Statistical Analysis Plan for Protocol 747-209

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Clinical Study Investigating the Effects of Obeticholic Acid and Atorvastatin Treatment on Lipoprotein Metabolism in Subjects with Nonalcoholic Steatohepatitis

The CONTROL Study

Combination OCA aNd STatins for MonitoRing Of Lipids

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apo	apolipoprotein
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ApoCII	apolipoprotein CII
ApoCIII	apolipoprotein CIII
ApoE	apolipoprotein E
APRI	aspartate aminotransferase (AST) to platelet ratio index
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUC_{0-6}	area under the concentration-time curve from hour 0 to last sampling time (hour 6)
AUDIT	Alcohol Use Disorders Identification Test
BARD	body mass index, aspartate aminotransferase to alanine aminotransferase ratio, and diabetes
BLQ	below the limit of quantitation
BMI	body mass index
C4	7α-hydroxy-4-cholesten-3-one
CA	cholic acid
cAMP	cyclic adenosine monophosphate
CAP	controlled attenuation parameter
CDCA	chenodeoxycholic acid
CETP	cholesterol ester transfer protein
CI	confidence interval
CK-18-M30	cytokeratin-18 neoepitope M30
CK-18-M65	cytokeratin-18 neoepitope M65
cm	centimeter(s)

Abbreviation or Specialist Term	Explanation
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CRN	clinical research network
CRP	C-reactive protein
CS	clinically significant
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DB	double-blind
DCA	deoxycholic acid
DOB	date of birth
DOIC	date of informed consent
eCRF	electronic case report form
ECG	Electrocardiogram
EE	efficacy evaluable
Eq	equivalents
FGF-19	fibroblast growth factor-19
FIB-4	Fibrosis-4
FRS	Framingham Risk Score
FXR	farnesoid X receptor
G	gram(s)
GGT	gamma-glutamyl transferase
glyco-CA	glycine 6α-ethyl cholic acid
glyco-CDCA	glycine 6α chenodeoxycholic acid
glyco-DCA	glycine 6α-ethyl deoxycholic acid
glyco-LCA	glycine 6α-ethyl lithocholic acid
glyco-OCA	glycine 6α-ethyl chenodeoxycholic acid
glyco-UDCA	glycine 6α-ethyl ursodeoxycholic acid
H	high/above the reference/normal range
HbA1c	hemoglobin-specific A1c fraction
HDL	high-density lipoprotein
HDLc	HDL cholesterol concentration
HDLs	HDL particle size
HDLpc	HDL particle concentration

Abbreviation or Specialist Term	Explanation
HOMA-β	homeostatic model assessment – beta-cell function
HOMA-IR	homeostatic model assessment – insulin resistance
hs-CRP	high-sensitivity C-reactive protein
In	inch(es)
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IL-6	interleukin-6
INR	International Normalized Ratio
IQR	interquartile range
ITT	intent-to-treat
Kg	kilogram(s)
JT	Joncheere-Terpstra
KM	Kaplan-Meier
L	low/below the reference/normal range
Lb	pound(s)
LCA	lithocholic acid
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LDLc	LDL cholesterol concentration
LDLs	LDL particle size
LDLpc	LDL particle concentration
LOCF	last observation carried forward
LLN	lower limit(s) of normal
LLOQ	lower limit of quantification
Lp(a)	lipoprotein(a)
LS	least squares
LTSE	long-term safety extension
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram(s)
mL	milliliter
mol	mole(s)
MW	molecular weight
NAFLD	nonalcoholic fatty liver disease

Abbreviation or Specialist Term	Explanation
NAS	nonalcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
ND	not determined
NFS	nonalcoholic fatty liver disease fibrosis score
ng	nanogram
NMR	nuclear magnetic resonance
NR	not reported
OCA	obeticholic acid
ODS	output delivery system
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PK	pharmacokinetic
PP	per protocol
QT	the time between the start of the Q wave and the end of the T wave
QTc	corrected measure between Q wave and T wave (in heart's electrical cycle)
QTcB	QT interval corrected by the Bazett's formula
QTcF	QT interval corrected by the Fridericia's formula
RR	time between two consecutive R waves
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	International System of Units
SMQ	standardized MedDRA query
SQRT	square root
tauro-CA	taurine 6α-ethyl cholic acid
tauro-CDCA	taurine 6α chenodeoxycholic acid
tauro-DCA	taurine 6α-ethyl deoxycholic acid
tauro-LCA	taurine 6α-ethyl lithocholic acid
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
tauro-UDCA	taurine 6α-ethyl ursodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}

Abbreviation or Specialist Term	Explanation
TG	triglycerides
TNF-α	tumor necrosis factor-alpha
UDCA	ursodeoxycholic acid
ULN	upper limit(s) of normal
VLDL	very low density lipoprotein
VLDLc	VLDL cholesterol concentration
VLDLpc	VLDL and chylomicron particle concentration
VLDLs	VLDL particle size
WADD	weighted average daily dose
WHODDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of the double-blind (DB) data collected within the scope of Intercept Pharmaceuticals, Inc. (henceforth referred to as Intercept or the Sponsor) for Protocol 747-209 (A Phase 2, Randomized, Double-Blind, Placebo-Controlled Clinical Study Investigating the Effects of Obeticholic Acid and Atorvastatin Treatment on Lipoprotein Metabolism in Subjects with Nonalcoholic Steatohepatitis). The purpose of this statistical analysis plan (SAP) is to provide specific guidelines from which the analyses will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR). The scope of this plan includes the detailed specifications of the statistical analyses for the DB only. A separate SAP will be written for the long-term safety extension (LTSE) phase of the study. The analyses described in this plan are considered a priori, in that they have been defined prior to database lock of the DB. Post hoc analyses will be labeled as such on the outputs and identified in the CSR. Further details about study design and procedures can be found in the protocol.

2. STUDY OBJECTIVES

The DB primary objective is to evaluate the effect of obeticholic acid (OCA) on low-density lipoprotein (LDL) metabolism in subjects with biopsy-confirmed nonalcoholic steatohepatitis (NASH) and to assess the ability of atorvastatin to modulate this effect.

The DB secondary objectives are:

- To evaluate the safety and tolerability of OCA alone and in combination with atorvastatin therapy in subjects with biopsy-confirmed NASH.
- To evaluate the effect of OCA with and without atorvastatin therapy, on
  - High-density lipoprotein (HDL), very low-density lipoprotein (VLDL), triglycerides (TG), total cholesterol, and apolipoprotein (Apo) concentrations
  - Components of the reverse cholesterol transport pathway

The DB exploratory objectives are:

- To evaluate the effect of OCA on:
  - Liver biochemistry, inflammation, and apoptosis
  - Markers of glucose metabolism including C-peptide, insulin, fasting plasma glucose, hemoglobin-specific A1c fraction (HbA1c), homeostatic model assessment – beta-cell function (HOMA-β), and homeostatic model assessment – insulin resistance (HOMA-IR)
  - Anthropometric measures including height (measured at Screening Visit 1 only), weight, waist and hip circumference measurements, body mass index (BMI), and waist-to-hip ratio calculations
  - Cardiovascular risk scores (eg, Framingham Risk Score [FRS] and Reynolds score)

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of OCA and its conjugates
- To evaluate the bioanalytical concentrations of atorvastatin and its metabolites
- To evaluate improvement in noninvasive-radiological assessment of fibrosis via transient elastography (TE; at sites where available)

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The DB primary endpoints are change and percentage change from Baseline to Week 16 in LDL cholesterol concentration (LDLc), particle size (LDLs), and particle concentration (LDLpc).

3.2. Secondary Endpoints

As defined in the protocol, the DB secondary endpoints are lipoprotein metabolism, reverse cholesterol transport, and safety and tolerability endpoints.

3.2.1. Lipoprotein Metabolism Endpoints

The secondary parameters related to lipoprotein metabolism include HDL cholesterol concentration (HDLc), particle size (HDLs) and particle concentration (HDLpc); VLDL cholesterol concentration (VLDLc), particle size (VLDLs), and VLDL and chylomicrons particle concentration (VLDLpc); TG and total cholesterol concentrations; and apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), apolipoprotein E (ApoE), apolipoprotein CII (ApoCII), apolipoprotein CIII (ApoCIII), lipoprotein(a) [Lp(a)], and proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme level concentrations.

For each of these parameters, the endpoints are:

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

3.2.2. Reverse Cholesterol Transport Endpoints

The secondary parameters related to reverse cholesterol metabolism include pre-β1 HDL concentration, macrophage cholesterol efflux, lecithin-cholesterol acyltransferase (LCAT) activity, cholesterol ester transfer protein (CETP) activity.

For each of these parameters, the endpoints are:

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

3.2.3. Safety and Tolerability Endpoints

The DB safety and tolerability endpoints include the following:

- Extent of exposure to OCA and Atorvastatin

- Incidence of Treatment-Emergent adverse events (TEAEs)
- Observed values and change from Baseline at each DB post-Baseline visit in quantitative clinical laboratory values for coagulation, hematology, and serum chemistry
- Shift tables (ie, low-normal-high at Baseline versus low-normal-high at each DB post-Baseline visit in a 3-by-3 contingency table) from Baseline to worst DB post-Baseline value, last DB post-Baseline value, and at each scheduled DB post-Baseline visit for quantitative hematology, coagulation, and serum chemistry
- Observed values and change from Baseline at each DB post-Baseline visit in vital signs (ie, body temperature, sitting heart rate, and respiratory rate). Note: blood pressure (sitting) is described below in Section 3.3.6
- Observed values at Baseline and each DB post-Baseline visit, and change from Baseline at each DB post-Baseline visit in electrocardiogram (ECG) parameters (time between 2 consecutive R waves [RR], heart rate, PR, QRS, the time from the start of the Q wave an T wave (in heart's electrical cycle) (QT), QT interval corrected by Bazett's formula (QTcB), and QT interval corrected by Fridericia's formula (QTcF))
- Categorical summaries of abnormal QTcF values (ie, > 450 msec, > 480 msec, and > 500 msec) and change from baseline values (> 30 msec and > 60 msec)

3.3. Exploratory Endpoints

As defined in the protocol, the DB exploratory endpoints are liver biochemistry and markers of liver function, markers of liver inflammation, markers of hepatic apoptosis and fibrosis, glycemic control, OCA pharmacokinetics (PK), atorvastatin bioanalytical concentrations, anthropometric measures, pharmacodynamics (PD), noninvasive radiological liver fibrosis measurements, and cardiovascular risk scores.

In addition, noninvasive scores of liver fibrosis including nonalcoholic fatty liver disease (NAFLD) fibrosis score (NFS) (Angulo 2007), fibrosis-4 (FIB-4) (Shah 2009), aspartate aminotransferase (AST) to platelet ratio index (APRI) (Calès 2009), and body mass index (BMI), AST to alanine aminotransferase (ALT) ratio, and diabetes (BARD) (Harrison 2008) will be computed based on Baseline characteristics and biochemistry values at scheduled visits.

3.3.1. Liver Biochemistry and Markers of Liver Function

For the laboratory parameters albumin, alkaline phosphatase (ALP (isoenzymes)), ALT (isoenzymes), AST, total and direct bilirubin, gamma-glutamyl transferase (GGT), and INR (International Normalized Ratio), and platelets:

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit
- Shift from Baseline to each DB post-Baseline visit

3.3.2. Markers of Liver Inflammation

For the laboratory parameters interleukin (IL-6), high-sensitivity C-reactive protein (hs-CRP), and tumor necrosis factor-alpha (TNF-α):

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

3.3.3. Markers for Hepatic Apoptosis and Fibrosis

For the laboratory parameters cytokeratin-18 neoepitope M30 (CK-18-M30) and cytokeratin-18 neoepitope M65 (CK-18-M65):

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

For noninvasive scores of liver fibrosis NFS, FIB-4, and APRI:

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

For noninvasive score of liver fibrosis BARD:

- Shift from Baseline to each DB post-Baseline visit

3.3.4. Glycemic Control

For the laboratory parameters fasting glucose, fasting insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR.

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

3.3.5. OCA Pharmacokinetics Endpoints

The OCA PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glycine 6α-ethyl chenodeoxycholic acid [glyco-OCA] taurine 6α-ethyl chenodeoxycholic acid [tauro-OCA]), total OCA, and potentially other conjugates or metabolites not yet identified. PK analyses will utilize standard non-compartmental methods.

PK parameter estimates will be summarized by active treatment group using descriptive statistics. Only samples that have a confirmed fasting of at least 8 hours or more before their visit will be included in the analysis.

- The PK endpoints include the Day 1 and Week 16 plasma concentrations at all collection time points. Plasma PK parameters will include maximum plasma concentration [C_{max}], time to reach C_{max} [t_{max}], and area under the concentration-time curve from hour 0 to last sampling time (hour 6) [AUC_{0-6}].
- OCA dose-normalized versions of C_{max}, and AUC_{0-6} will be calculated for Day 1 and Week 16.
- Steady-state accumulation ratios based on C_{max} (R_{ac} C_{max}) and AUC_{0-6} (R_{ac} AUC_{0-6}) will be calculated:

R_{ac} C_{max} = Week 16 C_{max}/Day 1 C_{max}

R_{ac} AUC_{0-6} = Week 16 AUC_{0-6}/Day 1 AUC_{0-6}

- Metabolite ratios based on C_{max} (MRC_{max}) and AUC_{0-6} ($MRAUC_{0-6}$) will be calculated:

  MR C_{max} = (C_{max} conjugate or metabolite / C_{max} parent) x (molecular weight parent / molecular weight conjugate or metabolite)
  MR AUC_{0-6} = (AUC_{0-6} conjugate or metabolite / AUC_{0-6} parent) x (molecular weight parent / molecular weight conjugate or metabolite)

3.3.6. Anthropometric Measures and Blood Pressure

Anthropometric measures include height (measured and recorded only at Screening Visit 1), body weight, waist and hip circumference measurements, BMI, and waist-to-hip ratio calculations. Blood pressure (sitting) will also be collected.

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

3.3.7. Pharmacodynamics

For 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor-19 (FGF-19), conjugated and unconjugated endogenous bile acids, and total bile acids:

- Observed values and change from Baseline at each DB post-Baseline visit

3.3.8. Noninvasive Radiological Liver Fibrosis Measurements

Noninvasive radiological methods to assess liver stiffness and steatosis will be conducted via transient elastography (TE) at selected centers where the devices are available.

- Observed liver stiffness values and change from Baseline at each DB post-Baseline visit
- Proportion of subjects with any reduction in liver stiffness value (kPa) at Week 16
- Observed controlled attenuation parameter (CAP) (dB/m) values and change from Baseline at each DB post-Baseline visit
- Both liver stiffness and CAP values are median values based on number of valid measurements

3.3.9. Cardiovascular Risk Scores

The cardiovascular risk scores include the Framingham Risk Score (FRS) and Reynolds score. Each score is derived from a subject's age, sex, smoking status, total cholesterol and HDL levels, and other factors including family history, BMI, ethnicity, and medications. Cardiovascular scores will be calculated at the time of data analysis.

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

3.3.10. Cardiovascular Markers of Risk

The cardiovascular markers of risk scores include adiponectin, plasminogen activator inhibitor-1(PAI-1), and B-type natriuretic peptide (BNP).

- Observed values, change from Baseline, and percentage change from Baseline at each DB post-Baseline visit

4. STUDY DESIGN AND PLAN

This is a Phase 2, double-blind, randomized, placebo-controlled, multicenter study, evaluating the effects of OCA, and the subsequent addition of statin therapy, on lipoprotein metabolism in subjects with NASH with fibrosis stage 1 to 4, but no evidence of hepatic decompensation, in the DB phase, followed by an open-label LTSE phase to evaluate long term safety and efficacy.

Approximately 80 subjects with histological evidence of definite or probable NASH, who meet all inclusion and none of the exclusion criteria will be enrolled in the study. The histological evidence of definite or probable NASH will be based on the central read of a liver biopsy obtained no more than 1 year prior to randomization and a nonalcoholic fatty liver disease activity score (NAS) of 4 or greater. Subjects not using statin therapy (ie, statin-free) and statin-treated subjects may be enrolled. Statin-treated subjects will be required to stop statin treatment (after signing informed consent) for up to 5 weeks, including a 4-week statin washout period, prior to Randomization/Day 1.

Subjects will have a screening period of up to 5 weeks prior to Randomization/Day 1. At the Randomization (Day 1) Visit, subjects will be randomized in a 1:1:1:1 ratio to receive OCA 5 mg, OCA 10 mg, OCA 25 mg, or placebo, orally, once daily, for 16 weeks. Randomization will be stratified by the pre-randomization fasting serum LDLc (≤125 mg/dL or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4).

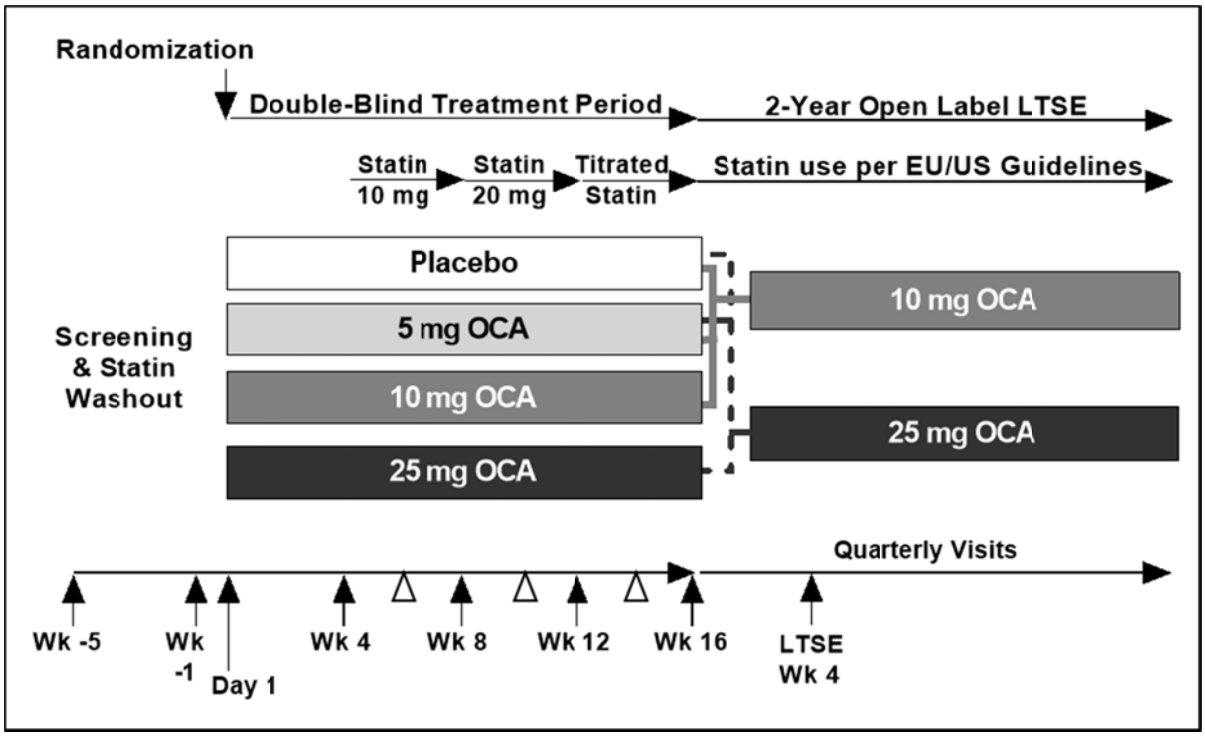
Subjects will attend on-site clinic visits at Weeks 2, 4, 8, 12, and 16 and will be contacted at Weeks 6, 10 and 14 to assess safety and treatment compliance. At the Week 4 Visit, all subjects will initiate treatment with atorvastatin at a dose of 10 mg once daily. At the Week 8 Visit, atorvastatin will be increased to 20 mg once daily (if 10 mg daily is tolerated), and continued for an additional 4 weeks. After 4 weeks of treatment at 20 mg, the atorvastatin dose may be titrated (up or down) as clinically indicated. The final visit during the DB phase will occur at Week 16, after which subjects may continue into the open-label LTSE.

During the LTSE phase, all subjects will be treated with open-label OCA 10 mg or 25 mg. Subjects randomized to placebo or OCA 5 mg during the double-blind phase will be randomized in a 1:1 ratio to receive OCA 10 mg or OCA 25 mg upon entry into and throughout the LTSE phase. Subjects randomized to OCA 10 mg or OCA 25 mg during the double-blind phase will continue on the same dose throughout the LTSE. In the event of OCA-related tolerability concerns, the Investigator may refer to the Investigator's Brochure (IB) for possible treatment options. Subjects may continue, discontinue, or modify the atorvastatin therapy as clinically indicated. The LTSE will continue for approximately 2 years.

The overall study duration is up to 125 weeks including a Screening period of up to 5 weeks (depending on current statin use); a 16-week DB; and a 2-year, open-label LTSE.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design Schematic



LTSE: long-term safety extension; Wk = week
Note: Statin therapy refers to atorvastatin.
Δ = Telephone Safety Contact at Week 6, Week 10, and Week 14

5. DETERMINATION OF SAMPLE SIZE

It is the intent of this study to characterize the components of LDL metabolism (ie, LDLc, LDLs, and LDLpc) in subjects with NASH before and after treatment with OCA and to assess the changes induced by HMG Coenzyme A reductase inhibitor (atorvastatin) therapy. Assuming a 22 mg/dL increase from Baseline with a standard deviation of 24 in LDLc in the OCA 25 mg group without atorvastatin therapy after 16 weeks of treatment based on data from FXR Ligand OCA in NASH Treatment (FLINT) study, a sample size of 20 subjects per group will provide greater than 97.3% power to demonstrate the statistically significant difference of LDLc increase from Baseline with a 2-sided type I error of 0.05.

6. GENERAL ANALYSIS CONSIDERATIONS

6.1. Data Reporting

The statistical analyses will be reported using summary tables, figures, and data listings. All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the ICH recommendations, and formatted to the appropriate page size(s).

Laboratory units will be summarized and presented in the International System of Units (SI) and conventional units.

Individual subject data obtained from the electronic case report forms (eCRFs), external laboratory data, and any derived data (such as change from Baseline and percent change from Baseline) will be presented in data listings by subject. Data from all assessments, whether scheduled or unscheduled, will be listed by subject and visit. Unscheduled visits and visits occurring more than one day outside protocol defined window will not be included in the table summaries, excluding transient elastography measurements

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock of the DB. Post hoc analyses will be labeled as such on the outputs and identified in the CSR.

Analyses and tabulations will be performed using SAS® Version 9.3 or higher. PK parameters will be estimated using Phoenix® WinNonlin® Version 6.3 or higher. The following processes will be employed to validate statistical outputs: analysis datasets, summary tables, and data listings will be verified through independent programming; graphical displays will be compared against supporting summary tables; and all outputs will undergo a senior-level statistical review. The process includes confirmation that statistically valid methods have been implemented and that all data manipulations and calculations are appropriate and accurate. Checks will be made to ensure accuracy, adherence to this SAP, consistency within tables, and agreement between tables and their corresponding data listings. Upon completion of validation/verification and quality review procedures, all documentation will be collected and filed in the study master file by the project statistician or designee.

6.2. Data Analysis and Summaries

Data distribution characteristics will determine which analysis methods are most appropriate. If methods do not allow for parametric modeling assumptions to be met, then non-parametric methods will be implemented.

6.2.1. Arithmetic Summaries

Continuous variables will be summarized with means, standard deviations (SDs), standard errors (SEMs) of the mean, medians, interquartile ranges (IQRs), minimums, and maximums.

6.2.2. Categorical Methods

Categorical variables will be summarized by counts and percentage of subjects in corresponding categories. Percentages will be based on the number of non-missing assessments unless otherwise specified.

6.2.3. Analysis of Covariance

Analysis of covariance (ANCOVA) will be performed to provide least squares (LS) mean estimates and 95% confidence intervals (CIs) of the change and percentage change from Baseline at each DB post-Baseline visit. Model covariates will include the randomization stratification values (ie, pre-randomization fasted serum LDLc [≤125 mg/dL or >125 mg/dL] and baseline fibrosis stage [stage 1, 2 or stage 3, 4]) and the Baseline value of the parameter being evaluated. The primary analysis will exclude the treatment by visit interaction term.

Example SAS code for the primary analysis is as follows:

```
ODS graphics on;
proc mixed data=ADEFF noclprint plots=residualpanel;
  by visit;
        class ldlcon fbstg trt;
        model change=Baseline ldlcon fbstg trt / ddfm=kr;
        lsmeans trt / cl diff alpha=0.05;
        title1 "Linear Mixed Effects Model Based Estimates of XXXX Means by Visit";
        title2 " Fixed Effects for Visit, Randomization Strata and Baseline as Covariates";
run;
ODS graphics off;
quit;
```

6.2.4. Analysis of Covariance (Repeated Measures)

Analysis of covariance (ANCOVA) with repeated measures will be performed to provide LS mean estimates and 95% CIs of the change and percentage change from Baseline at each DB post-Baseline visit. Model covariates will include the randomization stratification values (ie, pre-randomization fasted serum LDLc [≤125 mg/dL or >125 mg/dL] and baseline fibrosis stage [stage 1, 2 or stage 3, 4]) and the Baseline value of the parameter being evaluated. This will include the treatment by visit interaction term. Example SAS code for the secondary analysis is as follows:

```
ODS graphics on;
proc mixed data=ADEFF noclprint plots=residualpanel;
        class subjid week ldlcon fbstg trt;
        model change=trt week trt*week ldlcon fbstg Baseline/ ddfm=kr;
        repeated week / subject=subjid type=un;
        lsmeans trt*week / cl diff alpha=0.05;
        title1 "Linear Mixed Effects Model Based Estimates of XXXX Means by Visit";
        title2 " Fixed Effects for Visit, Randomization Strata and Baseline as Covariates, and
                Treatment by Visit Interaction";
run;
ODS graphics off;
quit;
```

6.2.5. Median and Confidence Interval Estimation Methods

Hodges Lehmann estimation will be used to provide estimators of the median and 95% CIs for the median.

6.2.6. Dose Trend Methods

The Joncheere-Terpstra (JT) approach will be used to provide an estimate of relationship between change in LDLc from DB Baseline to Week 16 and dose level.

Example SAS code as follows:

```
ODS graphics on;
proc freq data=ldlchg;
        Tables trt*chg/out=jtpval jt;
        Title1 “Jonckheere-Terpstra Trend Test for Continuous Data”;
Run;
ODS graphics off;
```

6.2.7. Geometric (Natural Log Transformed) Summaries

To calculate a geometric mean and corresponding 95% CI, the following steps are used:

- Transform the data by taking natural logarithms ($\log_e$)
- Calculate the mean and 95% CI of the $\log_e$-transformed data
- Exponentiate the mean and the lower and upper CIs back to the original scale to obtain the geometric mean and corresponding 95% CI

6.2.8. Multiple Comparisons/Multiplicity

As this is a descriptive study, no formal adjustments for multiple comparisons are being made. Therefore, CIs and p-values will be interpreted as purely descriptive.

6.2.9. Subgroup Analyses

The following subgroups will be assessed for some specific endpoints as noted.

Diabetes status (Yes/No) – defined as subjects with any condition in the Endocrine/Metabolic body system and medical term is coded to 'Type 2 diabetes melitus'.

Antihypertensive medication use (Yes/No) – Anatomical Therapeutic Chemical (ATC) codes starting with 'C02'; for blood pressure endpoints.

Prior statin medication use (Yes/No) – collected on eCRF Statin Use History; for lipoprotein evaluations.

If less than 10% of the ITT population subjects are not included in a subgroup, the subgroup analysis will not be performed.

6.3. Data Handling

6.3.1. Baseline Values

Baseline values are defined as the last value (using fasting blood sample values for lipoprotein and plasma glucose) prior to administration of investigational product on Day 1 (predose).

6.3.2. Missing Data

Primary analysis of efficacy endpoints will utilize observed data only; missing values will not be imputed. A sensitivity analysis using a last observation carried forward (LOCF) approach may be considered. If performed, the LOCF imputation will replace any missing value from a DB post-Baseline visit with the last available non-missing value from a DB post-Baseline visit.

6.3.3. Partial Dates

If only a partial date is available and is required for a calculation, the following standards will be applied:

- Diagnosis date (eg, NASH diagnosis date)
  - For missing day only: Day will be imputed as the first day of the month (ie, 01).

  - For missing day and month: Day and month will be imputed as the first day of the year (ie, 01 January).

- Start dates (eg, AE onset date or start date of medication)
  - For missing start day only: Day will be imputed as the first day of the month (ie, 01) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (eg, first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  - For missing start day and month: Day and month will be imputed as the first day of the year (ie, 01 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (eg, first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  - For missing start day, month, and year: Date will be imputed to the date being used in the calculation (eg., first dose date, informed consent date).
  - Imputed start dates must be prior to the stop date.
- Stop dates (eg, AE resolution date or stop date of medication)
  - For missing stop day only: Day will be imputed as the last day of the month (ie, 28, 29, 30, or 31).
  - For missing stop day and month: Day and month will be imputed as the last day of the year (ie, 31 December).
  - For missing stop day, year, and month: Date will be imputed as date of completion or discontinuation in the DB phase.
  - Imputed dates should not extend beyond the date of completion or discontinuation of the DB phase.
  - Imputed stop dates must be on or after the start date.

6.3.4. Data Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean, median, and IQR will be presented to 1 extra decimal place compared to the raw data, and the SD, SEM, LS Mean, and CIs will be displayed to 2 extra decimal places compared to the raw data. Coefficient of variation will be displayed with one decimal place.

The concentration versus time data as reported by the respective bioanalytical laboratory should be used without rounding for all analyses. The bioanalytical generated tables should not be reported to any greater accuracy than that of the concentration data. Default significant figures used for bioanalytical tables is three significant figures, with exception to time related parameters which will be reported as two decimal places.

Rounding will only occur after all calculations have been incorporated. For tables where rounding is required, rounding will be done to the nearest round-off unit; for example, when rounding to the nearest integer, values ≥XX.5 will be rounded up to XX + 1 (eg, 97.5 will round up to 98), whereas values <XX.5 will be rounded down to XX (eg, 97.4 will round down to 97).

Percentages based on frequency counts will be based on available data, and denominators will generally exclude missing values unless some form of imputation is defined or a 'missing' category is presented. For frequency counts of categorical variables, categories with zero counts will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of zero. Percentages based on frequency counts will be presented as a whole number (no decimal places), and values less than 1% will be presented as "<1%." Values less than 100% but that round up from 99.5% to 100% will be presented as ">99%."

6.3.5. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Days**: A duration expressed in days between one date (*date1*) and another later date (*date2*) will be calculated using the following formulas:

  duration in days = date2 – date1 + 1, where date2 ≥ date1

  duration in days = date2 – date1, where date2 < date1

- **Months**: A duration expressed in months is calculated as the number of days divided by 365.25 / 12.

- **Years:** A duration expressed in years between one date (*date1*) and another date (*date2*) is calculated using the following formulas:

  duration in years = (date2 – date1 + 1)/365.25, where date2 ≥ date1

  duration in years = (date2 – date1)/365.25, where date2 < date1

- **Age:** Age is calculated as the number of years from the date of birth (DOB) to the specified date, eg, date of informed consent (DOIC). If the month of DOIC < month of DOB or the month of DOIC=DOB and the day of DOIC < day of DOB, then the following formula is used:

  age (years) = year of DOIC – year of DOB – 1

  Otherwise, the following formula is used:

  age (years) = year of DOIC – year of DOB

- **Height**: Height measured in inches (in) are converted to centimeters (cm) using the following formula:

  height (cm) = height (in) × 2.54

- **Weight**: Weight measured in pounds (lb) are converted to kilograms (kg) using the following formula:

  weight (kg) = weight (lb) / 2.2046

- **Temperature**: Temperature measured in degrees Fahrenheit are converted to degrees Celsius using the following formula:

  temp (degrees Celsius) = 5 / 9 × (temp [degrees Fahrenheit] – 32)

- **Body Mass Index (BMI)**: BMI is calculated using height (cm) and weight (kg) using the following formula:

  BMI (kg/m^2) = weight (kg) / ([height (cm)/100]^2)

- **Change from Baseline**: Change from Baseline is calculated as:

  change from Baseline = post-Baseline value – Baseline value

- **Percentage Change from Baseline**: Percentage change from Baseline is calculated as:

  percentage change from Baseline = 100 × ([post-Baseline value – Baseline value] / Baseline value)

- **Geometric Mean:** In order to calculate a geometric mean and corresponding 95% CI, the following steps are used:
  - Transform the data by taking natural logarithms ($\log_e$)
  - Calculate the mean and 95% CI of the $\log_e$-transformed data
  - Exponentiate the mean and the lower and upper CIs back to the original scale in order to obtain the geometric mean and corresponding 95% CI.

  The geometric coefficient of variation (geometric CV%) is calculated as $100 \times \text{sqrt}(e^{SD\text{^}2}-1)$ where SD is the SD of the $\log_e$-transformed data.

- **Coefficient of Variation** - The coefficient of variation (CV%) will be calculated as the ratio of the standard deviation to the arithmetic mean using the following formula:

$$\text{Coefficient of variation} = \frac{\text{standard deviation}}{\text{arithmetic mean}}$$

6.3.6. Cardiovascular Risk Scores Calculations

Cardiovascular risk scores (ie, FRS and Reynolds) will be calculated at the time of data analysis using data collected via the Baseline Tobacco Use, Family Cardiovascular History eCRFs, and the central laboratory data. The calculations are as follows:

FRS:

The 10-year cardiovascular disease risk (%) for women = $[1 - 0.95012^{\exp(B - 26.1931)}] \times 100\%$, where

B = 2.32888 × natural logarithm (age) + 1.20904 × natural logarithm (total cholesterol) – 0.70833 × natural logarithm (high-density lipoprotein cholesterol) + 2.76157 × natural logarithm (systolic blood pressure if not treated) + 2.82263 × natural logarithm (systolic blood pressure if treated) + 0.52873 (if current smoker) + 0.69154 (if diabetic)

The 10-year cardiovascular disease risk (%) for men = $[1 - 0.88936^{\exp(B - 23.9802)}] \times 100\%$, where

B = 3.06117 × natural logarithm (age) + 1.2370 × natural logarithm (total cholesterol) – 0.93263 × natural logarithm (high-density lipoprotein cholesterol) + 1.93303 × natural logarithm (systolic blood pressure if not treated) + 1.99881 × natural logarithm (systolic blood pressure if treated) + 0.65451 (if current smoker) + 0.57367 (if diabetic) [Framingham Heart Study 2016].

Reynolds Score:

The 10-year cardiovascular disease risk (%) for women = $[1 - 0.98634^{(\exp(B - 22.325)}] \times 100\%$, where

B = 0.0799 × age + 3.137 × natural logarithm (systolic blood pressure) + 0.180 × natural logarithm (high-sensitivity C-reactive protein) + 1.382 × natural logarithm (total cholesterol) −1.172 × natural logarithm (high-density lipoprotein cholesterol) + 0.134 × hemoglobin A1c (%) (if diabetic) + 0.818 (if current smoker) + 0.438 (if family history of premature myocardial infarction) [Ridker, 2007].

The 10-year cardiovascular disease risk (%) for men = $[1 - 0.8990^{\exp(B - 33.097)}] \times 100\%$, where

B = 4.385 × natural logarithm(age) + 2.607 × natural logarithm(systolic blood pressure) + 0.963 ×natural logarithm(total cholesterol) − 0.772 × natural logarithm(high-density lipoprotein cholesterol) + 0.405 (if current smoker) + 0.102 × natural logarithm(high-sensitivity C-reactive protein) + 0.541 (if parental history of premature myocardial infarction) [Ridker, 2008].

6.3.7. Fibrosis Scores Calculations

Fibrosis scores (ie, NFS and APRI) will be calculated at the time of data analysis using data collected via the Medical History eCRF and the central laboratory data. The calculations are as follows:

NFS = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glucose(fasting glucose ≥110 mg/dL) / diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelets ($\times 10^9$/L) – 0.66 × albumin (g/dL)

APRI = ((AST(IU/L)/AST upper limit of normal)/ platelets ($x10^9$/L)) x 100

FIB-4 = (Age (years) x AST(IU/L))/(Platelets($x10^9$/L) x sqrt(ALT(IU/L)))

BARD score is calculated by designating 0 to 2 points to the following parameters: BMI ≥ 28 kg/m^2 = 1 point, BMI < 28 kg/m^2 = 0 point; AST/ALT ratio ≥ 0.8 = 2 points, AST/ALT ratio < 0.8 = 0 point; freshly recognized or preexisting diabetes mellitus type 2 = 1 point. A total of 2 to 4 points indicates significant fibrosis.

6.3.8. Anomalous Concentration Handling

Anomalous concentration values are those that, after verification of bioanalytical validity, are grossly inconsistent with the known or expected pharmacokinetic behavior of the drug. If an entire profile appears inconsistent with those of other subjects or previous periods, then the clinical pharmacologist/pharmacometrician will use her/his discretion regarding the handling of this data. The rationale will be documented within the CSR. Any such anomalous concentration data will also be identified in the relevant tables or as a stand-alone table of the CSR.

7. ANALYSIS POPULATIONS

7.1. Randomized Population

7.2. Intent-to-Treat (ITT) Population

All randomized subjects who receive any amount of investigational product within the DB phase will be included in the ITT Population. Treatment assignment will be based on the randomized treatment allocation.

7.3. Safety Population

The Safety Population will include all subjects who receive any amount of investigational product within the DB phase. Treatment assignment will be based on the actual treatment received.

7.4. Efficacy Evaluable (EE) Population

All subjects who complete the DB phase according to the indicated doses of investigational product and atorvastatin without any major protocol deviations that potentially affect the efficacy of the study drug will be included in the EE Population, which is the primary population used for efficacy analyses. If greater than 20% of the ITT Population subjects have such deviations as determined prior to database lock of the DB (see Section 8.2), then all efficacy analyses and selected other summaries will be repeated using the ITT Population.

7.5. OCA Pharmacokinetic (PK) Population

The PK Population will include all OCA treated subjects who consent to participate in the PK assessments and have at least one confirmed fasted OCA concentration. Subjects must have been fasting for at least 8 hours prior to dosing and must not have any major protocol deviations that potentially affect exposure levels.

8. STUDY POPULATION

8.1. Subject Disposition

Subject disposition information will be summarized and listed for all subjects. Summaries will include the following: the number of subjects randomized, the number of subjects in each analysis population, the number of subjects at each study site, the number of subjects completing the DB phase (Week 16) and each scheduled visit (Week 2, 4, 8, and 12), the primary reason for discontinuation from the DB phase, and the number of subjects enrolling in the LTSE. A subject will be considered as completing the DB phase if the subject has non-missing assessment of LDL metabolism at all scheduled visits (Weeks 2, 3, 4, 12, and 16). Percentages will be based on the ITT Population.

The reasons for discontinuation of investigational product (OCA/PBO) and discontinuation of study atorvastatin will be summarized in a similar manner.

8.2. Protocol Deviations

Protocol deviations for missed visits, missed assessments, out of window visits or assessments, and violations of inclusion/exclusion criteria will be determined based on available data. The clinical research associates will collect all other protocol deviations. Major protocol deviations identified during the DB phase that could potentially affect the conclusions of the study or result in a subject's removal from an analysis population will be classified as such prior to database lock of the DB phase. Major protocol deviations will be summarized by deviation category and treatment group. All protocol deviations and their classifications will be presented in a listing. Subjects with protocol deviations that result in a subject's removal from the ITT, Safety, EE, or PK Populations will be flagged in a listing.

8.3. Demographic and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent
- Age at informed consent categorized as < 65 years and ≥ 65 years
- Sex
- Race/ethnicity

Other Baseline characteristics will include the following:

- Weight (kg)
- Height (cm) at Screening visit
- BMI (kg/m^2)
- BMI categorized as < 30 kg/m^2 and ≥ 30 kg/m^2
- Liver fibrosis stage using NASH Clinical Research Network (CRN) scoring criteria categorized as Stage 1a, 1b, 1c, 2, 3, 4
- Liver fibrosis stage using NASH CRN scoring criteria categorized as Stage 1, 2 and Stage 3, 4
- Liver fibrosis stage using modified Ishak scoring criteria categorized as Stage 1, 2, 3, 4, 5, 6
- NAFLD Activity Score (NAS) and its components categorized as:
  - Steatosis: 0, 1, 2, 3
  - Hepatocellular Ballooning: 0, 1, 2
  - Lobular Inflammation: 0, 1, 2, 3
- NAS categorized as < 6 and ≥ 6 total points
- Diabetes status: Yes, No (defined as subjects with any condition in the Endocrine/Metabolic body system and medical term containing "diabetes type II" or

similar derivative, as collected on the eCRF Medical History; if unable to determine what type of diabetes, set diabetes status to yes)

- Concomitant medication use (ongoing on Day 1. If it cannot be determined whether the medication was ongoing at the Day 1 visit due to a partial start or stop date, then it will be counted as ongoing.)
  - Vitamin E (ATC codes = 'A11HA' and Trade name = 'E VITAMIN')
  - TZD (ATC codes starting with 'A10BG')
  - Antidiabetic medication (ATC codes starting with 'A10')
  - Antihypertension medication (ATC codes starting with 'C02')
- Screening fasted serum LDL cholesterol concentration categorized as ≤ and > 125 mg/dL
- Screemomg HDL cholesterol concentration (mg/dL) categorized as ≥ lower limit of normal (LLN), < LLN
- Baseline liver function test results as a continuous variable and categorized as follows by the LLN and the upper limit of normal (ULN) unless otherwise specified:
  - ALT: ≤ 40 U/L, > 40 U/L and ≤ ULN, > ULN
  - AST: ≤ 40 U/L, > 40 U/L and ≤ ULN, > ULN
  - Direct Bilirubin: ≤ ULN, > ULN
  - Total Bilirubin: ≤ ULN, > ULN
  - Platelets: ≥ LLN, < LLN

Arithmetic summary statistics as described in Section 6.2.1 will be presented for age, weight, height, BMI, and key liver function tests. Frequency counts and percentages will be presented for age groups, sex, race/ethnicity, BMI categories, liver fibrosis stage categories, NAS, concomitant medication use, diabetes status, LDL and HDL cholesterol categories, and key liver function test categories. Race and ethnicity will be summarized as follows:

- Race
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino

- Not reported
- Unknown

Demographic and Baseline characteristics will be summarized for the ITT, Safety, PK, and EE Populations (if warranted). All demographic and Baseline characteristics will be presented in data listings.

8.4. NASH Disease History

Baseline NASH disease characteristics will be summarized using data collected from the Medical History eCRF. Assessments include the following:

- Age at NASH diagnosis
- Age at NASH diagnosis categorized as < 50 years and ≥ 50 years
- Duration of NASH in years at time of informed consent
- Duration of NASH categorized as ≤ median years and > median years
- Method of confirmation for NASH diagnosis categorized as liver biopsy, elevated liver enzymes, non-invasive imaging, or other.

Arithmetic summary statistics as described in Section 6.2.1 will be presented for the age at NASH diagnosis and the duration of NASH. All other categorical NASH disease characteristics will be summarized using frequency counts and percentages. NASH disease history will be summarized for the ITT Population and, if warranted, the EE Population. NASH disease history will be presented in a data listing.

8.5. Alcohol Use Disorders Identification Test (AUDIT)

Baseline, Day 1, Week 16, and Early Termination/End of Study AUDIT scores will be summarized using arithmetic summary statistics as described in Section 6.2.1 and presented in a data listing.

8.6. Tobacco Use

Arithmetic summary statistics as described in Section 6.2.1 will be presented for duration of use (among former and current users) and amount of daily cigarette, cigar, smokeless tobacco (amount of pinches), pipe (amount of pipefuls), and other tobacco use (among former and current users) at Screening. Frequency counts and percentages will be presented for tobacco use (Yes/No) and frequency of use for each type of tobacco (among former and current users). Tobacco use data will be presented in a data listing.

8.7. Statin History

Baseline statin history use characteristics will be summarized using data collected from the Statin History Use eCRF. Assessments include the following:

- Statin use (Yes/No)
- Name of statin used

- Last statin medication dose
- Duration of statin use (years)
- Primary reason statin stopped

All categorical statin history will be summarized using frequency counts and percentages. Overall statin use will be summarized using the ITT Population as the denominator. The other characteristics will be summarized for each statin used with the number of subjects using the corresponding statin as the denominator. The continuous characteristics for each statin will be summarized using arithmetic summary statistics as described in Section 6.2.1. Subjects may have used more than 1 statin. All statin use history data will be listed (including comments).

8.8. Family Cardiovascular History

Baseline family cardiovascular history will be summarized using data collected from the Family Cardiovascular History (First Degree) eCRF. Assessments include the following:

- Family history of myocardial infarction, angina or dyslipidemia? (Yes/No)
- Person with event (father, mother, brother, sister, other - specify)
- Myocardial infarction (Yes/No) and age at time of event (categorical)
- Angina (Yes/No) and age at time of event (categorical)
- Dyslipidemia (Yes/No)

All categorical family cardiovascular history will be summarized using frequency counts and percentages for the ITT Population. Subjects may have more than one family member and type of event recorded. All family cardiovascular history data will be listed.

8.9. General Medical History

Verbatim medical history terms on eCRFs will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA; version 18.1). Frequency counts and percentages of the number of subjects reporting an abnormal Baseline medical history will be summarized by MedDRA system organ class and preferred term using the ITT Population.

Summaries that are displayed by system organ class and preferred term will be ordered by descending order of incidence for all OCA treated subjects of system organ class and by preferred term within each system organ class.

Medical History data will be presented in a data listing.

8.10. Prior and New Concomitant Medications

Verbatim terms on eCRFs will be mapped to ATC class and preferred term using the World Health Organization Drug Dictionary Enhanced (WHODDE; WHO-DDE-B2 Dec2015).

Pretreatment medications are those medications with start and stop dates prior to the first dose of investigational product in the DB phase. Prior concomitant medications are those medications started prior to, and continued after, the first OCA dose in the DB phase. New concomitant

medications are those medications that were started after the first OCA dose in the DB phase. If it cannot be determined whether the medication was a new concomitant medication due to a partial start or stop date or if the medication is taken on the same date as the first OCA dose in the DB phase, then it will be counted as a new concomitant medication.

Pretreatment medications will be presented in listings only. Prior and new concomitant medications will be summarized by World Health Organization ATC class and preferred term using the ITT Population. New concomitant medications will be summarized separately. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class and preferred name. A subject is counted once when 1 or more medications is reported at the ATC class or preferred term level. Each summary table will be ordered by descending order of incidence, for all OCA-treated subjects, of ATC class and preferred term within each ATC class.

Prior and new concomitant medications will be presented in a data listing.

9. EFFICACY ANALYSES

The primary and secondary efficacy analyses will be based on the EE Population. Analyses on the ITT Population will only be performed if greater than 20% of ITT subjects are excluded in the EE Population. All analyses are to be carried out on observed data, as there are no imputations planned. The efficacy data are a result of the centralized, specialized nuclear magnetic resonance (NMR) lipoprotein assay and the central laboratory serum chemistry. All analyses of lipoprotein metabolism will include fasted samples only. For all lipoprotein concentration values, the serum chemistry panel results will be used. For particle size and particle concentration, the NMR lipoprotein assay results will be used. Sensitivity analysis may be performed with the NMR lipoprotein concentration results.

9.1. Primary Efficacy Analyses

The primary efficacy analysis, changes in LDLc, LDLs, and LDLpc at Week 16 (end of DB) from Baseline will be summarized by treatment group, using the EE Population.

The observed values, change from Baseline, and percentage change from Baseline will be summarized by treatment group and visit using arithmetic summary statistics as described in Section 6.2.1.

In order to provide estimates of the change from Baseline and corresponding 95% CI, the ANCOVA methods described in Section 6.2.3 will be applied with change from Baseline as the dependent variable, including treatment group, and randomization stratification factor as fixed effects and Baseline as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable. Model fit will be assessed in order to determine the validity of the estimates. Estimates of LS means, SEs, and 95% CIs will be presented by treatment group.

The comparison of LDLc, LDLs, and LDLpc change from baseline and percentage change from baseline values between each active treatment group and placebo group at each DB post-Baseline visit will be performed as exploratory analyses. Estimates of the LS mean difference

between each active treatment group and placebo group, the SE of the difference, and 95% CI of the difference will be presented.

The relationship of OCA dose level and changes in LDLc will be explored using the Jonckheere-Terpstra (JT) test.

Sensitivity analysis for the primary efficacy analysis will be performed using the ITT Population using both the ANCOVA methods described in Section 6.2.3 and the ANCOVA with repeated measures methods described in Section 6.2.4.

9.2. Secondary Efficacy Analyses

The secondary efficacy parameters will be analyzed in the same manner as the primary efficacy variables. Descriptive statistics will be generated and will include change from Baseline, percentage change from Baseline at each DB post-Baseline visit, and estimates of LS means, SEs, and 95% CIs presented by treatment group.

9.2.1. Lipoprotein Metabolism

The secondary parameters related to lipoprotein metabolism include HDLc, HDLs, HDLpc, VLDLc, VLDLs, VLDLpc, TG, and total cholesterol concentrations; and ApoA1, ApoB, ApoE, ApoCII, ApoCIII, Lp(a), and PCSK9 concentrations.

9.2.2. Reverse Cholesterol Metabolism

The secondary parameters related to reverse cholesterol metabolism include pre-β1 HDL concentration, macrophage cholesterol efflux, LCAT activity, and CETP activity.

9.3. Exploratory Efficacy Analyses

9.3.1. Liver Biochemistry and Markers of Liver Function

The following laboratory parameters will be summarized by treatment group: albumin, ALP, ALT (isoenzymes), AST, direct bilirubin, GGT, INR, total bilirubin, and platelets.

Analyses of observed laboratory values will be carried out using a repeated measures ANCOVA model with change from Baseline as the dependent variable, including treatment group, and randomization stratification factors as fixed effects and Baseline as a covariate as described in Section 6.2.3. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Arithmetic summary statistics as described in Section 6.2.1 will be used to summarize the laboratory values by treatment group and visit. The results, change from baseline, and percentage change from baseline, as well as estimates of LS means, SEs, and 95% CIs, will be presented by treatment group. Estimates of the mean difference between each active treatment group and placebo group, the SE of the difference, and 95% CI of the difference will be presented.

9.3.2. Markers of Liver Inflammation, Hepatic Apoptosis, and Fibrosis

Markers of liver inflammation, hepatic apoptosis and/or fibrosis include IL-6, hs-CRP, TNF-α, CK-18-M30, and CK-18-M65. These biomarkers will be summarized by treatment group using arithmetic summary statistics as described in Section 6.2.1 at Baseline and at each DB post-Baseline visit. The absolute and percentage change from Baseline will be analyzed using the Wilcoxon Rank Sum Test to compare active treatment groups and placebo. The median differences and 95% CI of the median differences between treatment groups will be constructed using a Hodges-Lehmann estimate as described in Section 6.2.5 . The protocol specifies the Sign Test may be used when the median differences between treatments are not symmetrical around the median. The median differences between treatments will always be symmetrical, therefore, the Sign Test will not be used.

9.3.3. Glycemic Control

Glycemic control measures include fasting glucose, fasting insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR. These measures will be summarized using arithmetic summary statistics as described in Section 6.2.1 at Baseline and at each DB post-Baseline visit by treatment group. The change from Baseline will also be summarized. Baseline is defined as the last fasting assessment prior to the administration time of the first OCA dose. Treatment groups will be compared using an ANCOVA model with change from Baseline as the dependent variable, including treatment group, and randomization stratification factors as fixed effects and Baseline as a covariate as described in Section 6.2.3. The same analysis will be carried out using percentage change from Baseline as the dependent variable. Estimates of LS means, SEs, and 95% CIs will be presented by treatment group. Estimates of the mean difference between each active treatment group and placebo group, the SE of the difference, and 95% CI of the difference will be presented. The distribution of glycemic control measures will be evaluated for normality assumptions. If normality assumptions are violated, non-parametric methods, such as a rank ANCOVA model, will be used.

Subgroup analyses will also be presented by diabetes status, excluding the randomization stratification factors from the ANCOVA model.

9.3.4. Noninvasive Radiological Liver Fibrosis Measurements

Noninvasive radiological methods to assess liver stiffness and steatosis via TE will be conducted at selected centers where the devices are available. Liver stiffness values (kPa) and CAP (dB/m) values (based on available data) will be summarized by treatment group using arithmetic summary statistics as described in Section 6.2.1 at Baseline and at each DB post-Baseline visit. Treatment groups will be compared using a ANCOVA model at each visit with change from Baseline as the dependent variable, including treatment group and Baseline fibrosis stage based on NASH CRN criteria, and randomization stratification factors as fixed effects and Baseline as a covariate.

The proportion of fibrosis improvement based on liver stiffness value will be summarized using arithmetic summary statistics as described in Section 6.2.1 by treatment group at Week 16 of the DB phase. Fibrosis improvement is defined as any reduction in liver stiffness value. Treatment groups will be compared using a Cochran–Mantel–Haenszel (CMH) test stratified by the

Baseline fibrosis stage based on NASH CRN criteria and randomization strata. Missing values will be considered a nonresponse.

The correlation of Baseline liver stiffness value with baseline fibrosis stage based on NASH CRN criteria (Stage 1, 2 or 3, 4) and modified Ishak scoring criteria (Stage 1, 2, 3, 4, 5, 6) based on biopsy will also be assessed using Spearman's rank correlation coefficient. Arithmetic summary statistics of Baseline liver stiffness by each fibrosis stage scoring will be presented. A box and whisker plot of the data also will be produced. The correlation analysis and corresponding plot will be performed using the ITT population.

9.3.5. Noninvasive Scores and NAFLD Liver Fibrosis Scores

Noninvasive scores of liver fibrosis including FIB-4, APRI, and NFS will be summarized with descriptive statistics at Baseline and each DB post-Baseline visit. In addition, change and percentage change will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. The median differences and 95% CI of the median differences between treatment groups will be constructed using Hodges-Lehmann estimate.

In addition, BARD score shift changes from Baseline to each DB post-Baseline visit will be summarized by treatment group.

9.3.6. Anthropometric Measures and Blood Pressure

Anthropometric measures (ie, body weight, waist and hip circumference measurements, BMI, and waist-to-hip ratio calculations) and blood pressure will be summarized using arithmetic summary statistics as described in Section 6.2.1 at Baseline and at each DB post-Baseline visit. Change and percentage change from baseline will also be summarized in the same manner. Re-tests or unscheduled visit results after the first OCA dose administration time will not be summarized but will be included in the data listings.

Treatment groups will be compared using an ANCOVA model with change from Baseline as the dependent variable, including treatment group, and randomization stratification factors as fixed effects and baseline as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable. Estimates of LS means, SEs, and 95% CIs will be presented by treatment group. Estimates of the mean difference between each active treatment group and placebo group, the SE of the difference, and 95% CI of the difference will be presented.

Subgroup analyses will also be presented by diabetes status, excluding the randomization stratification factors from the ANCOVA model. Subgroup analyses of blood pressure will also be presented by use of antihypertensive medications.

9.3.7. Cardiovascular Risk Scores

Cardiovascular risk scores including FRS and Reynolds scores will be calculated at the time of data analysis using the formulas in Section 6.3.6. These scores will be summarized by treatment group and sex using arithmetic summary statistics as described in Section 6.2.1 at Baseline and at each DB post-Baseline visit. The change and percentage change from Baseline will also be summarized.

9.3.8. Cardiovascular Markers of Risk

Cardiovascular markers of risk including adiponectin, PAI-1, and BNP will be summarized by treatment using arithmetic summary statistics as described in Section 6.2.1 at Baseline and at each DB post-Baseline visit. The change and percentage change from Baseline will also be summarized.

While the protocol states PAI-1 and BNP will be stored for future analysis, it was later determined the samples would not maintain stability for future analysis, and thus were assayed for analysis.

10. EXPLORATORY PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

Total OCA will be calculated as the micromolar concentration sum of unconjugated OCA, glyco-OCA, and tauro-OCA. Concentrations will be converted from ng/mL units to micromolar units as follows: concentration (µM) = concentration (ng/mL) / molecular weight (MW). The MW weights for OCA are as follows: unconjugated OCA = 420.6 g/mol, glyco-OCA = 477.7 g/mol, and tauro-OCA = 527.8 g/mol. Total OCA in micromolar units can be converted to mass equivalents of OCA as follows: concentration (ng/mL) = concentration (µM) * 420.6. The PK Population will be used in the analyses of OCA PK (Day 1 and Week 16).

Further population PK/PD analyses may be conducted utilizing a separate appropriate plan to describe analysis methods. The methods and results would be included in a separate report.

10.1. Pharmacokinetic Measures

At selected investigational sites, subjects will have the option to provide blood samples for measurement of OCA concentrations. On Day 1 and Week 16, PK samples will be collected within 30 minutes prior to dosing (predose) and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 1-hour sample is collected.

10.2. Pharmacokinetic Data Handling

10.2.1. Missing Values

The lack of concentration values or dosing information due to failure to collect the sample or dosing information, a lost or compromised sample or due to the subject's early termination from the study may be termed "missing" in the dataset. If a missing value occurs for the time point prior to the first study drug administration, the value is set to zero. Otherwise, no imputation of missing values will be performed.

10.2.2. Results Below Limit of Quantification (BLQ)

For the purposes of PK parameter estimation, the following rules for BLQ results will be followed:

- BLQ values that occur prior to the first quantifiable concentration will be set to zero

- BLQ values occurring between two quantifiable values will be set to the lower limit of quantification (LLOQ) divided by 2
- BLQ values occurring after the last quantifiable value will be set to missing

10.2.3. PK Sampling Times

Actual (rather than nominal) PK sample collection times will be used for the purposes of PK parameter estimation.

10.2.4. Decision Paradigm for Reprocessing Samples

The PK sample reprocessing paradigm will be detailed in the bioanalytical report. Intercept Clinical Pharmacology may issue a request for sample reprocessing if an observed concentration represents an unexplained, significant deviation from temporal consistency with the prior and following samples in the affected subject's concentration-time profile. Reprocessing will only take place if sufficient sample volume exists.

10.2.5. Anomalous Concentration Handling

Anomalous concentration values are those that, after verification of bioanalytical validity, are grossly inconsistent with the known or expected pharmacokinetics behavior of the drug. The clinical pharmacologist will use his/her discretion regarding the handling of this data. The rationale will be documented within the study report. Any such anomalous concentrations data will be documented in the clinical study report.

10.2.6. Representation of Mean Concentrations

All values reported as below the limit of quantitation (BLQ) will be replaced with zero for mean representation in figures. In the tables presenting summary statistics of concentration-time series, the total number of values (n) and the number of values that are BLQ will be presented to allow appropriate interpretation of the data.

If missing observations at a nominal time point exceed 50% of the observations collected at that nominal time point, summary statistics for the time point will not be calculated.

If the mean concentration value is less than the LLOQ, then the mean concentration value will be set to BLQ in tables and missing in graphics.

The central tendency and dispersion of OCA (and its conjugates and metabolite) concentration-time data will be graphically represented as the Mean (optional +/- SD) by nominal time point in linear scale and semi-log scale by visit. Median by nominal time point representations may also be presented if deemed appropriate.

PK samples that have a significant time deviation from the planned sampling time will be considered as "missing" for the calculation of concentration summary statistics at that nominal time point. Acceptable PK sampling time windows are defined in the table below:

Nominal PK Sampling Time	Acceptable Sampling Window

Pre-dose	Within 30 minutes prior to dosing
0.5 h, 0.75 h	+/- 5 minutes relative to nominal
1 h	+/- 10 minutes relative to nominal
1.5h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h	+/- 15 minutes relative to nominal

Only samples from subjects with confirmed fasting of ≥ 8 hours prior to dosing will be included in summaries. Individual subject plasma concentrations, including derived concentrations for total OCA, will be listed by analyte and formulation and summarized with descriptive statistics on Day 1 and on Week 16 by treatment group as defined in Section 6.2.1 and Section 6.2.7, including geometric coefficient of variation (CV%).

10.3. Pharmacokinetic Analysis

10.3.1. Pharmacokinetic Methods

PK parameters for OCA and its conjugates, and total OCA will be determined using standard non-compartmental methods. Pharmacokinetics will be summarized in tabular and graphical forms. The primary PK parameter estimations in this study are:

For both Day 1 and Week 16:

- C_{max} (ng/mL): Maximum observed concentration obtained by inspection of the data. If all observations are below the limit of quantification (BLQ), C_{max} will be reported as zero.
- t_{max} (h): First time at which C_{max} is observed and is obtained by inspection of the data. If all observations are BLQ, t_{max} will be reported as not determined (ND).
- AUC_{0-6} (hr*ng/mL): Area under the concentration versus time curve from zero time until the last sampling time (hour 6).
  - The linear interpolation rule should be used for estimation of area under the concentration-time curve (AUC).
  - Where the clinical pharmacologist identifies that another method is more appropriate, the reason for this decision should be documented.
  - A minimum of 4 measurable values are required for AUC calculation
  - For last sampling times >6 hours, AUC_{0-6} will be interpolated. For last sampling times from 5.75 to 6 hours, AUC_{last} will be reported for AUC_{0-6}. For last sampling times <5.75 hours, AUC_{0-6} will not be reported.
- Dose-normalized versions of C_{max} and AUC_{0-6} will be calculated for Day 1 and Week 16.

- Metabolite ratios based on C_{max} (MRC_{max}) and AUC_{0-6} ($MRAUC_{0-6}$) will be calculated:

  MR C_{max} = (C_{max} conjugate or metabolite / C_{max} parent) x (molecular weight parent / molecular weight conjugate or metabolite)
  MR AUC_{0-6} = (AUC_{0-6} conjugate or metabolite / AUC_{0-6} parent) x (molecular weight parent / molecular weight conjugate or metabolite)

Accumulation [only for OCA and its conjugates]:

- Steady-state accumulation ratios based on C_{max} (R_{ac} C_{max}) and AUC_{0-6} (R_{ac} AUC_{0-6}) will be calculated:

  R_{ac} C_{max} = Week 16 C_{max}/Day 1 C_{max}

  R_{ac} AUC_{0-6} = Week 16 AUC_{0-6}/Day 1 AUC_{0-6}

Additional parameters may be calculated in order to further characterize PK, if deemed necessary.

10.3.2. Reporting and Significant Figures

The concentration data as reported by the respective bioanalytical group should be used without rounding for all analysis. The non-compartmental parameters should not be reported to any greater accuracy than that of the concentration data. Default significant figures used for reporting in text and tables of the study report is 3 significant figures, except for time related parameters (h) and for geometric least squares mean ratios. Time related parameters (h) which will be presented with 2 decimal places. Geometric least squares ratios will be presented with 2 decimal places.

In the instance where the full parameters set (as defined in the analysis plan) cannot be estimated, the parameters that can be estimated will be reported. The term "NR" (not reported) may be used to denote that a value cannot be reported for a particular profile.

10.4. Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses

The PK population will be used for all PK analyses. The ITT population will be used for all PD analyses. Using the PK population, scatter plots of the Week 16 actual values and change from Baseline in LDL cholesterol, particle size, and particle concentration, C4, FGF-19, and hs-CRP will be created versus total OCA plasma AUC_{0-6} and C_{max}. Additional PK/PD correlations may be identified and reported as deemed appropriate.

10.5. Bile Acid Pharmacodynamics

Analysis of conjugated and unconjugated bile acids may be undertaken per the protocol.

Bile acids include the following: total bile acids, UDCA (unconjugated-UDCA, glyco-UDCA, tauro-UDCA), chenodeoxycholic acid (CDCA) (unconjugated-CDCA, glyco-CDCA, tauro-CDCA), lithocholic acid (LCA) (unconjugated-LCA, glyco-LCA, tauro-LCA), cholic acid (CA) (unconjugated-CA, glyco-CA, tauro-CA), and deoxycholic acid (DCA) (unconjugated-DCA, glyco-DCA, tauro-DCA).

The bile acid assay comprises 15 sub-component bile acid concentrations that will be used to create totals of the individual bile acid concentrations. Bile acid concentrations will be converted from ng/mL units to micromolar units (μM) as follows: Concentration (μM) = Concentration (ng/mL) / molecular weight (MW). Bile acids totals should be summed on a molar basis (eg μM). The MWs of the bile acids and their conjugates are presented in Table 1. For each bile acid, the assay will provide 3 subcomponent values that will need to be summed to produce the total bile acid value, as shown below in Table 1. As an example, the total UDCA concentration would be the sum of the glyco-, tauro-, and parent molecules.

Table 1: Bile Acids and Their Sub-Components

Derived	**Sub-components (molecular weight)**		
Total UDCA	Glyco-UDCA (449.6 g/mol)	Tauro-UDCA (499.7 g/mol)	UDCA (392.6 g/mol)
Total CDCA	Glyco-CDCA (449.6 g/mol)	Tauro-CDCA (499.7 g/mol)	CDCA (392.6 g/mol)
Total DCA	Glyco-DCA (449.6 g/mol)	Tauro-DCA (499.7 g/mol)	DCA (392.6 g/mol)
Total CA	Glyco-CA (465.6 g/mol)	Tauro-CA (515.7 g/mol)	CA (408.6 g/mol)
Total LCA	Glyco-LCA (433.6 g/mol)	Tauro-LCA (483.7 g/mol)	LCA (376.6 g/mol)

Individual total bile acids are derived as the sum of all bile acids (total UDCA, total CDCA, total DCA, total CA, and total LCA).

Total endogenous bile acids are derived as the sum of all bile acids, excluding all forms of OCA and UDCA.

Proportions of each bile acid are derived as the individual bile acid total divided by total bile acids (eg, total UDCA/total bile acids).

The ITT population will be used to summarize the total bile acid concentrations. The total bile acids, total endogenous bile acids, individual bile acid totals, and each of the bile acid proportions will be summarized by treatment group using descriptive statistics. BLQ values will be treated as one-half the lower limit of quantification [(LLOQ/2)]. For total UDCA and total endogenous bile acid, the change from Baseline concentrations within each treatment group will be compared using a paired t-test. Only samples from subjects that have a confirmed fasting (based on eCRF) of approximately 8 hours or more prior to the subject's visit will be included in the analysis.

11. SAFETY ANALYSES

All safety analyses will be based on the Safety Population. The AE, vital signs, clinical laboratory evaluations, and ECG analyses are defined as secondary endpoints per the protocol. The anthropometric measures, blood pressure, and cardiovascular risk scores are defined as exploratory efficacy endpoints per the protocol.

11.1. Extent of Exposure

11.1.1. Investigational Product (OCA or Placebo)

Subjects may change their OCA or placebo dosing regimen while on treatment during the DB if deemed necessary by the Investigator. The duration of investigational product exposure at DB will be calculated as follows:

- Exposure to investigational product = {[(Date of last investigational product dose – Date of 1st investigational product dose) +1]

Total investigational product (mg) exposed to subject will be calculated by adding the doses taken by a subject during the study and will be summarized using descriptive statistics.

Subject's overall compliance (%) with investigational product will be calculated as follows:

- (# of investigational product tablets consumed during study / # of investigational product tablets expected to be consumed during study) × 100

where # of investigational product tablets consumed during study = # of days on treatment based – any missed doses, and # of investigational product tables expected to be consumed during study is the total # of days on study drug based on treatment start and stop dates, excluding drug holidays

Subject compliance with investigational product will be summarized by treatment group using descriptive statistics. Percent compliance will be summarized separately for subjects who completed the study versus those who withdrew early so as to distinguish between those subjects who were compliant throughout the entirety of the study versus those who were compliant until they withdrew from the study.

Additional summaries will present the number and percentage of subjects with any drug interruption and drug discontinuation. Denominators for calculating percentages will be based on the number of subjects who received at least one dose in the treatment group summarized.

All exposure data will be presented in a by-subject data listing.

11.1.2. Atorvastatin

The weighted average daily dose (WADD) of atorvastatin, the study medication, will be calculated as:

$$\text{WADD} = \frac{\sum_{\text{all doses}} (\text{dose} \times \text{number of days at specified dose})}{(\text{total number of days on atorvastatin (including any days on drug holiday)})}$$

For example, for a subject on 10 mg atorvastatin for 6 weeks and 20 mg atorvastatin for 6 weeks without any days off atorvastatin, WADD would be calculated as:

$$\text{WADD} = [(10 \text{ mg} \times 42 \text{ days}) + (20 \text{ mg} \times 42 \text{ days})]/ (84 \text{ days}) = 15 \text{ mg}$$

The WADD will also be categorized as ≤ 12 mg atorvastatin, > 12 mg to 20 mg atorvastatin, >20 mg atorvastatin.

Subject's overall compliance (%) with study medication will be calculated as follows:

- (# of study medication tablets consumed during study / # of study medication tablets expected to be consumed during study) × 100

Subject compliance with atorvastatin will be summarized by treatment group using descriptive statistics. Percent compliance will be summarized separately for subjects who completed the study versus those who withdrew early so as to distinguish between those subjects who were compliant throughout the entirety of the study versus those who were compliant until they withdrew from the study.

Additional summaries will present the number and percentage of subjects with any drug interruption and drug discontinuation. Denominators for calculating percentages will be based on the number of subjects who received at least one dose in the treatment group summarized.

All exposure data will be presented in a by-subject data listing.

11.2. Adverse Events (AEs)

AE data will be collected from the time that signed informed consent is obtained until the subject fully completes her/his study participation of the study.

Pre-treatment AEs and treatment-emergent adverse events (TEAEs) will be summarized. TEAEs are defined as any AEs that newly appear, increase in frequency, or worsen in severity following initiation of investigational product. If it cannot be determined whether the AE is Treatment-Emergent due to a partial onset date, then it will be counted as treatment-emergent. Verbatim terms on eCRFs will be mapped to preferred terms and system organ classes using MedDRA (version 18.1).

Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence, for all OCA-treated patients, of system organ class and by preferred terms within each system organ class. Summaries of the following types will be presented by treatment group:

- Overall summary of TEAEs
- Subject incidence of pre-treatment AEs and the total number of entries by MedDRA system organ class and preferred term
- Subject incidence of TEAEs and the total number of entries by MedDRA system organ class and preferred term
- Subject incidence of drug-related TEAEs by MedDRA system organ class and preferred term. Related AEs are those with relationships reported as “Definite,” “Probable,” “Possible,” or with a missing relationship. This analysis will be performed for relationship to investigational product and to atorvastatin.
- Subject incidence of liver biopsy-related TEAEs by MedDRA system organ class and preferred term. Related AEs are those with relationships reported as “Definite” or AEs with a missing relationship.
- Subject incidence of serious TEAEs by MedDRA system organ class and preferred term

- Subject incidence of TEAEs leading to investigational product withdrawal by MedDRA system organ class and preferred term
- Subject incidence of TEAEs leading to study medication withdrawal by MedDRA system organ class and preferred term
- Subject incidence of TEAEs leading to study discontinuation by MedDRA system organ class and preferred term
- Subject incidence of TEAEs leading the investigational product withdrawal, study medication withdrawal, or study discontinuation by MedDRA system organ class and preferred term
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and maximum severity will be presented. At each level of subject summarization, a subject is classified according to the maximum severity if the subject reported one or more events. AEs with missing severity will be considered severe for this summary.

The summaries above will be repeated presenting only preferred term ordered by descending order of incidence, for all OCA treated subjects, excluding system organ class.

In addition, other than Follow-up TEAEs, these summaries will be repeated for the time period up to Week 4, to evaluate the effects of OCA alone and in combination with atorvastatin. These analyses will include TEAEs with date of onset prior to the start of atorvastatin.

The following listings will be presented by subject:

- All AEs
- Serious AEs (subset of the AEs where serious is marked as "Yes")
- Death information will be provided in a separate listing, should any deaths occur
- AE's leading to withdrawal of investigational product
- AEs leading to withdrawal of study medication
- AEs leading to Study Discontinuation

11.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) are pruritus, hepatic disorders, dyslipidaemia, and myopathy. For each of these AESI, subject incidence of TEAEs and the total number of entries by MedDRA system organ class and preferred term will be presented. In addition, for each AESI, the time to first onset and time to most severe event will be summarized using descriptive statistics.

- Time to first onset of AESI event
  - The time to the onset of the first event will be calculated by date of onset of first event – date of first dose of investigational product + 1.
  - Subjects without AESI events will be censored at the date of completion or early termination.

- Time to start of most severe of AESI event
  - The time to the onset of the most severe event will be calculated by date of onset of most severe event – date of first dose of investigational product + 1.
  - Subjects without AESI events will be censored at the date of study completion or early termination.

11.3.1. Pruritus

Treatment-emergent pruritus, defined as any preferred term that contains "*Prur*," will be summarized separately by the MedDRA SOC, treatment group, and PT as a subset of all TEAEs.

An analysis of treatment-emergent pruritus event days per subject years on study will be performed. The days at each severity grade, including the total days of event, and the percent of event days on study at each severity grade, including the total, will be summarized.

In order to explore the relationship between pruritus and the investigational product, the following time-to-event analyses will be performed:

- Total duration of treatment-emergent pruritus
  - Duration of each treatment-emergent pruritus event will be calculated as end date – start date +1. For events that are ongoing at Week 16, the Week 16 date will be used as the end date. The sum of each event will be summed for an overall by-patient duration during the DB phase.
- Time to first onset of treatment-emergent pruritus
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Subjects who never report an AE of pruritus will be censored at the date of completion or discontinuation.
- Time to onset of the most severe treatment-emergent pruritus
  - The time to the start of the most severe pruritus will be calculated by date of onset of the most severe pruritus – date of first dose of investigational product + 1.
  - Subjects who never report a severe AE of pruritus will be censored at the date of study completion or discontinuation.
- Time to resolution of the most severe treatment-emergent pruritus event
  - The time to resolution of the most severe event of treatment-emergent pruritus will be calculated by date of resolution of the most severe event of treatment-emergent pruritus – start date of the most severe event of treatment-emergent pruritus + 1.
  - Subjects whose most severe event of treatment-emergent pruritus is ongoing will be censored at the date of study completion or discontinuation. For subjects that are lost to follow-up, the last contact date will be used.
  - Only subjects that report a pruritus event are included in this analysis.

- For subjects reporting multiple events at the most severe level, the event with the longest duration will be used.
- Separate summaries will be presented for those who discontinue due to pruritus.

The analysis of time-to-event will include the number of subjects with the event (first onset, most severe), the number of subjects without the event (censored), descriptive statistics of total duration of pruritus, descriptive statistics of time for those with an event, and range in days for all subjects. Kaplan-Meier (KM) estimates will be calculated by treatment group. The quartiles, including the median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve" for each treatment group, with the number at risk identified. The comparison of OCA to placebo will be summarized using a log-rank test stratified by randomization strata factors.

11.3.2. Hepatic Disorders

Hepatic disorders are defined as events included in the Hepatic Disorders Standardized MedDRA query (SMQ), excluding the following sub-SMQs: Congenital, familial, neonatal and genetic disorders of the liver; Hepatitis, non-infectious; Liver infections; and Pregnancy-related hepatic disorders. See Appendix B for a list of the preferred terms and their associated codes.

11.3.3. Dyslipidaemia

AE lipid profile changes, defined in the Dyslipidaemia SMQ, will be reported. See Appendix C for a list of the preferred terms and their associated codes.

11.3.4. Myopathy

Myopathy is defined as any condition in the Rhabdomyolysis and Myopathy SMQs. See Appendix D for a list of the preferred terms and their associated codes.

11.4. Adjudicated Cardiovascular Events

All suspected cardiovascular events that occur after administration of the first dose of investigational product will be reviewed and adjudicated by the Cardiovascular Adjudication Committee according to criteria defined in their charter. Events adjudicated by the committee will be included in the cardiovascular event analysis.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence, for all OCA-treated patients, of system organ class and by preferred terms within each system organ class. All summaries of incidence will include the associated exact binomial 95% CI. Summaries of the following types will be presented by treatment group:

- Subject incidence of adjudicated cardiovascular events and the total number of entries by MedDRA system organ class and preferred term

In order to explore the relationship between adjudicated cardiovascular events and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of adjudicated cardiovascular event

  - The time to the start of the first event will be calculated by date of onset of first event – date of first dose of investigational product + 1.
  - Subjects without adjudicated events will be censored at the date of completion or early termination.
- Time to onset of most severe adjudicated cardiovascular event
  - The time to the onset of most severe event will be calculated by date of onset of most severe event – date of first dose of investigational product + 1.
  - Subjects without adjudicated events will be censored at the date of completion or early termination.

The incidence and time-to-event analysis for adjudicated cardiovascular events will be repeated for suspected cardiovascular events.

11.5. On-Study Medical or Surgical Procedures

On-study medical or surgical procedure data will be collected from the time that signed informed consent is obtained until the subject fully completes her/his study participation of the study. Verbatim procedure terms on eCRFs will be mapped to preferred terms and system organ classes using MedDRA (version 18.1).

All on-study medical or surgical procedure data will be presented in a by-subject data listing.

11.6. Clinical Laboratory Evaluations

Clinical laboratory evaluations during the DB are assessed at the central laboratory. The central laboratory reference/normal ranges will be used in determining whether a subject's value is above (H) or below (L) the reference/normal range. A listing of available laboratory reference/normal ranges for each laboratory parameter will be provided including age, sex, and values with units.

Quantitative hematology, coagulation, and serum chemistry laboratory parameters will be summarized by treatment group in SI and conventional units using arithmetic summary statistics as described in Section 6.2.1 at Baseline and at each scheduled DB post-Baseline visit. Change from Baseline will also be summarized in the same manner. Re-tests or unscheduled visit results after first dose of investigational product in the DB will not be summarized but will be included in the data listings. Re-tests or unscheduled visit results prior to the administration time of the first dose in the DB will be included in the calculation of Baseline.

For laboratory test results that are below the quantifiable limits:

Imputed laboratory result = (numeric portion of the result) × 0.9.

For laboratory test results that are above the quantifiable limits:

Imputed laboratory result = (numeric portion of the result) × 1.1.

In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at DB post-Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each

scheduled DB post-Baseline visit will be provided for hematology, coagulation, and serum chemistry by treatment group. Worst post-Baseline value is defined as the most abnormal value.

Urinalysis results will not be summarized but will be provided in a data listing.

Listings of all laboratory values will flag values outside of the normal range as high (H) or low (L) and indicate whether or not a value is clinically significant (CS), based on Investigator judgment.

11.7. Vital Signs

Vital signs (body temperature, sitting heart rate, and respiratory rate) will be summarized using arithmetic summary statistics as described in Section 6.2.1 at Baseline and at each DB post-Baseline visit. Change from Baseline will also be summarized in the same manner. Re-tests or unscheduled visit results prior to the administration time of the first dose in the DB will be included in the calculation of Baseline. Re-tests or unscheduled visit results after the first OCA dose administration time will not be summarized but will be included in the data listings.

11.8. Electrocardiograms (ECGs)

The ECG data analysis will be conducted based on methodology recommended in the International Conference on Harmonization (ICH) E14 guideline, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs.

Baseline is defined as the mean of all available evaluations prior to treatment. Arithmetic summary statistics as described in Section 6.2.1 will be used to summarize ECG parameters (heart rate, RR, PR, QRS, QT, QTcB and QTcF) at Baseline and at each DB post-Baseline visit will be summarized by treatment group; absolute change from Baseline will also be summarized.

A categorical summary of abnormal QTcF values will be presented by treatment group. The number of subjects with values of > 450 msec, > 480 msec, and > 500 msec at each visit will be presented and the number of subjects with change from Baseline values of > 30 msec and > 60 msec will also be presented.

Overall interpretation of results for ECGs and the Investigator interpretation of results are collected as normal, abnormal not clinically significant, and abnormal clinically significant. Subjects whose result shifts from normal to abnormal will be listed separately including description of the abnormality and any associated comments.

12. CHANGES TO PROTOCOL-SPECIFIED ANALYSES AND ENDPOINTS

There has been one change between the protocol-defined statistical analyses and those presented in this statistical analysis plan. The bioanalytical atorvastatin concentration results did not pass incurred sample reanalysis testing. Therefore, pharmacokinetic analysis of atorvastatin will not be performed.

The non-invasive fibrosis scores were not specified in the protocol. However, the fibrosis score components are from protocol-defined data points, and thus, the addition of the scores does not change how the data was collected, nor how the data points are defined.

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APPENDIX A. LIST OF TABLES, FIGURES, AND LISTINGS

List of Tables

Table Number	Population	Table Title
14.1		**Demographic Data**
14.1.1	All Randomized Subjects	Summary of Analysis Populations
14.1.2.1	All Randomized Subjects	Summary of Subject Disposition
14.1.2.2	ITT	Summary of Investigational Product Discontinuation
14.1.2.3	ITT	Summary of Study Medication Discontinuation
14.1.3	ITT	Summary of Subject Protocol Deviations
14.1.4.1	ITT	Summary of Demographics and Baseline Characteristics
14.1.4.2	PK	Summary of Demographics and Baseline Characteristics
14.1.4.3	EE	Summary of Demographics and Baseline Characteristics (only produced if > 20% of ITT subjects are excluded from EE population)
14.1.5.1	ITT	Summary of NASH Disease History
14.1.5.2	EE	Summary of NASH Disease History
14.1.6	ITT	Summary of Tobacco Use Score
14.1.7	ITT	Summary of Statin History
14.1.8	ITT	Summary of Family Cardiovascular History
14.1.9	ITT	Summary of Abnormal Medical History at Baseline
14.2		**Efficacy Data**
14.2.1.1.1	EE	Summary of LDL Cholesterol Concentration – SI Units
14.2.1.1.2	EE	Summary of LDL Cholesterol Concentration – CV Units
14.2.1.1.3	EE	Summary of LDL Cholesterol Particle Size and Particle Concentration
14.2.1.2.1	ITT	Summary of LDL Cholesterol Concentration – SI Units
14.2.1.2.2	ITT	Summary of LDL Cholesterol Concentration – CV Units
14.2.1.2.3	ITT	Summary of LDL Cholesterol Particle Size and Particle Concentration
14.2.1.3.1	ITT	Summary of LDL Cholesterol Concentration – SI Units (MMRM)
14.2.1.3.2	ITT	Summary of LDL Cholesterol Concentration – CV Units (MMRM)
14.2.1.3.3	ITT	Summary of LDL Cholesterol Particle Size and Particle Concentration (MMRM)
14.2.1.4.1	ITT	Summary of Change in LDL Choleterol Concentration and Relationship to Treatment – CV Units
14.2.1.4.2	ITT	Summary of Change in LDL Choleterol Concentration and Relationship to Treatment – SI Units
14.2.2.1.1	EE	Summary of HDL Cholesterol Concentration – SI Units
14.2.2.1.2	EE	Summary of HDL Cholesterol Concentration – CV Units
14.2.2.1.3	EE	Summary of HDL Cholesterol Particle Size and Particle Concentration

Table Number	Population	Table Title
14.2.2.2.1	ITT	Summary of HDL Cholesterol Concentration – SI Units (MMRM)
14.2.2.2.2	ITT	Summary of HDL Cholesterol Concentration – CV Units (MMRM)
14.2.2.2.3	ITT	Summary of HDL Cholesterol Particle Size and Particle Concentration (MMRM)
14.2.3.1.1	EE	Summary of V:DL Cholesterol Concentration – SI Units
14.2.3.1.2	EE	Summary of VLDL Cholesterol Concentration – CV Units
14.2.3.1.3	EE	Summary of VLDL Cholesterol Particle Size and Particle Concentration
14.2.3.2.1	ITT	Summary of VLDL Cholesterol Concentration – SI Units (MMRM)
14.2.3.2.2	ITT	Summary of VLDL Cholesterol Concentration – CV Units (MMRM)
14.2.3.2.3		Summary of VLDL Cholesterol Particle Size and Particle Concentration (MMRM)
14.2.4.1	EE	Summary of Total Cholesterol and Triglyceride Concentrations – SI Units
14.2.4.2	EE	Summary of Total Cholesterol and Triglyceride Concentrations – CV Units
14.2.5	EE	Summary of ApoA1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a) Concentrations
14.2.6	EE	Summary of Reverse Cholesterol Metabolism
14.2.7	EE	Summary of Liver Biochemistry and Markers of Liver Function
14.2.8	EE	Summary of Liver Inflammation, Hepatic Apoptosis, and Fibrosis
14.2.9.1	EE	Summary of Glycemic Control
14.2.9.2	EE	Summary of Glycemic Control by Diabetes Status
14.2.10	EE	Summary of Liver Stiffness Measurements via Transient Elastography
14.2.11	EE	Summary of Liver Fibrosis Improvement via Transient Elastography
14.2.12.1	EE	Summary of Correlation Between Liver Stiffness via Transient Elastography and Liver Biopsy NASH CRN Criteria
14.2.12.2	EE	Summary of Correlation Between Liver Stiffness via Transient Liver Elastography and Liver Biopsy Modified Ishak Scoring Criteria
14.2.13.1	EE	Summary of FIB-4 Score
14.2.13.2	EE	Summary of APRI Score
14.2.13.3	EE	Summary of NFS Score
14.2.13.4	EE	BARD Score Shift from Baseline
14.2.14.1	EE	Summary of Anthropometric Measures and Blood Pressure
14.2.14.2	EE	Summary of Anthropometric Measures and Blood Pressure by Diabetes Status
14.2.14.3	EE	Summary of Blood Pressure by Antihypertensive Use
14.2.15.1	EE	Summary of Cardiovascular Risk Scores
14.2.15.2.1	EE	Summary of Cardiovascular Markers of Risk – SI Units
14.2.15.2.2	EE	Summary of Cardiovascular Markers of Risk – CV Units
14.2.16.1	PK	Summary of Plasma Concentrations for OCA, Glyco-OCA, Tauro-OCA, and Total OCA by Treatment and Visit
14.2.16.2	PK	Summary of PK Parameters for OCA, Glyco-OCA, Tauro-OCA, and Total OCA by Treatment and Visit

Table Number	Population	Table Title
14.2.17.1	APK	Summary of Week 16 Plasma Concentrations for Atorvastatin, 2OH-Atorvastatin, and 4OH-Atorvastatin by Treatment
14.2.17.2	APK	Summary of Week 16 PK Parameters for Atorvastatin, 2OH-Atorvastatin, and 4OH-Atorvastatin by Treatment
14.2.18.1	ITT	Summary of Total Bile Acids and Total Endogenous Bile Acids
14.2.18.2	ITT	Summary of Bile Acids and Bile Acid Sub-components
14.2.18.3	ITT	Summary of Bile Acid Proportions
14.3		**Safety Data**
14.3.1	Safety	Summary of Investigational Product Exposure
14.3.2	Safety	Summary of Atorvastatin Exposure
14.3.3.1	Safety	Summary of Prior and New Concomitant Medications
14.3.3.2	Safety	Summary of New Concomitant Medications
14.3.1		**Displays of Adverse Events**
14.3.1.1.1	Safety	Overall Summary of Treatment-Emergent Adverse Events
14.3.1.1.2	Safety	Overall Summary of Treatment-Emergent Adverse Events Up to Week 4
14.3.1.2.1	Safety	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.2.2	Safety	Summary of Treatment-Emergent Adverse Events by Preferred Term
14.3.1.2.3	Safety	Summary of Treatment-Emergent Adverse Events Up to Week 4 by System Organ Class and Preferred Term
14.3.1.2.4	Safety	Summary of Treatment-Emergent Adverse Events Up to Week 4 by Preferred Term
14.3.1.3.1	Safety	Summary of Investigational product-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.3.2	Safety	Summary of Investigational product-related Treatment-Emergent Adverse Events by Preferred Term
14.3.1.3.3	Safety	Summary of Investigational product-related Treatment-Emergent Adverse Events Up to Week 4 by System Organ Class and Preferred Term
14.3.1.3.4	Safety	Summary of Investigational product-related Treatment-Emergent Adverse Events Up to Week 4 by Preferred Term
14.3.1.4.1	Safety	Summary of Study Medication-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.4.2	Safety	Summary of Study Medication-related Treatment-Emergent Adverse Events by Preferred Term
14.3.1.5.1	Safety	Summary of Liver biopsy-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.5.2	Safety	Summary of Liver biopsy-related Treatment-Emergent Adverse Events by Preferred Term
14.3.1.6.1	Safety	Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term
14.3.1.6.2	Safety	Summary of Treatment-Emergent Serious Adverse Events by Preferred Term
14.3.1.6.3	Safety	Summary of Treatment-Emergent Serious Adverse Events Up to Week 4 by System Organ Class and Preferred Term

Table Number	Population	Table Title
14.3.1.6.4	Safety	Summary of Treatment-Emergent Serious Adverse Events Up to Week 4 by Preferred Term
14.3.1.7.1	Safety	Summary of Treatment-Emergent Adverse Events Leading to Investigational Product Withdrawal, Study Medication Withdrawal, or Study Discontinuation by System Organ Class and Preferred Term
14.3.1.7.2	Safety	Summary of Treatment-Emergent Adverse Events Leading to Investigational Product Withdrawal, Study Medication Withdrawal, or Study Discontinuation by Preferred Term
14.3.1.8.1	Safety	Summary of Treatment-Emergent Adverse Events Leading to Investigational Product Withdrawal by System Organ Class and Preferred Term
14.3.1.8.2	Safety	Summary of Treatment-Emergent Adverse Events Leading to Investigational Product Withdrawal by Preferred Term
14.3.1.8.3	Safety	Summary of Treatment-Emergent Adverse Events Up to Week 4 Leading to Investigational Product Withdrawal by System Organ Class and Preferred Term
14.3.1.8.4	Safety	Summary of Treatment-Emergent Adverse Events Up to Week 4 Leading to Investigational Product Withdrawal by Preferred Term
14.3.1.9.1	Safety	Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term
14.3.1.9.2	Safety	Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation by Preferred Term
14.3.1.9.3	Safety	Summary of Treatment-Emergent Adverse Events Up to Week 4 Leading to Study Discontinuation by System Organ Class and Preferred Term
14.3.1.9.4	Safety	Summary of Treatment-Emergent Adverse Events Up to Week 4 Leading to Study Discontinuation by Preferred Term
14.3.1.10.1	Safety	Summary of Treatment-Emergent Adverse Events Leading to Study Medication Withdrawal by System Organ Class and Preferred Term
14.3.1.10.2	Safety	Summary of Treatment-Emergent Adverse Events Leading to Study Medication Withdrawal by Preferred Term
14.3.1.11.1	Safety	Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term
14.3.1.11.2	Safety	Summary of Treatment-Emergent Adverse Events by Maximum Severity and Preferred Term
14.3.1.11.3	Safety	Summary of Treatment-Emergent Adverse Events Up to Week 4 by Maximum Severity, System Organ Class, and Preferred Term
14.3.1.11.4	Safety	Summary of Treatment-Emergent Adverse Events Up to Week 4 by Maximum Severity and Preferred Term
14.3.1.12.1	Safety	Summary of Pre-Treatment Adverse Events by System Organ Class and Preferred Term
14.3.1.12.2	Safety	Summary of Pre-Treatment Adverse Events by Preferred Term
14.3.1.13.1	Safety	Summary of Pre-Treatment Serious Adverse Events by System Organ Class and Preferred Term
14.3.1.13.2	Safety	Summary of Pre-Treatment Serious Adverse Events by Preferred Term
14.3.1.14.1	Safety	Summary of Pruritus Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

Table Number	Population	Table Title
14.3.1.14.2	Safety	Summary of Pruritus Treatment-Emergent Adverse Events by Preferred Term
14.3.1.14.3	Safety	Time to Onset of First Treatment-Emergent Pruritus
14.3.1.14.4	Safety	Time to Onset of Most Severe Treatment-Emergent Pruritus
14.3.1.14.5	Safety	Time to Resolution of Most Severe Treatment-Emergent Pruritus
14.3.1.14.6	Safety	Treatment-Emergent Pruritus Event Days
14.3.1.15.1	Safety	Summary of Treatment-Emergent Hepatic Disorder Adverse Events by System Organ Class and Preferred Term
14.3.1.15.2	Safety	Summary of Treatment-Emergent Hepatic Disorder Adverse Events by Preferred Term
14.3.1.15.3	Safety	Time to Onset of First Treatment-Emergent Hepatic Disorder
14.3.1.15.4	Safety	Time to Onset of Most Severe Treatment-Emergent Hepatic Disorder
14.3.1.16.1	Safety	Summary of Treatment-Emergent Dyslipidaemia Adverse Events by System Organ Class and Preferred Term
14.3.1.16.2	Safety	Summary of Treatment-Emergent Dyslipidaemia Adverse Events by Preferred Term
14.3.1.16.3	Safety	Time to Onset of First Treatment-Emergent Dyslipidaemia
14.3.1.16.4	Safety	Time to Onset of Most Severe Treatment-Emergent Dyslipidaemia
14.3.1.17.1	Safety	Summary of Treatment-Emergent Myopathy Adverse Events by System Organ Class and Preferred Term
14.3.1.17.2	Safety	Summary of Treatment-Emergent Myopathy Adverse Events by Preferred Term
14.3.1.17.3	Safety	Time to Onset of First Treatment-Emergent Myopathy
14.3.1.17.4	Safety	Time to Onset of Most Severe Treatment-Emergent Myopathy
14.3.1.18.1	Safety	Summary of Treatment-Emergent Adjudicated Cardiovascular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.18.2	Safety	Summary of Treatment-Emergent Suspected Cardiovascular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.18.3	Safety	Time to Onset of First Treatment-Emergent Adjudicated Cardiovascular Event
14.3.1.18.4	Safety	Time to Onset of First Treatment-Emergent Suspected Cardiovascular Event
14.3.4		**Clinical Laboratory Evaluations**
14.3.4.1.1	Safety	Summary of Hematology and Coagulation – SI Units
14.3.4.1.2	Safety	Summary of Hematology and Coagulation – CV Units
14.3.4.2.1	Safety	Hematology and Coagulation Shift Analysis – SI Units
14.3.4.2.2	Safety	Hematology and Coagulation Shift Analysis – CV Units
14.3.4.3.1	Safety	Summary of Serum Chemistry – SI Units
14.3.4.3.2	Safety	Summary of Serum Chemistry – CV Units
14.3.4.4.1	Safety	Serum Chemistry Shift Analysis – SI Units
14.3.4.4.2	Safety	Serum Chemistry Shift Analysis – CV Units
14.3.4.5.1	Safety	Summary of Vital Signs
14.3.4.5.2	Safety	Summary of Blood Pressure by Use of Antihypertensive Medications

Table Number	Population	Table Title
14.3.4.6	Safety	Summary of Electrocardiogram Parameters
14.3.4.7	Safety	Summary of Electrocardiogram Parameter Subgroups
14.3.4.8	Safety	Summary of Alcohol Use Disorders Identification Test (AUDIT) Score

List of Figures

Figure Number	Population	Figure Title
14.2		**Efficacy Data**
14.2.1.1	ITT	Baseline Liver Stiffness Measurements versus Baseline NASH CRN Liver Biopsy Stage
14.2.1.2	ITT	Baseline Liver Stiffness Measurements versus Baseline Modified Ishak Liver Biopsy Stage
14.2.1.1	PK	Individual Plasma Concentration of Unconjugated OCA Over Time
14.2.1.2	PK	Individual Plasma Concentration of Glyco-OCA Over Time
14.2.1.3	PK	Individual Plasma Concentration of Tauro-OCA Over Time
14.2.1.4	PK	Individual Plasma Concentration of Total OCA Over Time
14.2.2.1	PK	Mean (SD) Plasma Concentration of Unconjugated OCA Over Time by Dose (linear and semi-log plots)
14.2.2.2	PK	Mean (SD) Plasma Concentration of Glyco-OCA Over Time by Dose (linear and semi-log plots)
14.2.2.3	PK	Mean (SD) Plasma Concentration of Tauro-OCA Over Time by Dose (linear and semi-log plots)
14.2.2.4	PK	Mean (SD) Plasma Concentration of Total OCA Over Time by Dose (linear and semi-log plots)
14.2.3.1	PK	Boxplots of AUC_{0-6} and C_{max} versus Dose for OCA, Glyco-OCA, Tauro-OCA, and Total OCA by Visit (Day 1 and Week 16)
14.2.4.1.1	PK	Scatter Plot of Week 16 LDL Cholesterol Concentration versus Total OCA AUC_{0-6} – SI Units
14.2.4.1.2	PK	Scatter Plot of Week 16 LDL Cholesterol Concentration versus Total OCA AUC_{0-6} – CV Units
14.2.4.2.1	PK	Scatter Plot of Week 16 Change from Baseline in LDL Cholesterol versus Total OCA AUC_{0-6} – SI Units
14.2.4.2.2	PK	Scatter Plot of Week 16 Change from Baseline in LDL Cholesterol versus Total OCA AUC_{0-6} – CV Units
14.2.4.3.1	PK	Scatter Plot of Week 16 LDL Particle Size versus Total OCA AUC_{0-6}
14.2.4.3.2	PK	Scatter Plot of Week 16 Change from Baseline in LDL Particle Size versus Total OCA AUC_{0-6}
14.2.4.4.1	PK	Scatter Plot of Week 16 LDL Particle Concentration versus Total OCA AUC_{0-6}
14.2.4.4.2	PK	Scatter Plot of Week 16 Change from Baseline in LDL Particle Concentration versus Total OCA AUC_{0-6}
14.2.4.5.1	PK	Scatter Plot of Week 16 FGF-19 versus Total OCA AUC_{0-6}
14.2.4.5.2	PK	Scatter Plot of Week 16 Change from Baseline in FGF-19 versus Total OCA AUC_{0-6}
14.2.4.6.1	PK	Scatter Plot of Week 16 C4 versus Total OCA AUC_{0-6}

Figure Number	Population	Figure Title
14.2		**Efficacy Data**
14.2.4.6.2	PK	Scatter Plot of Week 16 Change from Baseline in C4 versus Total OCA AUC_{0-6}
14.2.4.7.1	PK	Scatter Plot of Week 16 CRP versus Total OCA AUC_{0-6}
14.2.4.7.2	PK	Scatter Plot of Week 16 Change from Baseline in CRP versus Total OCA AUC_{0-6}
14.2.4.8.1.1	PK	Scatter Plot of Week 16 LDL Cholesterol Concentration versus Total OCA C_{max} – SI Units
14.2.4.8.1.2	PK	Scatter Plot of Week 16 LDL Cholesterol Concentration versus Total OCA C_{max} – CV Units
14.2.4.8.2.1	PK	Scatter Plot of Week 16 Change from Baseline in LDL Cholesterol Concentration versus Total OCA C_{max} – SI Units
14.2.4.8.2.2	PK	Scatter Plot of Week 16 Change from Baseline in LDL Cholesterol Concentration versus Total OCA C_{max} – CV Units
14.2.4.9.1	PK	Scatter Plot of Week 16 LDL Particle Size versus OCA C_{max}
14.2.4.9.2	PK	Scatter Plot of Week 16 Change from Baseline in LDL Particle Size versus Total OCA C_{max}
14.2.4.10.1	PK	Scatter Plot of Week 16 LDL Particle Concentration versus Total OCA C_{max}
14.2.4.10.2	PK	Scatter Plot of Week 16 Change from Baseline in LDL Particle Concentration versus Total OCA C_{max}
14.2.4.11.1	PK	Scatter Plot of Week 16 C4 versus Total OCA C_{max}
14.2.4.11.2	PK	Scatter Plot of Week 16 Change from Baseline in C4 versus Total OCA C_{max}
14.2.4.12.1	PK	Scatter Plot of Week 16 FGF-19 versus Total OCA C_{max}
14.2.4.12.2	PK	Scatter Plot of Week 16 Change from Baseline in FGF-19 versus Total OCA C_{max}
14.2.4.13.1	PK	Scatter Plot of Week 16 CRP versus Total OCA C_{max}
14.2.4.13.2	PK	Scatter Plot of Week 16 Change from Baseline in CRP versus Total OCA C_{max}

List of Data Listings

Listing Number	Listing Title
16.2	**Subject Data Listings**
16.2.1	**Discontinued subjects**
16.2.1.1	Analysis Populations
16.2.1.2	Subject Disposition
16.2.2	**Protocol deviations**
16.2.2.1	Protocol Deviations
16.2.2.2.1	Inclusion and Exclusion Criteria Findings
16.2.2.2.2	Liver Biopsy Eligibility
16.2.4	**Demographic data**
16.2.4.1	Demographics
16.2.4.2	NASH Disease History

Listing Number	Listing Title
16.2.4.3	Alcohol Use Disorders Identification Test (AUDIT)
16.2.4.4	Tobacco Use
16.2.4.5	Statin History
16.2.4.6	Family Cardiovascular History
16.2.4.7	Medical History
16.2.4.8	Historical Procedures
16.2.5	**Compliance and/or drug concentration data**
16.2.5.1	Investigational Product Accountability
16.2.5.2	Investigational Product Exposure
16.2.5.3	Study Medication Accountability
16.2.5.4	Study Medication Exposure
16.2.5.5	Prior and New Concomitant Medications
16.2.5.6.1	Plasma Concentration Collection
16.2.5.6.2	Plasma Concentration Data for OCA, Glyco-OCA, Tauro-OCA, and Total OCA
16.2.5.6.3	PK Parameters for OCA, Glyco-OCA, Tauro-OCA, and Total OCA
16.2.5.8.1	Bile Acids and Bile Acid Subcomponents: UDCA, Glyco-UDCA, Tauro-UDCA, and Total UDCA
16.2.5.8.2	Bile Acids and Bile Acid Subcomponents: CDCA, Glyco-CDCA, Tauro-CDCA, and Total CDCA
16.2.5.8.3	Bile Acids and Bile Acid Subcomponents: DCA, Glyco-DCA, Tauro-DCA, and Total DCA
16.2.5.8.4	Bile Acids and Bile Acid Subcomponents: CA, Glyco-CA, Tauro-CA, and Total CA
16.2.5.8.5	Bile Acids and Bile Acid Subcomponents: LCA, Glyco-LCA, Tauro-LCA, and Total LCA
16.2.5.8.6	Total Bile Acids and Total Endogenous Bile Acids
16.2.6	**Individual efficacy response data**
16.2.6.1.1	Lipoprotein Serum Concentration – SI Units
16.2.6.1.2	Lipoprotein Serum Concentration – CV Units
16.2.6.2	Lipoprotein Particle Concentration and Size
16.2.6.3.1	ApoA1, ApoB, ApoA1/ApoB Ratio, ApoE, and Lp(a) Concentrations – SI Units
16.2.6.3.2	ApoA1, ApoB, ApoA1/ApoB Ratio, ApoE, and Lp(a) Concentrations – CV Units
16.2.6.4	Reverse Cholesterol Transport
16.2.6.5.1	Liver Biochemistry and Markers of Liver Function – SI Units
16.2.6.5.2	Liver Biochemistry and Markers of Liver Function – CV Units
16.2.6.6	Markers of Liver inflammation, Hepatic Apoptosis and Fibrosis
16.2.6.7.1	Markers of Glycemic Control – SI Units
16.2.6.7.2	Markers of Glycemic Control – CV Units
16.2.6.8.1	Markers of Cardiovascular Risk – SI Units
16.2.6.8.2	Markers of Cardiovascular Risk – CV Units
16.2.6.9.1	Nuclear Magnetic Resonance Lipoprotein Concentrations – SI Units
16.2.6.9.2	Nuclear Magnetic Resonance Lipoprotein Concentrations – CV Units

Listing Number	Listing Title
16.2.6.10	Transient Elastography
16.2.6.11	Fibrosis-4 Score
16.2.6.12	APRI Score
16.2.6.13	BARD Score
16.2.6.14	NSF Score
16.2.7	**Adverse events listings**
16.2.7.1	Adverse Events
16.2.7.2	Serious Adverse Events
16.2.7.3	Severe Adverse Events
16.2.7.4	Adverse Events Related to Investigational Product
16.2.7.5	Adverse Events Related to Study Medication
16.2.7.6	Adverse Events Related to Liver Biopsy
16.2.7.7	Adverse Events Leading to Investigational Product Withdrawal or Study Discontinuation
16.2.7.8	Adverse Events Leading to Death
16.2.7.9	Adjudicated Adverse Events
16.2.7.10	Adverse Events of Pruritus
16.2.7.11	Derived Time to Treatment-Emergent Pruritus Endpoints
16.2.7.12	Derived Time to Treatment-Emergent Adverse Events of Special Interest
16.2.8	**Listing of individual laboratory measurements by subject, when required by regulatory authorities**
16.2.8.1.1	Hematology and Coagulation – SI Units
16.2.8.1.2	Hematology and Coagulation – CV Units
16.2.8.2.1	Serum Chemistry – SI Units
16.2.8.2.2	Serum Chemistry – CV Units
16.2.8.3	Urinalysis
16.2.8.4	Laboratory Sample Collection
16.2.8.5.1	Laboratory Reference/Normal Ranges – SI Units
16.2.8.5.2	Laboratory Reference/Normal Ranges – CV Units
16.2.9	**Additional Safety Listings**
16.2.9.1	Vital Signs
16.2.9.2	Anthropometric Measures
16.2.9.3.1	12-lead Electrocardiograms (ECGs)
16.2.9.3.2	12-lead Electrocardiograms (ECGs) Central Reading Results
16.2.9.4.1	Cardiovascular Risk Scores – Framingham Risk Score
16.2.9.4.2	Cardiovascular Risk Scores – Reynolds Score
16.2.9.5	On-Study Medical or Surgical Procedure
16.2.9.6	Pregnancy Test Results
16.2.9.7	Subject Visit Information
16.2.9.8	Comments

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APPENDIX B. HEPATIC DISORDER PREFERRED TERMS AND ASSOCIATED CODES

Preferred Term	Code
5'nucleotidase increased	10000028
Acquired antithrombin III deficiency	10074561
Acquired protein S deficiency	10068370
Acute hepatic failure	10000804
Acute yellow liver atrophy	10070815
Alanine aminotransferase abnormal	10001547
Alanine aminotransferase increased	10001551
Alcoholic liver disease	10001627
Ammonia abnormal	10001942
Ammonia increased	10001946
Anorectal varices	10068924
Anorectal varices haemorrhage	10068925
Antithrombin III decreased	10049547
Ascites	10003445
Aspartate aminotransferase abnormal	10003477
Aspartate aminotransferase increased	10003481
Asterixis	10003547
Bacterascites	10068547
Benign hepatic neoplasm	10004269
Bile output abnormal	10051344
Bile output decreased	10051343
Biliary ascites	10074150
Biliary cirrhosis	10004659
Biliary cirrhosis primary	10004661
Biliary fibrosis	10004664
Bilirubin conjugated abnormal	10067718
Bilirubin conjugated increased	10004685
Bilirubin excretion disorder	10061009
Biopsy liver abnormal	10004792
Blood alkaline phosphatase abnormal	10059571
Blood alkaline phosphatase increased	10059570
Blood bilirubin abnormal	10058477

Preferred Term	Code
Blood bilirubin increased	10005364
Blood bilirubin unconjugated increased	10005370
Blood cholinesterase abnormal	10005429
Blood cholinesterase decreased	10005430
Blood fibrinogen abnormal	10005518
Blood fibrinogen decreased	10005520
Blood thrombin abnormal	10005818
Blood thrombin decreased	10005820
Blood thromboplastin abnormal	10005824
Blood thromboplastin decreased	10005826
Bromosulphthalein test abnormal	10006408
Child-Pugh-Turcotte score abnormal	10077020
Child-Pugh-Turcotte score increased	10068287
Cholaemia	10048611
Cholestasis	10008635
Cholestatic liver injury	10067969
Cholestatic pruritus	10064190
Chronic hepatic failure	10057573
Cirrhosis alcoholic	10009208
Coagulation factor decreased	10009736
Coagulation factor IX level abnormal	10061770
Coagulation factor IX level decreased	10009746
Coagulation factor V level abnormal	10061771
Coagulation factor V level decreased	10009754
Coagulation factor VII level abnormal	10061772
Coagulation factor VII level decreased	10009761
Coagulation factor X level abnormal	10061774
Coagulation factor X level decreased	10009775
Coma hepatic	10010075
Computerised tomogram liver	10076215
Cryptogenic cirrhosis	10063075
Deficiency of bile secretion	10071634
Diabetic hepatopathy	10071265
Drug-induced liver injury	10072268
Duodenal varices	10051010

Preferred Term	Code
Fatty liver alcoholic	10016262
Focal nodular hyperplasia	10052285
Foetor hepaticus	10052554
Galactose elimination capacity test abnormal	10059710
Galactose elimination capacity test decreased	10059712
Gallbladder varices	10072319
Gamma-glutamyltransferase abnormal	10017688
Gamma-glutamyltransferase increased	10017693
Gastric variceal injection	10076237
Gastric variceal ligation	10076238
Gastric varices	10051012
Gastric varices haemorrhage	10057572
Glutamate dehydrogenase increased	10049483
Guanase increased	10051333
Haemangioma of liver	10018821
Haemorrhagic ascites	10059766
Haemorrhagic hepatic cyst	10067796
Hepaplastin abnormal	10019621
Hepaplastin decreased	10019622
Hepatectomy	10061997
Hepatic adenoma	10019629
Hepatic angiosarcoma	10067388
Hepatic artery flow decreased	10068997
Hepatic atrophy	10019637
Hepatic calcification	10065274
Hepatic cancer	10073069
Hepatic cancer metastatic	10055110
Hepatic cancer recurrent	10073070
Hepatic cancer stage I	10059318
Hepatic cancer stage II	10059319
Hepatic cancer stage III	10059324
Hepatic cancer stage IV	10059325
Hepatic cirrhosis	10019641
Hepatic congestion	10019645
Hepatic cyst	10019646

Preferred Term	Code
Hepatic cyst ruptured	10053973
Hepatic encephalopathy	10019660
Hepatic encephalopathy prophylaxis	10066599
Hepatic enzyme abnormal	10062685
Hepatic enzyme decreased	10060794
Hepatic enzyme increased	10060795
Hepatic failure	10019663
Hepatic fibrosis	10019668
Hepatic fibrosis marker abnormal	10074084
Hepatic fibrosis marker increased	10074413
Hepatic function abnormal	10019670
Hepatic haemangioma rupture	10054885
Hepatic hydrothorax	10067365
Hepatic hypertrophy	10076254
Hepatic infiltration eosinophilic	10064668
Hepatic lesion	10061998
Hepatic mass	10057110
Hepatic necrosis	10019692
Hepatic neoplasm	10019695
Hepatic pain	10019705
Hepatic sequestration	10066244
Hepatic steato-fibrosis	10077215
Hepatic steatosis	10019708
Hepatic vascular resistance increased	10068358
Hepatitis alcoholic	10019728
Hepatitis cholestatic	10019754
Hepatitis fulminant	10019772
Hepatobiliary cancer	10073073
Hepatobiliary cancer in situ	10073074
Hepatobiliary disease	10062000
Hepatobiliary neoplasm	10061203
Hepatobiliary scan abnormal	10066195
Hepatoblastoma	10062001
Hepatoblastoma recurrent	10019823
Hepatocellular carcinoma	10073071

Preferred Term	Code
Hepatocellular foamy cell syndrome	10053244
Hepatocellular injury	10019837
Hepatomegaly	10019842
Hepatopulmonary syndrome	10052274
Hepatorenal failure	10019845
Hepatorenal syndrome	10019846
Hepatosplenomegaly	10019847
Hepatotoxicity	10019851
Hyperammonaemia	10020575
Hyperbilirubinaemia	10020578
Hypercholia	10051924
Hyperfibrinolysis	10074737
Hypertransaminasaemia	10068237
Hypoalbuminaemia	10020942
Hypocoagulable state	10020973
Hypofibrinogenaemia	10051125
Hypoprothrombinaemia	10021085
Hypothrombinaemia	10058517
Hypothromboplastinaemia	10058518
Icterus index increased	10021209
International normalised ratio abnormal	10022592
International normalised ratio increased	10022595
Intestinal varices	10071502
Intrahepatic portal hepatic venous fistula	10072629
Jaundice	10023126
Jaundice cholestatic	10023129
Jaundice hepatocellular	10023136
Kayser-Fleischer ring	10023321
Leucine aminopeptidase increased	10024275
Liver ablation	10074766
Liver and small intestine transplant	10052280
Liver carcinoma ruptured	10050842
Liver dialysis	10076640
Liver disorder	10024670
Liver function test abnormal	10024690

Preferred Term	Code
Liver induration	10052550
Liver injury	10067125
Liver iron concentration abnormal	10074352
Liver iron concentration increased	10074354
Liver operation	10062040
Liver palpable	10075895
Liver scan abnormal	10061947
Liver tenderness	10024712
Liver transplant	10024714
Lupoid hepatic cirrhosis	10025129
Minimal hepatic encephalopathy	10076204
Mitochondrial aspartate aminotransferase increased	10064712
Mixed hepatocellular cholangiocarcinoma	10027761
Mixed liver injury	10066758
Molar ratio of total branched-chain amino acid to tyrosine	10066869
Nodular regenerative hyperplasia	10051081
Non-alcoholic steatohepatitis	10053219
Ocular icterus	10058117
Oedema due to hepatic disease	10049631
Oesophageal varices haemorrhage	10030210
Parenteral nutrition associated liver disease	10074151
Perihepatic discomfort	10054125
Peripancreatic varices	10073215
Periportal oedema	10068821
Peritoneal fluid protein abnormal	10069000
Peritoneal fluid protein decreased	10068999
Peritoneal fluid protein increased	10068998
Peritoneovenous shunt	10052716
Pneumobilia	10066004
Portal fibrosis	10074726
Portal hypertension	10036200
Portal hypertensive enteropathy	10068923
Portal hypertensive gastropathy	10050897
Portal shunt	10036204
Portal vein cavernous transformation	10073979

Preferred Term	Code
Portal vein dilatation	10073209
Portal vein flow decreased	10067337
Portal vein pressure increased	10064936
Portopulmonary hypertension	10067281
Protein C decreased	10037005
Protein S abnormal	10051736
Protein S decreased	10051120
Prothrombin level abnormal	10037048
Prothrombin level decreased	10037050
Prothrombin time abnormal	10037057
Prothrombin time prolonged	10037063
Prothrombin time ratio abnormal	10061918
Prothrombin time ratio increased	10037068
Renal and liver transplant	10052279
Retinol binding protein decreased	10048473
Retrograde portal vein flow	10067338
Reye's syndrome	10039012
Reynold's syndrome	10070953
Small-for-size liver syndrome	10069380
Spider naevus	10041519
Splenic varices	10067823
Splenic varices haemorrhage	10068662
Spontaneous intrahepatic portosystemic venous shunt	10076239
Steatohepatitis	10076331
Stomal varices	10075186
Subacute hepatic failure	10056956
Thrombin time abnormal	10051319
Thrombin time prolonged	10051390
Total bile acids increased	10064558
Transaminases abnormal	10062688
Transaminases increased	10054889
Ultrasound liver abnormal	10045428
Urine bilirubin increased	10050792
Urobilinogen urine decreased	10070480
Urobilinogen urine increased	10070479

Preferred Term	**Code**
Varices oesophageal	10056091
Varicose veins of abdominal wall	10072284
X-ray hepatobiliary abnormal	10056536
Yellow skin	10048245
Zieve syndrome	10048255

APPENDIX C. DYSLIPIDEMIA PREFERRED TERMS AND ASSOCIATED CODES

Preferred Term	Code
Acquired lipoatrophic diabetes	10073667
Acquired mixed hyperlipidaemia	10071236
Apolipoprotein B/Apolipoprotein A-1 ratio increased	10065516
Autoimmune hyperlipidaemia	10071577
Blood cholesterol abnormal	10005423
Blood cholesterol decreased	10005424
Blood cholesterol esterase increased	10071304
Blood cholesterol increased	10005425
Blood triglycerides abnormal	10005837
Blood triglycerides decreased	10005838
Blood triglycerides increased	10005839
Diabetic dyslipidaemia	10070901
Dyslipidaemia	10058108
Familial hypertriglyceridaemia	10059183
Fat overload syndrome	10074028
High density lipoprotein abnormal	10020051
High density lipoprotein decreased	10020060
High density lipoprotein increased	10020061
Hypercholesterolaemia	10020603
Hyperlipidaemia	10062060
Hypertriglyceridaemia	10020869
Hypo HDL cholesterolaemia	10068961
Hypotriglyceridaemia	10021128
Intermediate density lipoprotein decreased	10064237
Intermediate density lipoprotein increased	10064236
LDL/HDL ratio decreased	10052338
LDL/HDL ratio increased	10049030
Lipid metabolism disorder	10061227
Lipids abnormal	10024588

Preferred Term	Code
Lipids decreased	10024591
Lipids increased	10024592
Lipoprotein (a) abnormal	10054023
Lipoprotein (a) decreased	10054021
Lipoprotein (a) increased	10054009
Low density lipoprotein abnormal	10024901
Low density lipoprotein decreased	10024909
Low density lipoprotein increased	10024910
Non-high-density lipoprotein cholesterol decreased	10064235
Non-high-density lipoprotein cholesterol increased	10063967
Remnant hyperlipidaemia	10038316
Remnant-like lipoprotein particles increased	10073041
Total cholesterol/HDL ratio abnormal	10058633
Total cholesterol/HDL ratio decreased	10058631
Total cholesterol/HDL ratio increased	10058630
Type I hyperlipidaemia	10060749
Type II hyperlipidaemia	10045254
Type IIa hyperlipidaemia	10045261
Type IIb hyperlipidaemia	10045263
Type III hyperlipidaemia	10060751
Type IV hyperlipidaemia	10060753
Type V hyperlipidaemia	10060755
Very low density lipoprotein abnormal	10047352
Very low density lipoprotein decreased	10047360
Very low density lipoprotein increased	10047361

APPENDIX D. RHABDOMYOLYSIS AND MYOPATHY PREFERRED TERMS AND ASSOCIATED CODES

Preferred Term	Code
Muscle necrosis	10028320
Myoglobin blood increased	10028625
Myoglobin blood present	10059888
Myoglobin urine present	10028631
Myoglobinaemia	10058735
Myoglobinuria	10028629
Myopathy	10028641
Myopathy toxic	10028648
Necrotising myositis	10074769
Rhabdomyolysis	10039020
Acute kidney injury	10069339
Anuria	10002847
Biopsy muscle abnormal	10004803
Blood calcium decreased	10005395
Blood creatine phosphokinase abnormal	10005468
Blood creatine phosphokinase increased	10005470
Blood creatine phosphokinase MM increased	10005477
Blood creatinine abnormal	10005481
Blood creatinine increased	10005483
Chromaturia	10008796
Chronic kidney disease	10064848
Compartment syndrome	10010121
Creatinine renal clearance abnormal	10068447
Creatinine renal clearance decreased	10011372
Diaphragm muscle weakness	10012708
Electromyogram abnormal	10014431
Glomerular filtration rate abnormal	10018356
Glomerular filtration rate decreased	10018358
Hypercreatininaemia	10062747

Preferred Term	**Code**
Hypocalcaemia	10020947
Muscle disorder	10028300
Muscle enzyme increased	10057945
Muscle fatigue	10049565
Muscle haemorrhage	10028309
Muscle rupture	10028331
Muscular weakness	10028372
Musculoskeletal discomfort	10053156
Musculoskeletal disorder	10048592
Musculoskeletal pain	10028391
Myalgia	10028411
Myalgia intercostal	10028413
Myositis	10028653
Oliguria	10030302
Renal failure	10038435
Renal impairment	10062237
Renal tubular necrosis	10038540
Tendon discomfort	10074599