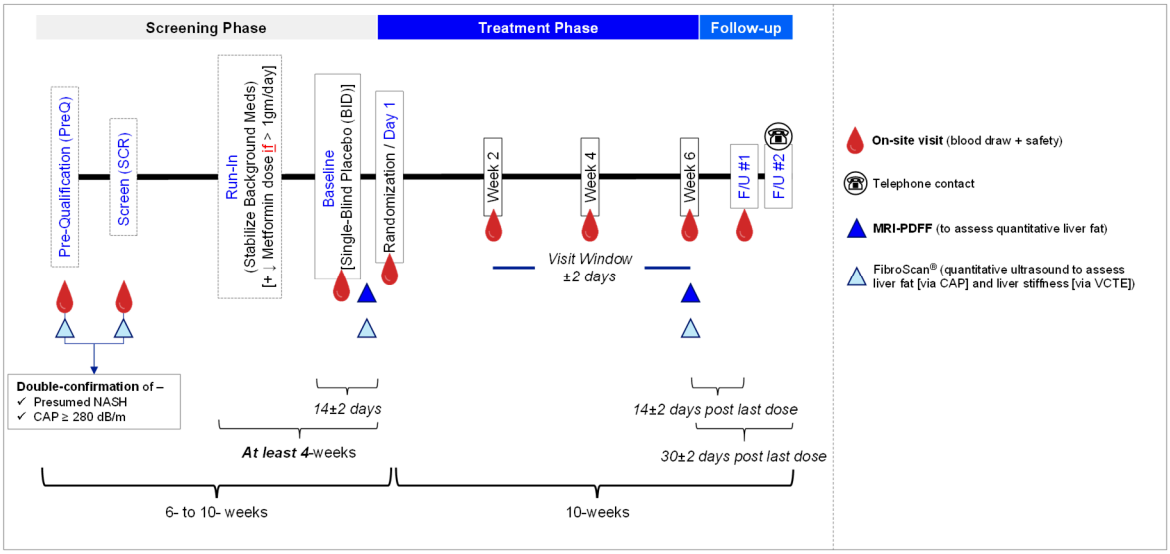
This is a multicenter, 2-part, sequentially conducted, randomized, double-blind, double-dummy, placebo-controlled, parallel-group evaluation of DGAT2i + ACCi as summarized in Figure 1.

Figure 1. Overall Study Design



Determination of eligibility will occur via a sequential, 2-step process starting with Prequalification visit (PreQ). Participants identified to be eligible at PreQ will transition to the main study, starting with Screening (SCR) visit. The double-confirmation (at PreQ and SCR) will permit progression of only a selected subset of participants confirmed to meet Sponsor-defined presumed NASH criteria (along with other eligibility criteria) to the Run-In/Visit 2. At the Run-In/Visit 2, stabilization of concomitant medicines may occur, as needed/appropriate (refer to Section Section 6.5 of the protocol*). All eligible participants must complete the Run-In/Visit 2, followed by Baseline/Visit 3. On Day 1/Visit 4, participants who meet the randomization criteria (*refer to Section 5.3 of the protocol*) will be assigned to receive 1 of* pre-defined *double-blind, double-dummy regimens* (refer to Section 4.1.1 [for Part 1] and Section 4.1.2 [for Part 2] of the protocol) *for a duration of up to 6 weeks, refer to* Figure 2 [updated to reflect the PACL that removed Acuson Sequoia® assessments].

Figure 2. Study Design for Part 1 and Optional Part 2



In Part 1, *approximately 90 participants (18 per group) with Sponsor-defined presumed NASH will be randomly assigned to the study intervention to ensure approximately 75 evaluable participants (15 per group) offer evaluable data.* In Part 2, *a maximum of 4 active doses (plus placebo) will be evaluated in Part 2; furthermore, the total number of participants will not exceed 90 (with no more than approximately 27 participants per each active dose).*

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Liver Fat Assessed Using MRI-PDFF at Week 6

Percent change from baseline in liver fat content measured at Week 6 using MRI-PDFF constitutes the primary endpoint. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.4.

Baseline is defined as described in Section 3.4.

Note: Relative Change from Baseline = Post-dose timepoint Value / Baseline Value

3.2. Secondary Endpoint(s)

3.2.1. Fasting Serum Triglycerides Over Time

Percent change from baseline in fasting serum triglycerides over time constitutes one of the secondary endpoints. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline over time as described in Section 5.2.5.

Baseline is defined as described in Section 3.4.

3.2.2. Safety and Tolerability

The proportion of participants with treatment-emergent adverse events (TEAEs) and clinically significant, abnormal clinical laboratory tests, vital signs, and 12-lead ECGs constitute the other secondary endpoint.

Baseline is defined as described in Section 3.4.

3.3. Other Endpoint(s)

3.3.1. Liver Fat determined by Quantitative Ultrasound Using FibroScan®

Liver fat, as obtained by controlled attenuation parameter (CAP®) measurement using FibroScan®, will be assessed at timepoints described in the Schedule of Activities of the protocol. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.4.

Baseline is defined as described in Section 3.4.

Note: Relative Change from Baseline = Post-dose timepoint Value / Baseline Value

3.3.2. Liver Stiffness Determined by Quantitative Ultrasound Using FibroScan®

Liver stiffness, as obtained by vibration-controlled transient elastography (VCTE™) measurement using FibroScan® will be assessed at timepoints described in the Schedule of Activities of the protocol.

Baseline is defined as described in Section 3.4.

3.3.3. Liver Function Tests Over Time

Liver function tests include ALT, AST, ALKP, GGT, and Total Bilirubin. For all these laboratory parameters, baseline is defined as described in Section 3.4.

3.3.3.1. Alanine Aminotransferase (ALT)

Alanine Aminotransferase (ALT) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

Percent change from baseline in ALT over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.3.2. Aspartate Aminotransferase (AST)

Aspartate Aminotransferase (AST) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

Percent change from baseline in AST over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.3.3. Alkaline Phosphatase (ALKP)

Alkaline Phosphatase (ALKP) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

Percent change from baseline in alkaline phosphatase over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of Relative change from baseline as described in Section 5.2.5.

3.3.3.4. Total Bilirubin (TBIL)

Total Bilirubin (TBIL) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

Percent change from baseline in total bilirubin over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.3.5. Gamma Glutamyl Transferase (GGT)

Gamma Glutamyl Transferase (GGT) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

Percent change from baseline in GGT over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.4. Metabolic Parameters Over Time

All of the following parameters, assessed following a fast of at least 8 hours (except HbA1C which is deemed evaluable even when assessed in a non-fasted state), will have baseline defined as described in Section 3.4.

3.3.4.1. Total Cholesterol

Total Cholesterol levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

Percent change from baseline in total cholesterol over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.4.2. Direct Low Density Lipoprotein (Direct LDL)

Direct Low Density Lipoprotein (Direct LDL) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

Percent change from baseline in direct LDL over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.4.3. High Density Lipoprotein Cholesterol (HDL-C)

High Density Lipoprotein cholesterol (HDL-C) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

Percent change from baseline in HDL-C over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.4.4. Direct Very Low Density Lipoprotein (Direct VLDL)

Direct Very Low Density Lipoprotein (Direct VLDL) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.4.5. Apolipoproteins

The apolipoproteins of interest are apolipoprotein A1 (ApoA1), apolipoprotein B Total ($ApoB_{Total}$), apolipoprotein B100 ($ApoB_{100}$), apolipoprotein B48 ($ApoB_{48}$), apolipoprotein C3 (ApoC3), and apolipoprotein E (ApoE) and their levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

For each apolipoprotein described above, percent change from baseline over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.4.6. Derived non-High-Density Lipoprotein Cholesterol (Non-HDL-C)

Non High-Density Lipoprotein cholesterol (Non-HDL-C) levels will be derived, as follows, at timepoints described in the Schedule of Activities of the protocol for ***fasting TG, direct LDL-C, HDL-C, total cholesterol -***

Derived non-HDL-C = total cholesterol minus HDL-C

where all parameters are reported in mg/dL.

Percent change from baseline over time will be the endpoint of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.4.7. Glycated Hemoglobin A1C (HbA1C)

Glycated Hemoglobin A1C (HbA1C) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

The change from baseline in HbA1C over time will be the endpoint of interest and will be analyzed as described in Section 5.2.5.

3.3.4.8. Fasting Plasma Glucose (FPG)

Fasting Plasma Glucose (FPG) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

The change from baseline in FPG over time will be the endpoint of interest. and will be analyzed as described in Section 5.2.5.

3.3.4.9. Fasting Plasma Insulin (FPI)

Fasting Plasma Insulin (FPI) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

The change from baseline in FPI over time will be the endpoint of interest and will be analyzed as described in Section 5.2.5.

3.3.4.10. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

The change from baseline in HOMA-IR over time will be the endpoint of interest. The change from baseline in HOMA-IR over time will be the endpoint of interest and will be analyzed as described in Section 5.2.5.

As described in the Schedule of Activities of the protocol, HOMA-IR values will be derived at each timepoint as follows:

$$\text{HOMA-IR} = (\text{Glucose}_{\text{Fasting Concentration}} \times \text{Insulin}_{\text{Fasting Concentration}}) / 405$$

where fasting plasma glucose concentrations is reported in mg/dL and fasting plasma insulin is reported in mU/L. As such, HOMA-IR is unit-less.

3.3.5. Biomarkers

Baseline for all the following endpoints is defined as described in Section 3.4 .

3.3.5.1. Markers of Apoptotic Activity (CK18-M30 and CK18-M65)

Markers of apoptotic activity will be assessed at timepoints described in the Schedule of Activities of the protocol. These include the caspase-cleaved cytokeratin-18-M30 (ie CK18-M30) produced during apoptosis or the caspase-cleaved and intact cytokeratin-18-M65 (ie CK18-M65) usually released from cells undergoing necrosis.

The percent change from baseline in CK18-M30 and CK18-M65 over time will be the endpoints of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.5.2. Markers of fibrinogenesis (ProC3 and ProC6)

Markers of collagen/fibrin formation will be assessed at timepoints described in the Schedule of Activities of the protocol. These include N-terminal pro-peptide of type III procollagen (ie ProC3) or C-terminal fragment of the α3 chain of procollagen type VI (ie ProC6).

The percent change from baseline in ProC3 and ProC6 over time will be the endpoints of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.5.3. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

The percent change from baseline in PCSK9 over time will be the endpoints of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.5.4. Adiponectin

Adiponectin levels will be assessed at timepoints described in the Schedule of Activities of the protocol.

The percent change from baseline in adiponectin over time will be the endpoints of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.3.5.5. High Sensitive C-Reactive Protein (hsCRP)

High Sensitive C-Reactive Protein (hsCRP) will be assessed at timepoints described in the Schedule of Activities of the protocol.

The percent change from baseline in hsCRP over time will be the endpoints of interest. The analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

3.4. Baseline Variables

Baseline *for all endpoints* described in section 2, section 3, section 5 and section 6 *is defined as the evaluable result closest* ***prior*** *to dosing on Day 1* 0H (ie pre-dose).

In Particular, for each participant, for each of the following parameters, baseline will be defined as:

- Liver fat content, via MRI-PDFF, defined as the value of WLPDFF (see Appendix 2.2.1) obtained between Visit 3 and Visit 4 (ie, labeled as baseline)
- Liver fat assessment via CAP® using FibroScan® obtained between Visit 3 and Visit 4 (ie, labeled as baseline)
- Liver stiffness assessment via VCTE® using FibroScan® obtained between Visit 3 and Visit 4 (ie, labeled as baseline)
- Result closest prior to dosing on Day 1 [Visit 4] for the remaining pharmacodynamic endpoints **and all** safety-related continuous endpoints
    - As such would be results as reported on Day 1 [Visit 4], and **if** these are not reported would be the results reported on Day -14 [Visit 3]
    - If results on Day 1 [Visit 4] and on Day -14 [Visit 3] are missing the baseline will be considered as missing.
- For Adverse events, refer to definition of treatment-emergent outlined in Section 3.5.1.

Change from baseline (CBL), relative change from baseline (RCBL) and percent change from baseline (PBL) will be calculated as follows:

- CBL = Observed Value – Baseline Value
- RCBL = Observed Value / Baseline Value
- PBL = 100 × (Observed Value – Baseline Value) / Baseline Value

3.5. Safety Endpoints

3.5.1. Adverse Events

Any adverse event included in the adverse CRF page will be considered as treatment emergent.

In fact, an adverse event will be considered ***treatment emergent*** (ie, TEAEs) relative to a given treatment if:

- event occurs for the first time during the effective duration of treatment and was not seen prior to 1st dose of double-blinded study medication on Day 1 [Visit 4], for example, during the internal between when participants offered informed consent for pre-qualification up to the day prior to 1st dose

- ***NOTE:*** Adverse events deemed non-treatment emergent observed during the interval between when participants offering informed consent for pre-qualification up to 1st dose on Day 1 (Visit 4) but resolved before 1st dose on Day 1).

The effective duration of treatment is determined by the lag time defined as the Pfizer Standard of 999 days post last dose of double-blinded study medication. Any **treatment-emergent** event occurring within the lag time, whether it occurs during a break in treatment or at the end of treatment, will be attributed to the assigned randomized regimen.

A 3-tier approach will be used to summarize TEAEs. Under this approach, TEAEs will be classified into 1 of 3 tiers. Different analyses will be performed for different tiers (See Section 6.6.1).

Tier-1 events: These are pre-specified events of clinical importance (TMEs, DMEs, and CPTs) and are maintained in a program level list in CATEList.

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA preferred term (PT) is defined as a tier-2 event if there are at least 4 participants with at least one occurrence in any treatment group, per Pfizer Standard to distinguish Tier-2 events from Tier-3 events.

Tier-3 events: These are events that do not meet criteria for either tier-1 nor tier-2 events

3.5.2. Laboratory Data

For the specific laboratory parameters listed in Table 2 below, the following endpoints will be evaluated using CaPS:

- Absolute value and change from baseline at week 2, week 4, week 6, and 1st Follow-up visit.
- Number of occurrences of these abnormalities defined as "Flag Level" or "Alert Level"
- Number of participants with these abnormalities defined as "Flag Level" or "Alert Level"

Table 2. Clinical Laboratory Parameters of Interest in Study C3711005

Parameter	Flag Level	Alert Level	Conventional Units
Fasting Serum Triglycerides	≥ 400	≥ 600	mg/dL
	--	≥ 800	mg/dL
Platelet Count	< 100,000	< 75,000	/mm^3
Fasting Plasma Glucose	< 70	≤ 49	mg/dL

Table 2. Clinical Laboratory Parameters of Interest in Study C3711005			
Parameter	**Flag Level**	**Alert Level**	**Conventional Units**
	≥ 140	> 270	mg/dL
Alanine aminotransferase	≥ 2x ULN	--	U/L
	> 3x ULN	--	U/L
	> 5x ULN	>8x ULN	U/L
Aspartate aminotransferase	≥ 2x ULN	--	U/L
	> 3x ULN	--	U/L
	> 5x ULN	>8x ULN	U/L
Alkaline Phosphatase	≥ 2x ULN	--	U/L
	> 3x ULN	--	U/L
	>5x ULN	--	U/L
Gamma Glutamyl Transferase	> ULN	--	U/L
Total Bilirubin	> 1.5x ULN	>3x ULN	mg/dL
Direct (Conjugated) Bilirubin	> ULN	--	mg/dL

*All flag level changes are cumulative from baseline (defined as result closest prior to dosing at Visit 4 (Day 1); reflect either threshold for entry criteria into study or clinically significant thresholds

^All alert changes are cumulative from baseline (defined as result closest prior to dosing at Visit 4 (Day 1); values when noted during the study, by central laboratory necessitates rapid notification (via fax/e-mail) to site and Study Clinician, Pfizer Medical Monitor, and Global Clinical Lead, *in parallel*

ULN – upper limit of normal as determined by the central laboratory

Across all the laboratory-related analytes (for safety and pharmacodynamics/biomarker), inclusion of results when assessed at scheduled nominal visits meet the following criteria:-

1. Collection must be prior to AM dose of double-blinded study medication
2. Collection permitted to be *nonfasted for the following analytes and will be permitted to be grouped with fasted results* given that nonfasted state is not known to impact results

Chemistry panel	**Hematology**	**Other**	**Urinalysis**
Direct bilirubin	Hemoglobin	aPTT	pH
Indirect bilirubin	Hematocrit	PT	Protein
Urea Nitrogen	RBC	INR	Glucose
Creatinine	MCV	Urine-drug-testing	Ketones
Uric acid	MCH	Serology testing	Bilirubin
Calcium	MCHC	[hepatitis B,	Urobilinogen
Total protein	WBC	hepatitis C, HIV]	Blood
Albumin	Neutrophils (abs)	Alpha-1-antitrypsin	Nitrite
Creatine kinase	Lymphocytes (abs)	Ceruloplasmin	Leukocyte esterase
Sodium	Monocytes (abs)	β-hCG	Microscopic UA
Potassium	Eosinophils (abs)	FSH	
Bicarbonate	Basophils (abs)		
Chloride	Platelets		
	Reticulocyte count%		
	Reticulocyte count		

3. ***But,*** the *following analytes will only be included in summary outputs if collections are confirmed to be following an overnight fast of at least 8 hours* as it is well known that fasting status impacts numerical results (***or*** there is insufficient data regarding effect of meals on results)

Biomarkers	Lipid-related	Other Blood-related
% CDT Plasma Glucose Plasma Insulin Total Bile Acids Plasma PCSK9 CK18-M30 CK18-M65 ProC3 ProC6	Total cholesterol HDL-C Direct LDL-C Triglycerides VLDL Apolipoprotein A1 Apolipoprotein B_{Total} Apolipoprotein B_{48} Apolipoprotein B_{100} Apolipoprotein C3 Apolipoprotein E	Prep B1.5 (plasma) and B2.5 (serum) related mechanistic/disease-related biomarkers

Note: Prep samples (ie Prep B1.5 (plasma) and B2.5 (serum)) if analyzed will consider the fasted collection and will be reported in a supplemental CSR.

3.5.3. Standard Safety Other than AEs

3.5.3.1. Vital Signs of Special Clinical Concerns

Individual participants' vital signs outlined in Table 3 of special clinical concern, which align with the Pfizer standard criteria, will be summarized by treatment, as part of standard safety-related outputs.

Table 3 Vital Signs to be Monitored

Parameter	*Flag Level**	*Conventional Units*
Systolic Blood Pressure (seated)	*< 90*	*mm Hg*
	≥ 30 change from baseline	*mm Hg*
Diastolic Blood Pressure (seated)	*< 50*	*mm Hg*
	≥ 20 change from baseline	*mm Hg*
Pulse rate (seated)	*<40*	*Bpm*
	> 120	*Bpm*

**All flag level changes are cumulative from baseline (defined as result closest prior to dosing at Visit 4 (Day 1)*
bpm – beats per minute

In addition Pfizer standard criteria for reporting of cardiac conduction intervals will be summarized by treatment.

3.5.3.2. ECG of Special Clinical Concerns

Individual participants' ECG outlined in Table 4 of special clinical concern, which align with the Pfizer standard criteria, will be summarized by treatment, as part of standard safety-related outputs.

Table 4 ECG QT and QTc Interval Criteria to be Monitored

Degree of Prolongation	QTcF Interval Prolongation (msec)			Uncorrected QT Interval (msec)
	Mild (msec)	Moderate (msec)	Severe (msec)	
Absolute value	>450-480	>480-500	>500	>500

Table 4 ECG QT and QTc Interval Criteria to be Monitored

Degree of Prolongation	QTcF Interval Prolongation (msec)			Uncorrected QT Interval (msec)
	Mild (msec)	Moderate (msec)	Severe (msec)	
Increase from baseline		30-60	>60	

Note: For purposes of reporting study-level results, QTcF interval will be derived using Fridericia's heart rate correction formula (see below) applied to databased QT interval, and RR interval.

QTc not otherwise specified as captured in CRF will be only listed. Summary outputs will summarize only programmatically derived QTcF.

QTcF (ie, Fridericia's heart rate correction formula) is:

QTcF (msec) = QT(msec) / (RR, in msec)^(1/3)

3.5.3.3. Background Medications of Special Interest

Across the many background medications being taken by the population enrolled, the number/proportion of participants using (***and*** proportion needing changes in) selected medications of special interest will be summarized. These include

- Agents for glycemic control (see list in Protocol section 6.5.1)
- Agents for lipid control (see list in Protocol section 6.5.2)
- Agents for blood pressure control (see list in Protocol section 6.5.3)

The number of participants using glycemic control agents, lipid-modifying agents medication, and agents for BP control will be summarized by treatment as well.

For each category of medication (ie Glycemic, Lipid, and BP), the number of participants receiving 0, 1, 2, or 3 medications will also be tabulated by treatment.

Given the relatively short duration of the double-blind, double-dummy dosing in this study, if changes in background medications related to glycemic control, lipid control, or blood pressure are reported/observed, they will be summarized as follows, at any time after Day 1 and up to the last dose of study drug (ie, Week 6 or premature discontinuation) whichever is first –

- Dose increase and decrease in concomitant medication for glycemic control (see list in Protocol section 6.5.1),
- Dose increase and decrease in concomitant lipid-modifying medications (see list in Protocol section 6.5.2),
- Dose increase and decrease in concomitant blood pressure management medications (see list in Protocol section 6.5.3).

3.5.3.4. Platelet Count

Percent and absolute change from baseline in platelet count over time will be the endpoint of interest. Both endpoints will be analyzed as described in Section 5.2.5.

Baseline is defined as described in Section 3.4 .

3.5.3.5. Estimated Glomerular Filtration Rate

The estimated glomerular filtration rate (eGFR) at each time point defined in the Schedule of Activities will be calculated using cystatin-C as follows:

If cystatin-C > 0.8 mg/L:

$$\text{eGFR} = 133 * [(\text{cystatin} - \text{C})/0.8]^{-1.328} * 0.996^{\text{Age}} * 0.932(\text{if Female})$$

If cystatin-C ≤ 0.8 mg/L:

$$\text{eGFR} = 133 * [(\text{cystatin} - \text{C})/0.8]^{-0.499} * 0.996^{\text{Age}} * 0.932(\text{if Female})$$

Where eGFR unit is mL/min/1.73 m^2,
Age is subject's age at screening in years,
(cystatin-C) is cystatin-C concentration in mg/dL.

The change from baseline in eGFR over time will be the endpoint of interest and will be analyzed as described in Section 5.2.5.

Baseline is defined as described in Section 3.4.

3.5.3.6. Alcohol Intake

For the entire study population, alcohol intake will be assessed 1 of 3 ways; with only 2 of these being databased and reported –

1. %CDT – reported using descriptive summary statistics over time
2. Total score on interview-based AUDIT questionnaire – reported using description summary statistics over time
3. Participants' self-reported intake of alcohol-containing drinks *[not databased]*

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

All analyses will be performed on an "as-treated" basis and will not include data from participants who are randomized but not treated.

If a participant takes a treatment that is not consistent with the treatment they are randomized to, for example, error in dispensation of blister cards relative to assigned made by IRT, then they will be reported under the treatment that they actually receive (so called actual treatment) for all safety, PK and PD analyses, where applicable.

A full list of protocol deviations will be compiled and reviewed to identify major deviations, which may potentially impact inclusion in the applicable estimand, prior to database lock and release.

For purposes of analysis, the following analysis sets are defined:

Participants Analysis Set	***Description***
Enrolled	*All participants who sign the preQ ICD.*
Randomly assigned to investigational product	*All participants randomly assigned to IP, on Day 1/Visit 4, regardless of whether or not study intervention was administered.*
Evaluable	*All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the randomized intervention.*
Safety	*All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the treatment arm they actually received.*
Defined Population for Analysis	***Description***
PK Concentration Set	*All participants randomly assigned to study intervention and who take at least 1 dose of DGAT2i + ACCi and in whom at least 1 concentration value is reported.*

Note: *Analysis set for Part 2 is envisioned to be identical to Part 1.*

5. GENERAL METHODOLOGY AND CONVENTIONS

Data from Parts 1 and 2 will be pooled for purposes of summarizing/analyzing end-of-study results and will be reported from placebo followed by ascending order of the DGAT2i to ACCi total daily dose (TDD) ratio (mg:mg).

In case the same co-administration ratio for BID and QD dosing regimen is evaluated, data will be reported 1st for BID and then QD while still in the ascending order for DGAT2i to ACCi TDD ratio (mg:mg).

5.1. Hypotheses and Decision Rules

Not applicable

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Not applicable

5.2.2. Analyses for Continuous Endpoints

Continuous endpoints and relevant safety endpoints will be presented using summary statistics: number of randomized participants, number of participants contributing to summary, arithmetic mean, standard deviation, median, minimum and maximum values.

5.2.3. Analyses for Categorical Endpoints

Categorical endpoints and relevant safety endpoints will be presented using summary statistics: number of randomized participants, number of observations, counts and percentages.

5.2.4. Analysis of Covariance (ANCOVA)

The effect of DGAT2i + ACCi on primary, secondary, and tertiary endpoints at Week 6 will be analyzed using ANCOVA approach.

Analysis of change from baseline:

The ANCOVA model will include the change from baseline of the relevant endpoint as specified in Section 6 as the dependent variable and will include treatment as a fixed effect and baseline as a covariate.

Missing values will not be imputed.

The Least Squares Means (LSMeans) together with 80% confidence intervals and standard errors will be obtained for each treatment. Differences in LSMeans between each treatment and placebo, together with 80% confidence intervals and standard errors, will also be obtained.

Standard SAS output will be provided to support the main statistical summary table for the models.

Example SAS code is provided in Appendix 3.

Analysis of percent change from baseline:

The ANCOVA model will include the natural logarithmic transformed of relative change from baseline of the relevant endpoint as specified in Section 6 as the dependent variable and will include treatment as a fixed effect and baseline as a covariate.

Missing values will not be imputed.

The adjusted geometric Least Squares Means (LSMeans) together with 80% confidence intervals and standard errors will be obtained for each treatment. Differences in adjusted geometric LSMeans between each treatment and placebo, together with 80% confidence intervals and standard errors, will also be obtained. All LSMeans and LSMeans differences (including CI's) will be back transformed to provide adjusted geometric LSMeans and ratios of adjusted geometric LSMeans. Then, percent change from baseline will be calculated as follows:

$$\text{Percent change} = 100^* (\text{RCBL} - 1)$$

where RCBL is either the adjusted geometric LSMeans estimate or the ratio of adjusted geometric means coming from the statistical model. The corresponding 80% CIs will be calculated as well.

Standard SAS output will be provided to support the main statistical summary table for the models.

Example SAS code is provided in Appendix 3.

5.2.5. Longitudinal Analysis

The effect ***over time*** of DGAT2i + ACCi on secondary, and tertiary endpoints (see list in Section 3) will be analyzed using a Mixed-Model Repeated Measures (MMRM) approach with treatment, week and treatment by-week interaction as fixed effects, participant as random effect. An unstructured covariance matrix will be used to estimate the variances and covariance within participants across time points. If convergence is not obtained or model fit is not adequate, other covariance structures will be investigated as necessary. The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. Missing values will not be imputed as part of the MMRM model assumptions.

Baseline (in raw scale or log scale depending on the endpoint) will be included as covariate in the model.

Analysis to report percent change from baseline:
MMRM models will include the natural log transformed of relative change from baseline (RCBL) of the relevant endpoints as specified in Section 6.

The adjusted geometric Least Squares Means (LSMeans) together with 80% confidence intervals and standard errors will be obtained for each treatment and week. Differences (and corresponding confidence intervals) between LSMeans estimates will be obtained comparing treatments for each week. All LSMeans and LSMeans differences (including CI's) will be back transformed to provide adjusted geometric LSMeans and ratios of adjusted geometric LSMeans. Then, percent change from baseline will be calculated as follows:

Percent change = 100* (RCBL - 1)

where RCBL is either the adjusted geometric LSMeans estimate or the ratio of adjusted geometric means coming from the statistical model. The corresponding 80% CIs will be calculated as well.

Standard SAS output will be provided to support the main statistical summary table for the models.

Example SAS code is provided in Appendix 3.

Analysis of change from baseline:
MMRM models will include change from baseline (CFB) of the relevant endpoints as specified in Section 6.

The Least Squares Means (LSMeans) together with 80% confidence intervals and standard errors will be obtained for each treatment and week. Differences (and corresponding

confidence intervals) between LSMeans estimates will be obtained comparing treatments for each week.

Standard SAS output will be provided to support the main statistical summary table for the models.

Example SAS code is provided in Appendix 3.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

5.3.1. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

5.3.2. Pharmacokinetic Parameters

- Missing pharmacokinetic data will be treated as such and no imputed values will be derived when presenting descriptive statistics at scheduled assessments.
- In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

5.3.3. Pharmacodynamic Parameters

- Missing data for ***all*** the pharmacodynamic parameters will be treated as such and no imputed values will be derived when presenting descriptive statistics at scheduled assessments.
- Concentrations below Lower Limit of Quantification (LLQ) will be set to half-LLQ (ie LLQ/2) for summary outputs; in listings BLQ values will be reported as "<LLQ".
- Derived data by calculation (eg indirect bilirubin) will not follow the rule described above and will be reported as <LLQ (in listings) with a derived value of (<negative value> minus 0.0001 = positive value) when generating summary statistics, as required.
- Any values above the Upper Limit of Quantification (ULQ) will be assigned to the ULQ for display purposes in Figures and for computation of summary statistics; in listings ULQ values will be reported as ">ULQ".
- Observed cases will be used when analyzing continuous variables using Mixed-Model Repeated Measures (MMRM), analysis of covariance (ANCOVA) and nonlinear models.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Liver Fat Content Assessed Using MRI-PDFF at Week 6

- Estimand strategy: Estimand 1

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

- Figures for summary Outputs:
  - ✓ Box and whisker plots for individual percent change from baseline at Week 6 versus treatment will be presented and overlaid with arithmetic means. Only box, whiskers, median, arithmetic mean, and outliers should be reported in this graphic.

The statistical analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.4.

- Statistical outputs:
  - ✓ Adjusted geometric LSMeans estimates with 80% confidence interval for each treatment along with the translation in percent change (with their associated confidence interval),
  - ✓ Ratio of adjusted geometric LSMeans estimates for each active treatment against placebo and the corresponding 80% confidence interval along with the translation in percent difference (with their associated confidence interval). P-values for the ratio of adjusted geometric LSMeans estimates for each active treatment against placebo will be reported as well,
  - ✓ Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

- Figures from statistical outputs
  - ✓ Plot of percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval over time,
  - ✓ Plot of percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence interval over time.

Note regarding the figures;

Instead of producing 2 independent figures, and in order to having a better understanding of the placebo effect, 1 figure containing side-by-side two panels presenting bullet 1 and 2 outputs (right panel for response per treatment and left panel for placebo adjusted response)

6.2. Secondary Endpoint(s)

6.2.1. Fasting Serum Triglycerides Over Time

- Estimand strategy: Estimand 2

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

- Figure for summary Outputs:
  - Box and whisker plots by treatment and by week will be displayed to characterize the distribution of percent changes from baseline over time. Only box, whiskers, median, arithmetic mean, and outliers should be reported in this graphic.

The statistical analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

- Statistical outputs:
  - ✓ Adjusted geometric LSMeans estimates with 80% confidence interval for each treatment along with the translation in percent change (with their associated confidence interval) over time,
  - ✓ placebo and the corresponding 80% confidence interval along with the translation in percent difference (with their associated confidence interval) over time. P-values for the ratio of adjusted geometric LSMeans estimates for each active treatment against placebo at each time point will be reported as well,
  - ✓ Ratio of adjusted geometric LSMeans estimates for each active treatment against Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

- Figures from statistical outputs
  - ✓ Line plot of percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval over time,
  - ✓ Line plot of percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence interval over time,
  - ✓ Percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval at Week 6,
  - ✓ Percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence at Week 6.

  Note regarding the figures;
  Instead of producing 4 independent figures, and in order to having a better understanding of the placebo effect, 1 figure containing side-by-side two panels presenting bullet 1 and 2 outputs (right panel for response over time and left panel for placebo adjusted response over time), and 1 figure with two panels presenting side-by-side bullet 3 and 4 outputs (right panel for response at Week 6 and left panel for placebo adjusted response at Week 6) should be produced. Both sets of figures should start X-axis at Day 1/Baseline.

6.2.2. Safety and tolerability

Unless otherwise noted, all safety data, including the following, will be summarized descriptively by actual dose group through appropriate data tabulations and descriptive statistics:

- Tier-3 adverse events will be summarized according to Pfizer standards. Tier-1 and tier 2 events will also be included in these standard summary.
- Safety laboratory tests will be summarized according to Pfizer standards (note that actual visit window will be applied as defined in Appendix 2.1 in relation to actual treatment).
- ECGs will be summarized by visits. Categorical summary of ECGs will be presented according to Pfizer standards (note that baseline is defined as in Appendix 2 in relation to actual treatment).
- Vital signs will be summarized according to Pfizer standards (note that baseline is defined as in Appendix 2. in relation to actual treatment).
- For the safety endpoints of special clinical concern other than AEs as defined in Section 3.5.3, they will be presented with descriptive statistics as appropriate for continuous or categorical data as defined in section 5.2.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

6.3. Other Endpoint(s)

6.3.1. Liver Fat Content Using CAP® by FibroScan®

- Estimand strategy: Estimand 1

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

The statistical analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.4.

- Statistical outputs:
  - ✓ Adjusted geometric LSMeans estimates with 80% confidence interval for each treatment along with the translation in percent change (with their associated confidence interval),
  - ✓ Ratio of adjusted geometric LSMeans estimates for each active treatment against placebo and the corresponding 80% confidence interval along with the translation in percent difference (with their associated confidence interval),

- ✓ Summary tables reporting MMRM outputs will included the number of participants included in the analysis.

- Figures from statistical outputs
  - ✓ Plot of percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval over time,
  - ✓ Plot of percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence interval over time.

Note regarding the figures;

Instead of producing 2 independent figures, and in order to having a better understanding of the placebo effect, 1 figure containing side-by-side two panels presenting bullet 1 and 2 outputs (right panel for response per treatment and left panel for placebo adjusted response)

6.3.2. Liver Stiffness Assessed Using by FibroScan®

- Estimand strategy: Estimand 1

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

6.3.3. Liver Function Tests Over Time

- Estimand strategy: Estimand 2

For each liver Function test, ALT, AST, Alkaline Phosphatase, Total Bilirubin, and GGT

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

The statistical analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

- Statistical outputs:
  - ✓ Adjusted geometric LSMeans estimates with 80% confidence interval for each treatment along with the translation in percent change (with their associated confidence interval) over time,
  - ✓ Ratio of adjusted geometric LSMeans estimates for each active treatment against placebo and the corresponding 80% confidence interval along with the translation in percent difference (with their associated confidence interval) over time.
  - ✓ Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

- Figures from statistical outputs

- ✓ Line plot of percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval over time,
- ✓ Line plot of percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence interval over time,
- ✓ Percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval at Week 6,
- ✓ Percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence at Week 6.

Note regarding the figures;
Instead of producing 4 independent figures, and in order to having a better understanding of the placebo effect, 1 figure containing side-by-side two panels presenting bullet 1 and 2 outputs (right panel for response over time and left panel for placebo adjusted response over time), and 1 figure with two panels presenting side-by-side bullet 3 and 4 outputs (right panel for response at Week 6 and left panel for placebo adjusted response at Week 6) should be produced. Both sets of figures should start X-axis at Day 1/Baseline.

6.3.4. Other Fasting Serum Lipids Over Time

- Estimand strategy: Estimand 2

For each of the following fasting serum lipids, Total Cholesterol, Direct LDL-C, HDL-C,* Non-HDL-C, *and Direct VLDL

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

- Figures for summary Outputs:
  - Box and whisker plots by treatment and by week will be displayed to characterize the distribution of percent changes from baseline over time. Only box, whiskers, median, arithmetic mean, and outliers should be reported in this graphic.

The statistical analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

- Statistical Outputs:
  - ✓ Adjusted geometric LSMeans estimates with 80% confidence interval for each treatment along with the translation in percent change (with their associated confidence interval) over time,
  - ✓ Ratio of adjusted geometric LSMeans estimates for each active treatment against placebo and the corresponding 80% confidence interval along with the translation in percent difference (with their associated confidence interval) over time.
  - ✓ Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

- Figures from statistical outputs
  - ✓ Line plot of percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval over time,
  - ✓ Line plot of percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence interval over time,
  - ✓ Percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval at Week 6,
  - ✓ Percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence at Week 6.

Note regarding the figures;
Instead of producing 4 independent figures, and in order to having a better understanding of the placebo effect, 1 figure containing side-by-side two panels presenting bullet 1 and 2 outputs (right panel for response over time and left panel for placebo adjusted response over time), and 1 figure with two panels presenting side-by-side bullet 3 and 4 outputs (right panel for response at Week 6 and left panel for placebo adjusted response at Week 6) should be produced. Both sets of figures should start X-axis at Day 1/Baseline.

6.3.5. Apolipoproteins Over Time

- Estimand strategy: Estimand 2

For each of the following apolipoprotein, ApoA1, $ApoB_{total}$, $ApoB_{100}$, $ApoB_{48}$, ApoC3 and ApoE:

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

- Figures for summary Outputs:
  - Box and whisker plots by treatment and by week will be displayed to characterize the distribution of percent changes from baseline over time. Only box, whiskers, median, arithmetic mean, and outliers should be reported in this graphic.

The statistical analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

- Statistical Outputs:
  - ✓ Adjusted geometric LSMeans estimates with 80% confidence interval for each treatment along with the translation in percent change (with their associated confidence interval) over time,
  - ✓ Ratio of adjusted geometric LSMeans estimates for each active treatment against placebo and the corresponding 80% confidence interval along with the translation in percent difference (with their associated confidence interval) over time.
  - ✓ Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

- Figures from statistical outputs
  - ✓ Line plot of percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval over time,
  - ✓ Line plot of percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence interval over time,
  - ✓ Percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval at Week 6,
  - ✓ Percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence at Week 6.

Note regarding the figures;
Instead of producing 4 independent figures, and in order to having a better understanding of the placebo effect, 1 figure containing side-by-side two panels presenting bullet 1 and 2 outputs (right panel for response over time and left panel for placebo adjusted response over time), and 1 figure with two panels presenting side-by-side bullet 3 and 4 outputs (right panel for response at Week 6 and left panel for placebo adjusted response at Week 6) should be produced. Both sets of figures should start X-axis at Day 1/Baseline.

6.3.6. HbA1C, FPG, FPI and HOMA-IR Over Time

- Estimand strategy: Estimand 3

For each parameter:

Raw data, and changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

The statistical analysis will be performed using the change from baseline as described in Section 5.2.5.

- Statistical outputs:
  - ✓ The LSMeans estimates, and 80% confidence interval for each treatment at each time-point,
  - ✓ Difference between the LSMeans for active treatment against placebo and the corresponding 80% confidence interval will be presented at each time point.
  - ✓ Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

- Figures from statistical outputs
  - ✓ Line Plot of LSMeans estimates and 80% confidence interval over time,
  - ✓ Line Plot of placebo adjusted LSMeans and 80% confidence interval over time.
  - ✓ Change from baseline of adjusted-LSMeans with 80% confidence at Week 6.
  - ✓ Change from baseline placebo-adjusted of adjusted-LSMeans with 80% confidence at Week 6.

Note regarding the figures;
Instead of producing 4 independent figures, and in order to having a better understanding of the placebo effect, 1 figure containing side-by-side two panels presenting bullet 1 and 2 outputs (right panel for response over time and left panel for placebo adjusted response over time), and 1 figure with two panels presenting side-by-side bullet 3 and 4 outputs (right panel for response at Week 6 and left panel for placebo adjusted response at Week 6) should be produced. Both sets of figures should start X-axis at Day 1/Baseline.

6.3.7. Mechanism/Disease-Related Biomarkers Over Time

- Estimand strategy: Estimand 2

For each of the following biomarker: CK18-M30, CK18-M65, ProC3, ProC6, PCSK9, Adiponectin, and hsCRP:

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

The statistical analysis will be performed using the natural-logarithmic transformation of relative change from baseline as described in Section 5.2.5.

- Statistical Outputs:
  - ✓ Adjusted geometric LSMeans estimates with 80% confidence interval for each treatment along with the translation in percent change (with their associated confidence interval) over time,
  - ✓ Ratio of adjusted geometric LSMeans estimates for each active treatment against placebo and the corresponding 80% confidence interval along with the translation in percent difference (with their associated confidence interval) over time.
  - ✓ Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

- Figures from statistical outputs
  - ✓ Line plot of percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval over time,
  - ✓ Line plot of percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence interval over time,
  - ✓ Percent change from baseline after back transformation of adjusted geometric LSMeans with 80% confidence interval at Week 6,
  - ✓ Percent change from baseline placebo-adjusted after back transformation of adjusted geometric LSMeans ratios with 80% confidence at Week 6.

Note regarding the figures;
Instead of producing 4 independent figures, and in order to having a better understanding of the placebo effect, 1 figure containing side-by-side two panels presenting bullet 1 and 2 outputs (right panel for response over time and left panel for placebo adjusted response over time), and 1 figure with two panels presenting side-by-side bullet 3 and 4 outputs (right panel for response at Week 6 and left panel for

placebo adjusted response at Week 6) should be produced. Both sets of figures should start X-axis at Day 1/Baseline.

6.3.8. Body Weight

- Estimand strategy: Estimand 2

Raw data, changes from baseline, and percent changes from baseline will be summarized at each time point with statistics as described in Section 5.2.2 and will be presented per treatment and week.

- Figures for summary Outputs:

  - ✓ Box and whisker plots by treatment and by week will be displayed to characterize the distribution of changes from baseline over time. Only box, whiskers, median, arithmetic mean, and outliers should be reported in this graphic.

6.3.9. Pharmacokinetic Analysis

All pharmacokinetic analyses will be performed on the PK concentration set.

Plasma concentration data for DGAT2i and ACCi will be listed and summarized (C_{trough} only) by actual *Treatment*.

In addition, as permitted by data and determined by the Sponsor, exposure-response relationships between plasma concentrations of DGAT2i and/or ACCi and effect on primary, secondary and tertiary endpoints may be characterized using a population PK/PD approach. The objectives of such an analysis, if conducted, would aim to characterize exposure-response relationships and explore potential covariates (eg, age, race, gender, and body weight, etc.) influencing the observed PK and/or response to DGAT2i and/or ACCi.

The population PK and/or PK/PD analyses, if conducted, will be reported separately from the main clinical study report.

6.4. Subset Analyses

Not applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Physical Examination

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data (unless noted below), ECGs, and vital signs, will be required to be reported for

randomized participants. Amount of information databased for participants who screen fail will be limited and not summarized. Demographic data collected at screening will be reported.

6.5.2. Standard Analyses

- Listings that account for all participants who offered at least consent for pre-qualification and whether screen failed (at any point ***after*** the consent offered at the prequalification visit and ***before*** randomization on Day 1/Week 0/Visit 4 will be presented.
- Study Conduct and Participant Disposition: The number of participants randomized, treated, completing and discontinuing from the study. For participants who did not complete the study, the reasons for withdrawal from the study will be presented.
- Baseline Characteristics: Demographic characteristics such as participant age, gender, height, weight, body mass index (BMI), race, and total per arm, by treatment group will be tabulated. ***In addition,***
    - The number of participants randomized and treated will be summarized per arm, by treatment group, with each of the pre-defined medical history terms (ie, T2DM, Hyperglycemia, HDL increased, TG increased, hypertension, waist circumference increased).
    - The number of participants in each analysis population will be included in each summarized output (for safety set, PK concentration set, and for each estimand strategy) by actual treatment.

- Overall compliance (Day 1 to Week 6 or premature termination during treatment phase) will be summarized by frequency (%) in the following two categories by treatment. Formula to compute compliance is defined in Appendix 2.4.
    - $< 80\%$
    - $\geq 80\%$ (and up to 110%)

6.5.3. Baseline Summaries

For each PD endpoint (ie primary, secondary or tertiary endpoint), baseline values will be listed and summarized by treatment). Descriptive statistics for these endpoints and derived endpoints will be also tabulated.

6.5.4. Concomitant Medications and Non-Drug Treatments

The concomitant medications of special interest (see Section 3.5.3.3) will be summarized by treatment. However, all remaining concomitant drugs and non-drug treatments will only be listed.

Dose increases, dose decreases, or no changes in dose of concomitant medications of special interest observed at Week 6 (ie, end of dosing of study drug) or premature discontinuation relative to 1st dose of study drug will be summarized by treatment arm.

6.5.5. Alcohol Intake

6.5.5.1. AUDIT Questionnaire

AUDIT questionnaire results will be listed and summarized by treatment, and Week as described in Section 5.2.2.

6.5.5.2. % Carbohydrate-Deficient Transferrin (%CDT)

%CDT values reported at PreQ, and Screen visits when available ***plus*** for randomized participants at Week 1 and Week 6 will be summarized as described in Section 5.2.2.

6.5.6. Other Analyses

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

6.6. Safety Summaries and Analyses

All safety analyses will be performed on the safety population.

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive study intervention (safety population) will be included in the safety analyses.

All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations.

6.6.1. Adverse Events

The MedDRA dictionary will be used to classify all AEs with respect to system organ class and preferred term. Summaries of AEs will include treatment-emergent AEs according to treatment group.

The primary analyses will be on the incidence and severity of all treatment emergent adverse events (TEAE), that will be reported by treatment group. The number of participants and percent will be presented.

- Analysis of Tier-1 and Tier-2 TEAEs:
  - ✓ Unconditional exact test will be utilized. Risk difference will be used for the comparison.
  - ✓ No multiplicity adjustment will be made.
  - ✓ Tables and graphs will be generated. For tier-1 events, point estimates, 95% confidence intervals for the risk difference and p-values will be presented; for

tier-2 events, point estimates and 95% confidence intervals for the risk difference will be presented.

- ✓ TEAEs, by preferred term, will be sorted in descending point estimate of risk difference.
- ✓ Pair-wise comparison will be made for each active treatment (each dose of DGAT2i+ACCi) against placebo.
- ✓ For table/graphic output, include the following footnotes to provide proper interpretation of p-values and/or confidence intervals, describe how comparison is conducted. E.g. P-values and confidence intervals are not adjusted for multiplicity and should be used for screening purpose only. 95% Confidence intervals are provided to help gauge the precision of the estimates for Risk Difference. Risk Difference is computed as < PF-06865571 xx mg + PF-05221304 xx mg, <dosing frequency>, versus Placebo>.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

6.6.2. Vital Signs Analyses

Vital signs will be summarized according to Pfizer standards (note that baseline is defined as in Section 3.4 in relation to actual treatment).

Changes from baseline in systolic blood pressure, diastolic blood pressure and pulse rate will be summarized by treatment and time. The number (%) of participants with maximum increases from baseline will be tabulated by treatment as defined in Section 5.2.3. Numbers and percentages of participants meeting the categorical criteria will be provided and individual values listed in the study report.

No formal inferential statistics will be applied to the vital signs data.

6.6.3. Electrocardiogram Analyses

ECGs will be summarized by visits. Categorical summary of ECGs will be presented according to Pfizer standards (note that baseline is defined as in Section 3.4 in relation to actual treatment).

Changes from baseline for the ECG parameters QT interval, RR interval, calculated QTcF interval (using QT and RR interval), PR interval, and QRS interval will be summarized by treatment and time. QTcF will be derived using Fridericia's correction formula. The number (%) of participants with maximum increases from baseline will be tabulated by treatment as defined in the Section 5.2.3. Numbers and percentages of participants meeting the categorical criteria will be provided and individual values listed in the study report.

No formal inferential statistics will be applied to the ECG data.

6.6.4. Other Safety Data

6.6.4.1. Platelet count

Raw data, changes from baseline, and percent changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

- Figures from summary outputs
  - ✓ Box and whisker plots by treatment and by week will also be displayed to characterize the distribution of changes from baseline over time. Only box, whiskers, median, arithmetic mean, and outliers should be reported in this graphic.
  - ✓ Box and whisker plots by treatment and by week will also be displayed to characterize the distribution of percent changes from baseline over time. Only box, whiskers, median, arithmetic mean, and outliers should be reported in this graphic.
  - ✓ For participants with any **after** Day 1 (ie post-randomization) platelet count result of $< 100{,}000/mm^3$, individual plots with overlay of platelet count, aPTT, and INR up to Week 6 (*include* unplanned in chronological/continuous order – not categorical) will be generated, by treatment. To do so, real date as reported in e-data load from Covance will be used.
    - If possible, a figure containing 4x4 panels (1 panel per participant) by treatment will be created with LEFT Y-axis reporting platelet count and aPTT levels and RIGHT Y-axis reporting INR levels.

Two statistical analyses will be performed on platelets levels.

The first statistical analysis will be performed using change from baseline over time.

The second analysis will be performed using the natural-logarithmic transformation of relative change from baseline in order to report percent change from baseline.

Both analyses will be performed and reported as described in Section 5.2.5.

- Statistical Outputs for changes from Baseline:
  - ✓ The LSMeans estimates, and 80% confidence interval for each treatment at each time-point,
  - ✓ Difference between the LSMeans for active treatment against placebo and the corresponding 80% confidence interval will be presented at each time point.

- ✓ Summary tables reporting MMRM outputs will included the number of participants included in the analysis.

- Statistical Outputs for Percent Changes from Baseline:
  - ✓ Adjusted geometric LSMeans estimates with 80% confidence interval for each treatment along with the translation in percent change (with their associated confidence interval) over time,
  - ✓ Ratio of adjusted geometric LSMeans estimates for each active treatment against placebo and the corresponding 80% confidence interval along with the translation in percent difference (with their associated confidence interval) over time.
  - ✓ Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

6.6.4.2. Estimated Glomerular Filtration Rate

Raw data, and changes from baseline will be summarized by treatment, and week as described in Section 5.2.2.

The statistical analysis will be performed using the change from baseline as described in Section 5.2.5_Ref41484348.

- Statistical Outputs:
  - ✓ The LSMeans estimates, and 80% confidence interval for each treatment at each time-point,
  - ✓ Difference between the LSMeans for active treatment against placebo and the corresponding 80% confidence interval will be presented at each time point.
  - ✓ Summary tables reporting MMRM outputs will include the number of participants included in the analysis.

- Figures from statistical outputs
  - ✓ Line Plot of LSMeans estimates and 80% confidence interval over time,
  - ✓ Line Plot of placebo adjusted LSMeans and 80% confidence interval over time.

6.6.4.3. Additional Graphical Representation

A figure containing 4x4 panels (1 panel per participant) by treatment will be created with LEFT Y-axis reporting TG and FPG levels and RIGHT Y-axis reporting FPI and ApoC3 levels when triglycerides levels ≥ 600 mg/dL post dosing.

7. IRC REVIEW OF UNBLINDED SAFETY DATA (DURING STUDY CONDUCT)

*This study will use an IRC. The IRC will undertake periodic unblinded review of the safety data while the study is on-going. These reviews are envisioned, at a minimum, after approximately 33%, and 66%, of planned total sample size in Part 1 (and **separately** if conducted, Part 2), has been randomized. The IRC is independent of the study team.*

These reviews will include an assessment of the observed safety – using unblinded outputs.

7.1.1. Analyses and Summaries

For the planned unblinded safety reviews, IRC members will receive the following data summarized/analyzed by treatment along with the relevant data listings.

Study conduct and Baselined characteristics of Population Randomized:

- Study conduct issues (e.g., enrollment status, currentness of the database, time between randomization and first treatment, eligibility violations)
- Participant evaluation groups
- Demographic and other baseline characteristics

Safety Data: The Committee will monitor certain specific safety-related laboratory parameters, vital sign parameters, and treatment-emergent adverse events (TEAEs) as well as serious adverse events (SAEs including death) listings in an unblinded manner for overall frequency of events. To do so, the listings which will be provided include:

- TEAEs (and SAEs) leading to temporary discontinuation of dosing;
- TEAEs (and SAEs) leading to permanent discontinuation and withdrawal;
- The listing of individual TEAEs and SAEs;
- All instances of hyperglycemia, or platelet reduction, or hypertriglyceridemia leading to permanent withdrawal;
- Listing of Treatment emergent adverse events (TEAEs) as defined in section 6.6 of this SAP;
- Listings of SAEs/deaths and narratives requested from the safety database (ie, ARGUS or similar)
- eGFR values and laboratory parameters outlined in Table 2 of this SAP represent the minimum list of parameters which will be listed and provided to the committee.
- This list may be expanded depending on team blinded review.

The Committee will receive the distribution of participants over time whose values cross the boundaries (ie Flag and Alert levels separately) for each of the parameters included in Table 2 of this SAP.

Percent change from baseline in fasting lipid parameters (ie triglycerides, total cholesterol, direct LDL-C, VLDL, HDL-C, and derived non-HDL-C), fasting apolipoproteins (ie ApoA1, $ApoB_{total}$, $ApoB_{100}$, $ApoB_{48}$, ApoC3, and ApoE), liver function parameters (ie ALT, AST, Total Bilirubin, GGT, and Alkaline Phosphatase), eGFR, and will be provided for review.

Change from baseline in glycemic parameters (ie HbA1c, FPI and FPG) will be provided for review as well.

The following graphical representations will be provided:

- Box and whiskers plots of percent change from baseline for parameters in Table 2, eGFR, fasting lipid parameters (see list above), fasting apolipoproteins (see list above), and liver function test.

- Box and whiskers plots of changes from baseline for glycemic parameters (see lest above):

Individual vital signs (blood pressure and pulse rate) via a listing of the raw data as well as values meeting the criteria outlined in Table 3 of this SAP will be provided.

No formal statistical analyses (eg MMRM) will be performed on safety data, for purposes of IRC review of unblinded safety data.

7.2. Planned Interim Analysis Post Part 1 (and before start of Part 2)

Interim analyses will be performed after completion of Part 1 to determine whether to conduct Part 2 and if so, guide selection of doses of DGAT2i and/or ACCi to evaluate in Part 2. Interim analysis results may be used to conduct a sample size re-estimation (eg, observed variability in Part 1 is higher than assumed for derivation of sample size for Part 1), facilitate PK/PD modeling, and internal business decisions regarding planning of future trials with DGAT2i and/or DGAT2i+ACCi.

A limited number of individuals not on the study team will be unblinded according to Sponsor SOPs with the purpose of composing PK/PD analysis sets and conducting PK/PD analysis. Data draws are expected at approximately 50%, and 100% of total study data from Part 1. These data are expected to include the primary endpoint (MRI-PDFF), plasma PK for DGAT2i and ACCi, fasting serum lipid parameters including fasted serum triglycerides (and fasted serum apolipoproteins, if available). Other data outlined in Section 3 *may also be considered. The PK/PD analysis output at the completion of Part 1 (ie, achievement of LPLV in Part 1) will be shared as part of the planned Interim Analysis with selected members of the Sponsors' study team to enable decision to conduct Part 2 and if so, the dose(s) and dosing regimen(s) of DGAT2i + ACCi evaluated in Part 2.*

8. REFERENCES

1. Westfall and Krishen, "Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures", Journal of Statistical Planning and Inference 2001; 99, 25-40.

2. Littell, R.C, Milliken, G A., Stroup, WW, and Wolfinger, R D., "SAS System for Mixed Models (second edition)" , Cary, NC: SAS Institute Inc, 2006.

3. Inker LA, Schmid CH, Tighiouart H et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. N Engl J Med 2012; 367: 20-29.

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Estimand Strategy	Statistical Method	Model/ Covariates/ Strata	Missing Data	Interpretation
Percent Change from Baseline in % Liver Fat assessed by MRI-PDFF at Week 6	Estimand 1	ANCOVA on log-transformed relative change	Treatment as fixed effects with log(baseline) as covariate.	No Imputation	Primary Analysis
Percent change from Baseline in Fasting Serum Triglycerides Over Time	Estimand 2	MMRM on log-transformed relative change	Treatment, week and treatment-by-week interaction as fixed effects, participant as random effect with log(baseline) as covariate.	No Imputation	Secondary Analysis
Tertiary endpoints: Percent change from Baseline over time	Estimand 2	MMRM on log-transformed relative change	Treatment, Week and Treatment-by-Week interaction as fixed effects, participant as random effect and log(baseline) as covariate.	No Imputation	Tertiary Analysis
Tertiary endpoints Percent Change from Baseline at Week 6	Estimand 1	ANCOVA on log-transformed relative change	Treatment as fixed effects with log(baseline) as covariate.	No Imputation	Tertiary analysis
Tertiary endpoints: Change from Baseline over time	Estimand 3	MMRM on change from baseline	Treatment, Week and Treatment-by-Week interaction as fixed effects, participant as random effect and baseline as covariate	No Imputation	Tertiary analysis

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

Visit label	Protocol defined Window	Visit	Visit window as part of final reporting* For efficacy, PD, PK and safety endpoints
Pre-Qualification	NA	0	NA
Screening	NA	1	NA
Run-In	NA	2	NA
Week -2	-14 ± 2	3	• Intent is for baseline to be the result closest ***prior to*** dosing on randomized regimen on Day 1 [Visit 4] • Window for baseline measurements is from Day -20 to Day 1 [Visit 4] pre-dose
Week 0 Day 1	1	4	
Week 2	14 ± 2	5	'Date of assessment' – 'Baseline date' + 1 = [8; 20]; ie, ±6 days
Week 4	28 ± 2	6	'Date of assessment' – 'Baseline date' + 1 = [22 ; 34]; ie, ±6 days
Week 6	42 ± 2	7	'Date of assessment' – 'Baseline date' + 1 = [36 ; 48]; ie, ±6 days with all assessments within 72 hours of last dose
1st Follow-up visit	14 ± 2 days post last dose	8	'Date of assessment' – 'Last Dose date' + 1 = [8 ; 20]; ie, ±6 days
2nd Follow-up visit	30 ± 2 days post last dose	9	'Date of assessment' – 'Last Dose date' + 1 = [24 ; 36]; ie, ±6 days

Note: * permitted to be wider than window defined in protocol for purposes of reporting data by nominal visit.

Special consideration:

- For participants withdrawn early, the follow-up visit window (F/U) should be excluded from windowing algorithm, and the visit label is defined in accordance with the nominal label as recorded on the "E_TERM/FOLLOW_UP" Administration CRF.
- If 2 or more observations fall within the visit window for Week N, the observation used will be the one closest to Day 7N (randomization day is Day 1). If the 2 closest observations are equidistant from Day 7N, the earlier observation will be used.

An assessment is considered 'on treatment' if the following is true:

- 'Date (time when databased) of assessment' > 'Baseline date (time)' and ≤'Last dose date (time)'

All PD endpoints defined in section 6.1, 6.2.1, 6.3.1-6.3.9, 6.6.4.1, 6.6.4.2 are applied for visit window. For safety data (including laboratory analytes), there are no summary outputs planned by visit window; and for Vitals/12-lead ECG data as well as PK data, summaries will be generated based on reported nominal visit (and ***not*** use above visit windowing).

Appendix 2.2. Endpoint Derivations

Appendix 2.2.1. % Liver Fat using MRI-PDFF

For each participant in the study, the Whole Liver PDFF (WLPDFF in %) will be calculated from the pre-defined individual segmental PDFF (SPDFF in %) measured in Segments I, II, III, IVa, IVb, V, VI, VII and VIII as follows:

$$WLPDFF = (SPDFF_{\text{Segment I}} + SPDFF_{\text{Segment II}} + SPDFF_{\text{Segment III}} + SPDFF_{\text{Segment IVa}} + SPDFF_{\text{Segment IVb}} + SPDFF_{\text{Segment V}} + SPDFF_{\text{Segment VI}} + SPDFF_{\text{Segment VII}} + SPDFF_{\text{Segment VIII}}) / (\text{number of segments assessed and no missing/mapping at Baseline, and on Week 6})$$

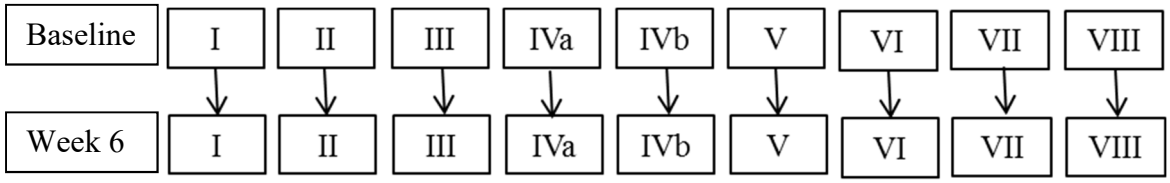
Note: If any negative values is reported by the central vendor for an individual segment, the value of this segment will be imputed to "0" before inclusion into derivation of whole liver PDFF. However, the negative value, as offered by the central vendor, will be included in the listing.

Calculation Rule for % Liver Fat when Assessed with MRI-PDFF:

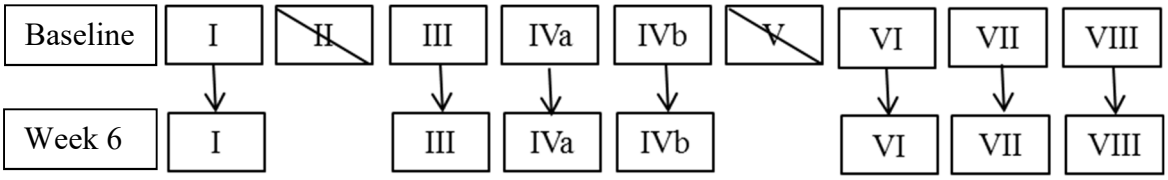
WLPDFF will be calculated on mapping no missing segments at Baseline, and on Week 6.

For instance,

if results are reported for all segments at Baseline, and on Week 6 (see below), The number of segments assessed is equal to 9.



If at Baseline, all segment data are available, but, on Week 6 only 7 segments have results reported, WLPDFF will be calculated at Baseline, and on Week 6 and using the matching individual segments providing values on ***both*** weeks. For instance, based on the schema below, Segment II and Segment V will not be used to calculate WLPDFF on any of the time points reported. In this case, WLPDFF will be calculated using data in the 7 segments reported at **both imaging** visits.



WLPDFF and individual % liver fat measured in each individual segment will be listed. WLPDFF will be summarized by actual treatment, and Week as described in Section 5.2.2.

Appendix 2.2.2. Compliance

Compliance with double-blinded study medication will be calculated using data entry exclusively from the **Double Blinded treatment** CRF pages on Week 2, Week 4 and Week 6.

Compliance between any two visits in the study will be calculated as:

% Compliance = 100 x (# of pills actually taken since the previous visit) / (# of pills expected to be taken since the previous visit)

The **# of pills actually taken since the previous visit** will be taken directly from the "Actual Dose" field in the Double Blinded treatment CRFs (sites will be instructed to enter the total number of tablets that the participant has consumed since the last on-site visit).

The **# of pills expected to be taken since the previous visit** = (Date of current visit – Date of previous visit)* (Expected Tablets per day in each part[1])

Compliance across the overall study treatment period will be calculated as:

% Compliance =100 x (# of pills actually taken during the double-blind treatment phase) / (# of pills expected to be taken during the double-blind treatment phase)

The **# of pills actually taken during the double-blind treatment phase =** sum of all "Actual dose" fields for all visits during the double-blind treatment phase (ie, the sum of the total number of tablets that the participant has consumed during the double-blind treatment phase).

The **# of pills expected to be taken during the double-blind treatment phase** = (Week 6 (V7) or Early Term visit date – Baseline visit date (V4))* (Expected Tablets per day in each part[1])

[1] To be determined for part 2. For instance in Part 1 the total daily dose will be administered using 6 tablets

Appendix 3. Statistical Methodology Details

Appendix 3.1.1. MMRM for Safety Analysis and PD analysis:

On raw scale:

```
proc mixed data = dataset method = reml;
      class subjid treatment day;
      model cfb = treatment base day base*day day*treatment/ ddfm = kr
      residual;
      repeated day / subject = subjid type = un;
      lsmeans treatment*day / diff cl alpha = 0.1;
 run;
```

On natural logarithmic scale:

```
proc mixed data = dataset method = reml;
      class subjid treatment day;
      model log(RCBL) = treatment log(base) day log(base)*day day*treatment/ ddfm = kr
      residual;
      repeated day / subject = subjid type = un;
      lsmeans treatment*day / diff cl alpha = 0.1;
 run;
```

Appendix 3.1.2. ANCOVA for Safety Analysis and PD Analysis:

On raw scale:

```
proc mixed data = dataset method = reml;
      class treatment;
      model CFB = treatment base /residual;
      lsmeans treatment / diff cl alpha = 0.1;
 run;
```

On natural logarithmic scale:

```
proc mixed data = dataset method = ml;
      class treatment;
      model log(RCBL) = treatment log(base) /residual;
      lsmeans treatment / diff cl alpha = 0.1;
 run;
```

Appendix 4. List of Abbreviations

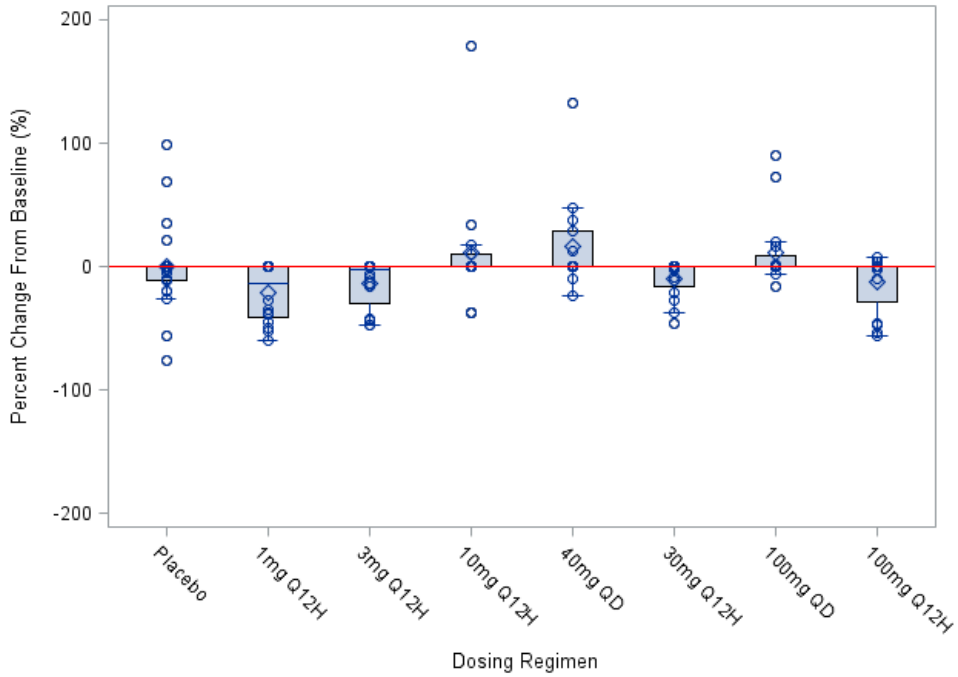
Abbreviation	Term
Abs	absolute
AE	adverse event
ALKP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ApoA1	Apolipoprotein A1
$ApoB_{100}$	Apolipoprotein B100
$ApoB_{48}$	Apolipoprotein B48
$ApoB_{Total}$	Apolipoprotein B Total
ApoC3	Apolipoprotein C3
ApoE	Apolipoprotein E
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
AUDIT	alcohol use disorders identification test
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
BP	blood pressure
CAP®	Controlled Attenuation Parameter
CBL	Change from baseline
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CI	confidence interval
CK18-M30	Cytokeratin-18-M30
CK18-M65	Cytokeratin-18-M65
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FPG	Fasting Plasma Glucose
FPI	Fasting Plasma Insulin
GCP	Good Clinical Practice

Abbreviation	Term
GGT	Gamma Glutamyl Transferase
GLIMMIX	generalized linear mixed-effects model with repeated measures
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HbA1C	Glycated Hemoglobin A1C
HDL-C	High Density Lipoprotein Cholesterol
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
hsCRP	High Sensitive C-Reactive Protein
ICD	informed consent document
ICH	International Council for Harmonisation
IRC	internal review committee
IST	independent statistical team
ITT	intent-to-treat
LDL	Low Density Lipoprotein
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
MMTT	mixed meal tolerance test
MNAR	missing not at random
N/A	not applicable
NNB	number needed to benefit
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
Non-HDL-C	Non High-Density Lipoprotein Cholesterol
PBL	Percent change from baseline
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PPAS	per-protocol analysis set
PRO	patient-reported outcome
ProC3	N-terminal pro-peptide of type III procollagen
ProC6	C-terminal fragment of the α3 chain of procollagen type VI
PT	preferred term

Abbreviation	Term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCBL	Relative change from baseline
RCDC	reverse cumulative distribution curve
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGS	Statistical Guidance Standards
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TA	therapeutic area
TBIL	Total bilirubin
TEAE	Treatment emergent adverse event
ULN	upper limit of normal
VCTE™	Vibration-Controlled Transient Elastography
VLDL	Very Low Density Lipoprotein cholesterol
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
%CDT	% Carbohydrate-Deficient Transferrin

Appendix 5. Graphical Representations

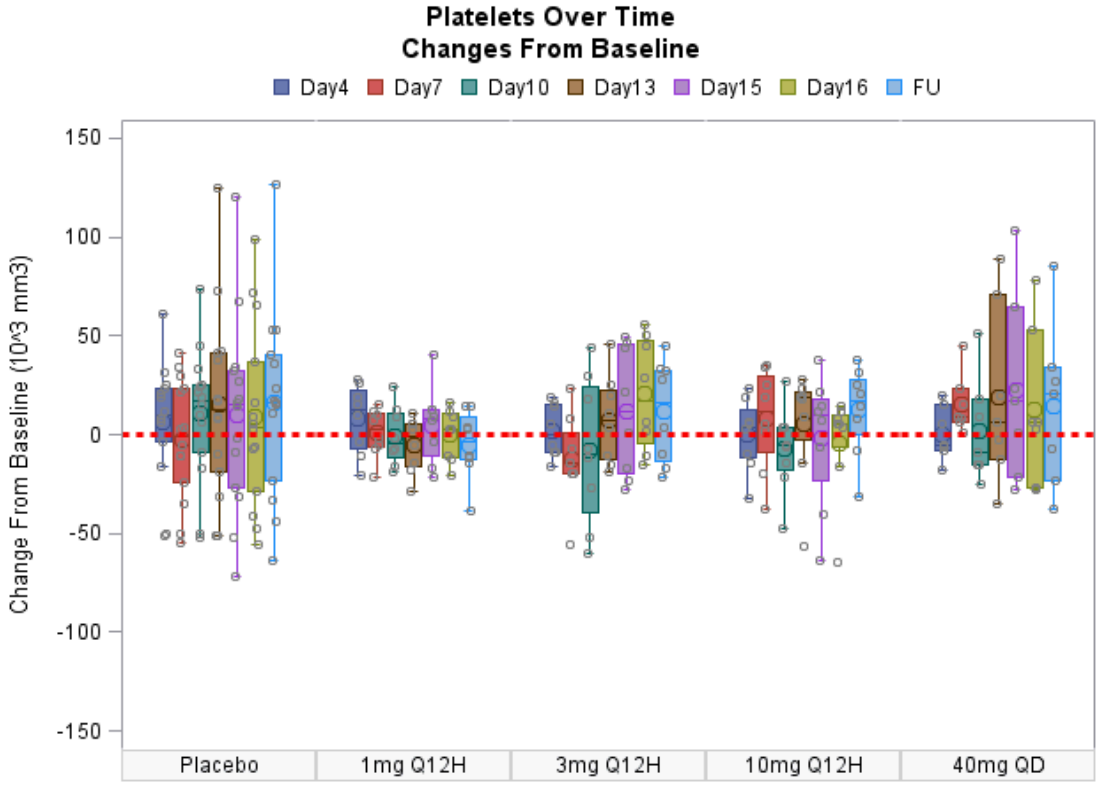
Appendix 5.1. Box and Whisker Plot Representation for Changes/Percent Changes from Baseline at Week 6 by Treatment



Note: To be adapted for C3711005 design with correct total daily dose and orderd by ratio then by dosing regimen (eg BID vs QD). Only box, whiskers, median, arithmetic mean and outliers should be reported in this graphic (individual participant data [open circles within 5th and 95th whisker should not be included] only the individual values which are outliers/outside whiskers).

Appendix 5.2. Box and Whisker Plot for Changes/ Percent Changes From Baseline by Treatment and Week

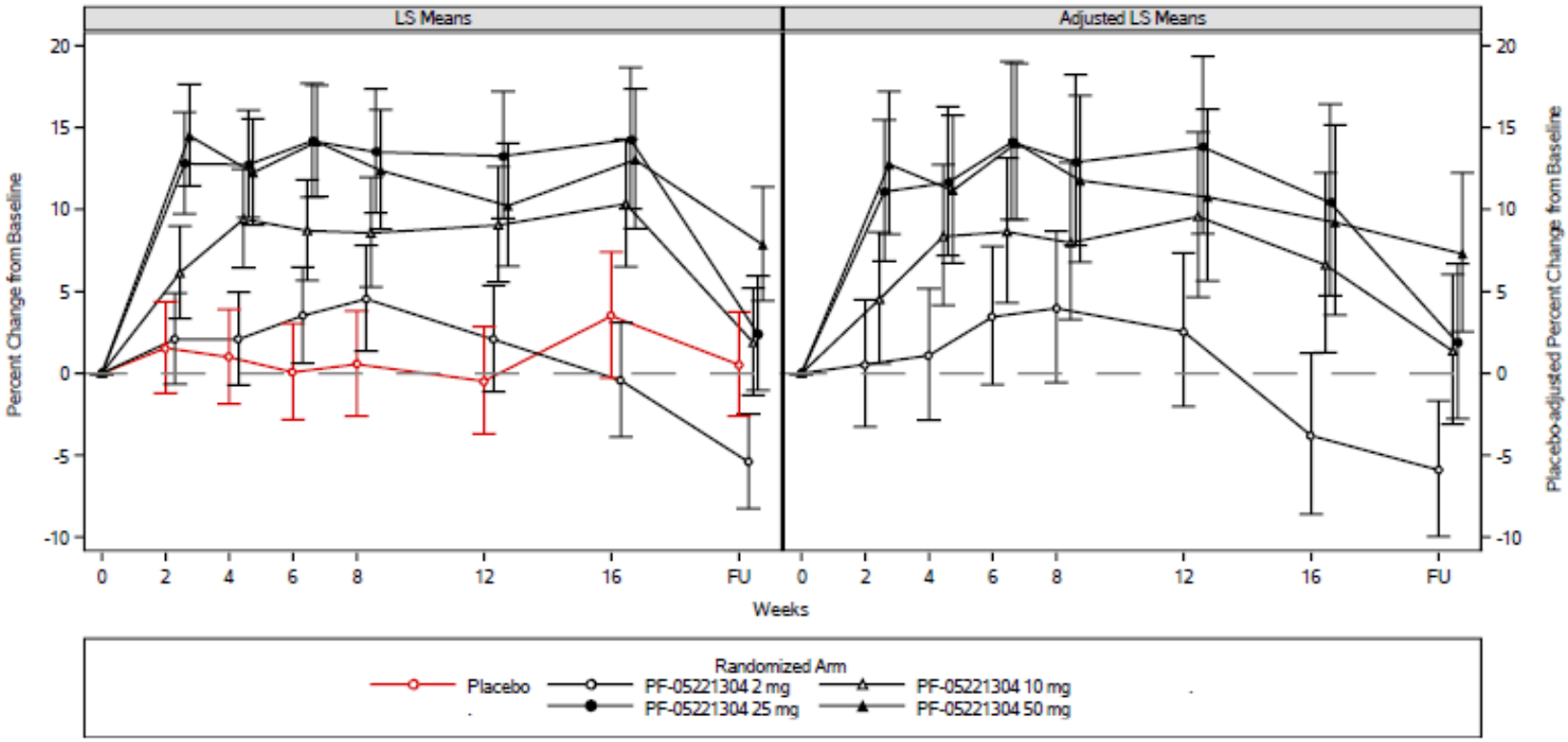
Note: To be adapted for C3711005 design (eg weeks as legend) with correct total daily dose. Only box, whiskers, median, arithmetic mean and outliers should be reported in this graphic (individual participant data [open circles within 5th and 95th whisker should not be included] only the individual values which are outliers/outside whiskers).



[redacted]

[redacted]

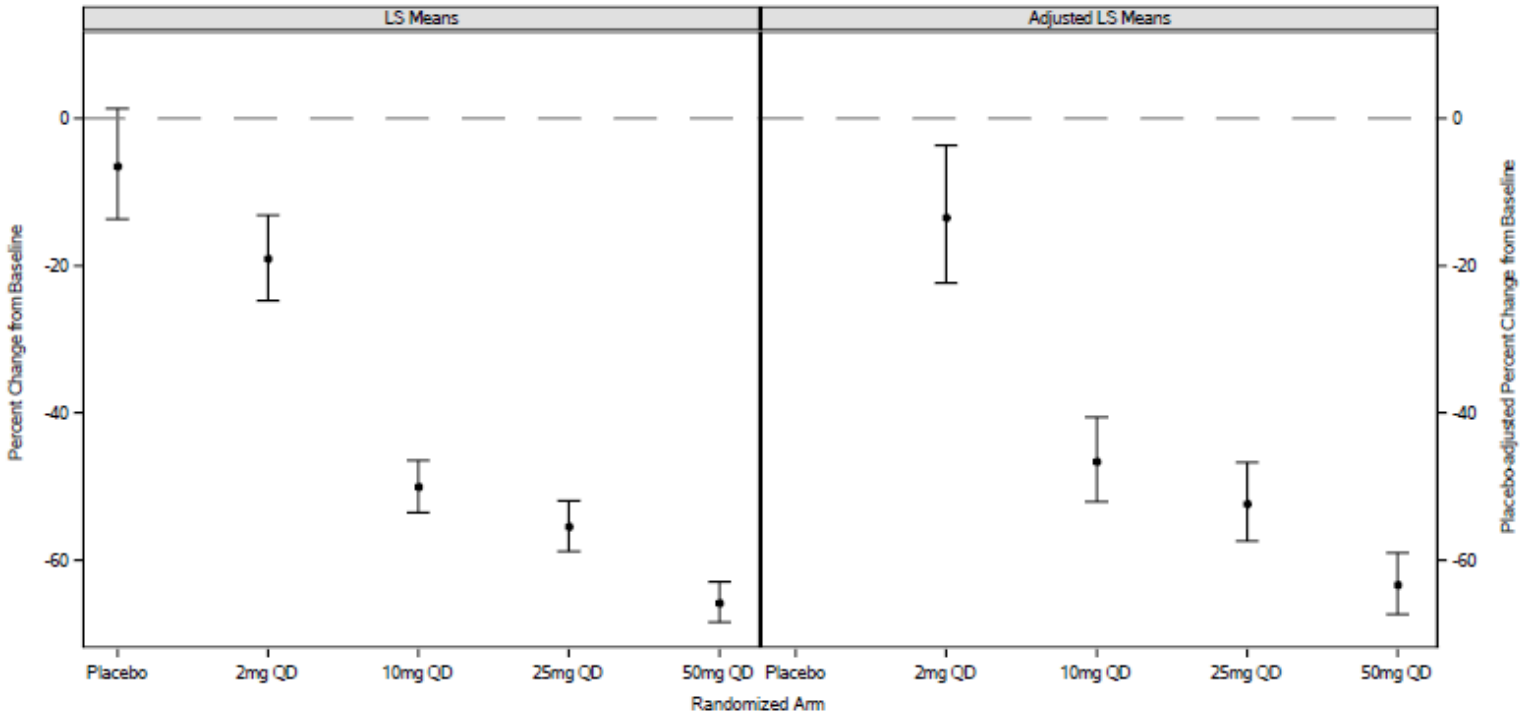
Appendix 5.3. LS Means and Placebo Adjusted LS Means with 80% CI from MMRM Analysis Over Time Versus Week per Treatment (to be adapted for C3711005 Design)



[redacted]

[redacted]

Appendix 5.4. Example for LS Means and Placebo Adjusted LS Means with 80% CI from ANCOVA Analysis at Week 6 per Treatment (to be adapted for C3711005 Design)



Appendix 5.5. Example for Figure Reporting Multiple Laboratory Parameters Over Time Simultaneously (to be adapted for C3711005 Design)