Clinical Study Protocol 747-209

OBETICHOLIC ACID

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

Version 4: 19 December 2016

Sponsor

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SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

12/19/16

Leigh MacConell, PhD — Date

Vice President, Clinical Development
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INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-209. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected subjects according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, electronic case report forms (eCRFs), and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the Sponsor.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 747-209 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki and all regulatory requirements for protection of human subjects in clinical studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____
Investigator's Name (Printed)

_____ _____
Investigator's Signature Date

STUDY PERSONNEL CONTACT INFORMATION

Medical Monitor

Investigators are encouraged to call the PRA Medical Support Center phone number for the United States and Canada at +1 866 326 5053 or send an email to the NASH medical monitor at CONTROL@prahs.com with safety questions as these lines of contact are monitored 24 hours a day.

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2. SYNOPSIS

Name of Sponsor/Company:
Intercept Pharmaceuticals, Inc.

Name of Investigational Product:
Obeticholic Acid

Name of Active Ingredient:
Obeticholic Acid (OCA); 6α-ethyl-chenodeoxycholic acid (6-ECDCA); INT-747; DSP-1747

Title of Study:
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

Study Center(s):
Approximately 30 investigational sites in the United States

Study Period:	**Phase of Development:**
Duration of individual subject participation: up to 5 weeks in Screening (depending on current statin use) and 16 weeks during the double-blind treatment phase, followed by an optional open-label long-term safety extension (LTSE) expected to last approximately 2 years.	Phase 2

Objectives:

Primary Objective

- To evaluate the effect of 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

Secondary Objectives

- 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 (TGs), total cholesterol, and apolipoprotein concentrations
  - Components of the reverse cholesterol transport pathway

Exploratory Objectives

- 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, and waist and hip circumference measurements; and 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)

Methodology:

This Phase 2, double-blind, randomized, placebo-controlled, multicenter study, with an open-label LTSE, will evaluate the effect 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. Approximately 80 subjects with histological evidence of definite or probable NASH, who meet all inclusion and none of the exclusion criteria will be enrolled. The histological evidence of definite or probable NASH will be based on the central reading 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 in the study. Statin-treated subjects will be required to stop statin treatment (after signing informed consent) for up to 5 weeks, including a 4-week washout period, prior to Randomization/Day 1.

Screening Period:

Subjects will have a screening period of up to 5 weeks prior to Randomization/Day 1.

Subjects using statins within 30 days of the initial Screening visit (Screening Visit 1) are required to stop statin therapy immediately following this initial visit and must undergo a 4-week statin washout period prior to Screening Visit 2. At Screening Visit 2, these subjects will have a pre-randomization visit for assessment of their fasting LDL cholesterol levels. Subjects with fasting LDL cholesterol values >200 mg/dL at Screening Visit 2 will be excluded from the study and their dyslipidemia should be managed according to standard of care.

Subjects who are not using statin therapy at Screening Visit 1 are required to provide a fasting blood sample at Screening Visit 2, which can occur at any time prior to randomization but after signing of the ICF. Statin-free subjects with fasting LDL cholesterol values >200 mg/dL at either Screening Visit will be excluded from the study and should be managed according to standard of care.

Double-Blind Phase:

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 LDL concentration (fasting serum LDL cholesterol at Screening Visit 2; ≤125 mg/dL or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4).

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 double-blind phase will occur at Week 16, after which subjects may continue into the open-label LTSE phase.

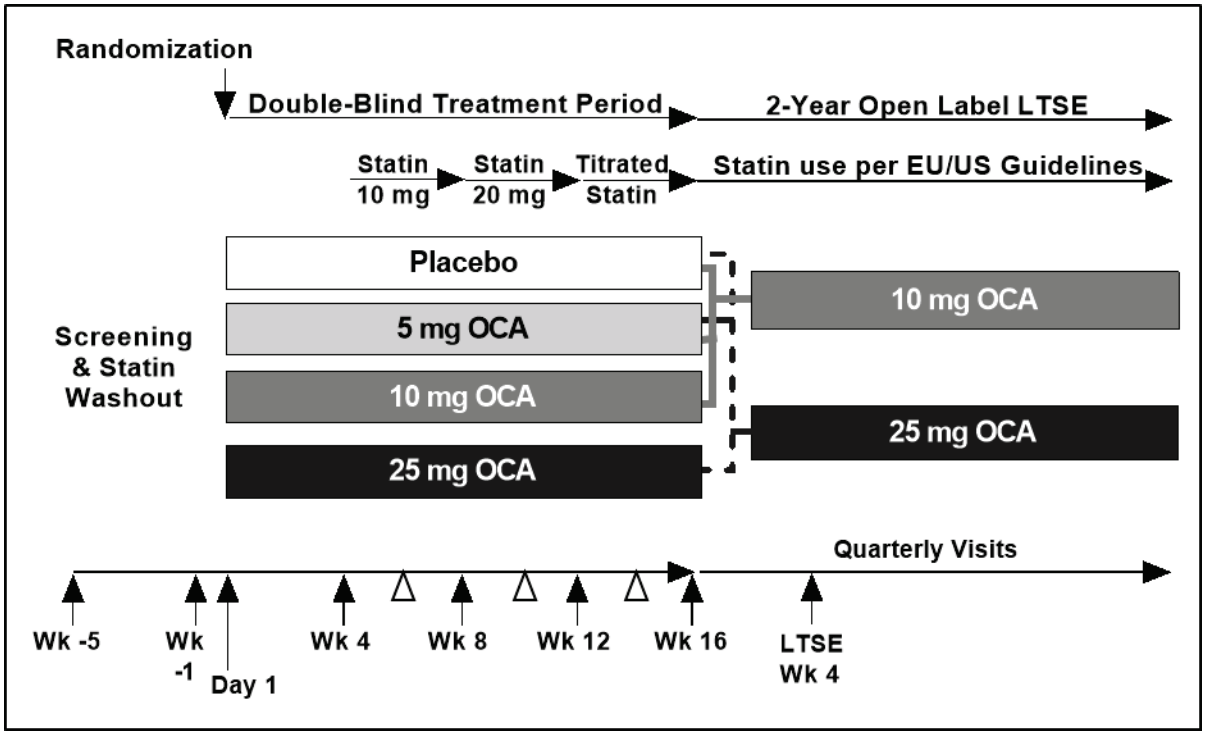
Subjects who discontinue investigational product or atorvastatin during the double-blind phase are still expected to attend scheduled study visits and are to be followed through the Week 16 Visit.

Subjects who discontinue atorvastatin during the double-blind phase are eligible to continue OCA during the double-blind phase and enroll into the LTSE at the discretion of the Investigator, provided they continue to meet the LDLc cutoff of exclusion criteria #4 (ie, LDLc <200 mg/dL).

LTSE Phase:

During the LTSE phase, all subjects will be treated with open-label OCA 10 mg or OCA 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. During the LTSE, subjects may continue with atorvastatin therapy as clinically indicated.

Study Design Diagram



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

Number of Subjects (Planned):

Approximately 80 subjects with biopsy-confirmed NASH and evidence of liver fibrosis, but no hepatic decompensation, who meet eligibility criteria, will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups. A maximum of 30% of subjects will have stage 4 fibrosis.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Subjects must satisfy all of the following criteria to be eligible for enrollment:

1. Age ≥18 years of age
2. Histologic evidence of NASH as assessed by central reading of a liver biopsy obtained no more than 1 year prior to randomization defined by the presence of all 3 key histological features of NASH with a score of at least 1 for each and a combined score of 4 or greater out of a possible 8 points according to NASH Clinical Research Network (CRN) criteria.
3. Histologic evidence of fibrosis stage 1 to stage 4 (as defined by the NASH CRN scoring of fibrosis) without any evidence of hepatic decompensation.
4. If subject has type 2 diabetes, is on stable dose of anti-diabetic medication (except thiazolidinediones [TZDs]) for ≥3 months prior to Day 1.
5. Is either not taking or is on stable doses of TZDs and/or Vitamin E for ≥6 months prior to Day 1
6. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below.

- Barrier method, ie, condom (male or female) with spermicide or diaphragm with spermicide
- Intrauterine device
- Vasectomy (partner)
- Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
- Abstinence (defined as refraining from heterosexual intercourse)

7. Must provide written informed consent and agree to comply with the study protocol including adherence to protocol-described statin withdrawal and statin therapy.

Exclusion Criteria

Subjects who satisfy any of the following exclusion criteria will be ineligible for enrollment:

1. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to Screening Visit 1 (significant alcohol consumption is defined as more than 2 units/day in females and more than 4 units/day in males, on average).
2. Prior intolerance to treatment with atorvastatin or other 3-hydroxy-3-methyl-glutaryl (HMG) Coenzyme A reductase inhibitors (including but not limited to rhabdomyolysis).
3. LDL cholesterol ≥190 mg/dL and already on statin therapy at Screening Visit 1.
4. LDL cholesterol >200 mg/dL at any Screening visit in subjects who are not on statin therapy, or at Screening Visit 2 in statin washout subjects.
5. Planned change in diet or exercise habits during participation in the double-blind period, or a significant weight change of >5% in the prior 6 months.
6. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.
7. History of biliary diversion.
8. Uncontrolled diabetes defined as HbA1c ≥9.5% within 60 days prior to randomization (Day 1).
9. Administration of any of the following medications as specified below:
   - Prohibited 30 days prior to Day 1:
     - bile acid sequestrants including cholestyramine and it's derivatives, colesevelam, colestipol, or
     - omega-3 fatty acid-containing dietary supplements
   - Prohibited 3 months prior to Day 1:
     - nicotinic acid and derivatives, ezetimibe, or
     - any prescription or over-the-counter medication or herbal remedy with putative NASH efficacy (except Vitamin E or TZDs), or
     - ursodeoxycholic acid, or
     - fenofibrate or other fibrates, or
     - Any over-the-counter or health foods used to treat lipids including plant sterols and berberine
   - Prohibited 6 months prior to Day 1:
     - azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate, mofetil, pentoxifylline; budesonide and other systemic corticosteroids, or
     - potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)

- Prohibited 12 months prior to Day 1:
  - antibodies or immunotherapy directed against interleukins, or
  - other cytokines or chemokines

10. Evidence of other forms of known chronic liver disease including but not limited to:
    - Positive test result at Screening for hepatitis B surface antigen
    - Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or history of positive HCV RNA test result
    - Primary biliary cirrhosis (also known as primary biliary cholangitis), primary sclerosing cholangitis, autoimmune hepatitis or overlap syndrome
    - Alcoholic liver disease
    - Wilson's disease or hemochromatosis or iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy
    - Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level less than normal; exclusion at the Investigator's discretion)
    - Prior known drug-induced liver injury within 5 years before Day 1
    - Known or suspected hepatocellular carcinoma
11. History of liver transplant, current placement on a liver transplant list, or current Model for End-Stage Liver Disease (MELD) score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (eg, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.
12. Presence of hepatic decompensation, including:
    - Gastroesophageal varices
    - Ascites
    - Hepatic encephalopathy
    - Spontaneous bacterial peritonitis
    - Hepatorenal or hepatopulmonary syndromes
13. Total bilirubin ≥2x upper limit of normal (ULN) at any Screening visit (subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >2x ULN if their conjugated bilirubin is <2x ULN).
14. Creatine phosphokinase >5x ULN at Screening Visit 2.
15. Serum creatinine ≥1.5 mg/dL at any Screening visit.
16. Serum ALT >300 U/L at any Screening visit.
17. Platelet count <75 000/mm3 at any Screening visit.
18. Known positivity for human immunodeficiency virus (HIV) infection.
19. Subjects with recent history (within 1 year of randomization) of cardiovascular disease or with history or planned cardiovascular interventions to treat atherosclerotic cardiovascular disease, including:
    a. Peripheral or Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting)
    b. Coronary angioplasty, stenting, or carotid atherectomy
    c. Cardiac pacemaker or defibrillator (placement of cardiac pacemaker or defibrillator for reasons other than atherosclerotic cardiovascular disease [eg, for treatment of atrial fibrillation subsequent to nodal ablation] is not exclusionary)

d. Prosthetic heart valves
e. Myocardial infarct, unstable angina, or acute coronary syndrome
f. Other clinically significant atherosclerotic cardiovascular disease
g. Cerebrovascular accident (stroke), cerebrovascular ischemia, or transient ischemic attack
h. Unstable hypertension
i. Familial hypercholesterolemia or other genetic lipid abnormality

20. Other concomitant disease, malignancy, or condition likely to significantly decrease life expectancy to <5 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphocytic leukemia) and moderate to severe congestive heart failure.
21. Known substance abuse, including inhaled or injected drugs in the year before Screening.
22. For female subjects: pregnancy, planned pregnancy, potential for pregnancy and unwillingness to use effective birth control during the study, or breastfeeding.
23. Participation in a clinical research study with any investigational product being evaluated for the treatment of diabetes or NASH in the 6 months before Day 1.
24. Receipt of any investigational product not being evaluated for the treatment of diabetes or NASH from Screening Visit 1 to Day 1, within 30 days prior to Day 1, or within 5 half-lives of the compound before Day 1 (whichever was longer).
25. Previous exposure to OCA.
26. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
27. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.
28. Any other condition which, in the opinion of the Investigator, would impede compliance or hinder completion of the study.
29. Acute cholecystitis or acute biliary obstruction

Investigational Product, Dosage and Mode of Administration:

OCA: 5 mg, 10 mg, or 25 mg or placebo tablets, once daily, oral administration

Study Medication, Dosage and Mode of Administration:

Atorvastatin: 10 mg, 20 mg, 40 mg, 80 mg once daily, oral administration

Duration of Subject Participation:

- Screening period for statin-using subjects: Up to 5 weeks (including a 4-week statin washout period)
- Screening period for non-statin-using subjects: Up to 5 weeks
- Double-Blind period: 16 weeks
- LTSE: 2 years

Duration of Treatment:

Double-Blind period:

- OCA/placebo: 16 weeks (Day 1 to Week 16)
- Atorvastatin: 12 weeks (Week 4 to Week 16), administered open-label

LTSE:

- OCA: 2 years
- Atorvastatin: As clinically indicated

Reference Therapy, Dosage and Mode of Administration:

Not applicable

Criteria for Evaluation:

Statistical Methods:

The assessments supporting the primary, secondary, and exploratory objectives of the study are as follows:

Primary Endpoints	**Assessment**
LDL metabolism	LDL cholesterol concentration, particle size, and particle concentration
Secondary Endpoints	
Lipoprotein metabolism	HDL cholesterol concentration, particle size and particle concentration; VLDL cholesterol concentration, particle size and particle concentration; TG and total cholesterol concentrations; apolipoprotein (Apo)A1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a) concentrations; PCSK9 concentration
Reverse cholesterol transport	Pre-β1 HDL concentration, macrophage cholesterol efflux; LCAT activity; CETP activity
Safety and tolerability	TEAEs (including cardiovascular events), physical exams, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)
Exploratory Endpoints	
Liver biochemistry and markers of liver function	Albumin, ALP (isoenzymes), ALT, AST, , direct bilirubin, GGT, INR, total bilirubin
Markers of liver inflammation	IL-6, hs-CRP, and TNF-α
Marker for hepatic apoptosis and fibrosis	CK-18-M30 and CK-18-M65
Glycemic Control	Glucose, insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR
OCA pharmacokinetics	OCA, tauro-OCA, glyco-OCA, total OCA, potentially other conjugates or metabolites not yet identified
Atorvastatin bioanalytical concentrations	Atorvastatin and its metabolites
Anthropometric measures	Height (at Screening Visit 1 only), weight, and waist and hip circumference measurements; and body mass index (BMI), and waist-to-hip ratio calculations
Pharmacodynamics	C4 (7α-hydroxy-4-cholesten-3-one), and FGF-19; possible analysis of conjugated and unconjugated endogenous bile acids
Noninvasive radiological liver fibrosis measurements	By TE (where available)
Cardiovascular risk scores	FRS and Reynolds scores

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; ApoCII = apolipoprotein CII; ApoCIII = apolipoprotein CIII; ApoE = apolipoprotein E; AST = aspartate aminotransferase; BMI = body mass index; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope M30; CK-18-M65 = cytokeratin-18 neoepitope M65; CTEP = cholesterol ester transfer protein; FGF-19 = fibroblast growth factor-19; FRS = Framingham Risk Score; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin-specific A1c fraction; HDL = high-density lipoprotein; HOMA-β: homeostatic model assessment –beta-cell function; HOMA-IR = homeostatic model assessment – insulin resistance; hs-CRP = high sensitivity C-reactive protein; IL-6 = interleukin-6; INR = international normalized ratio; LCAT = lecithin cholesterol acyltransferase; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamics; TE = transient elastography; TEAE = treatment emergent adverse event; TG = triglyceride; TNF-α = tumor necrosis factor-α; VLDL = very low-density lipoprotein

Analysis Populations:

The following analysis populations will be used:

Intent-to-Treat (ITT) Population

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

Safety Population

The Safety Population will include all subjects who receive any amount of investigational product. Treatment assignment will be based on the treatment actually received. The Safety Population will be used for the analysis of all safety data.

Efficacy Evaluable Population

All subjects who complete the double-blind phase according to the indicated doses of investigational product and atorvastatin without any significant protocol deviations. The Efficacy Evaluable Population will be the primary population used for efficacy analyses.

Pharmacokinetic Populations

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

LTSE Population

All subjects who receive any amount of investigational product as part of the LTSE will be included in the LTSE Population.

Efficacy Analyses:

The primary efficacy analyses will be based on the Efficacy Evaluable Population.

The primary efficacy parameter, changes in LDL cholesterol, particle size and particle concentration at Week 16 (end of the double-blind phase) compared to Baseline will be summarized by treatment group.

Analyses of observed LDL values will be carried out using an analysis of covariance (ANCOVA) model at each visit 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.

Descriptive statistics of the values will be summarized by treatment group and visit. The results, change from baseline, and percentage change from baseline values as well as estimates of least-square (LS) means, standard errors, and 95% confidence intervals (CIs) will be presented by treatment group.

The comparison of LDL change from baseline and percentage change from baseline values between each active treatment group and placebo group will be performed as exploratory analysis. Estimates of the LS mean difference between each active treatment group and placebo group, the standard error of the difference, and 95% CI of the difference will be presented.

The secondary 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, and estimates of LS means, standard errors, and 95% CIs presented by treatment group.

The secondary parameters related to lipoprotein metabolism include HDL cholesterol concentration, particle size and particle concentration; VLDL cholesterol concentration, particle size and particle concentration; TG and total cholesterol concentrations; and apolipoprotein (Apo)A1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a) concentrations.

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

The baseline value for efficacy analyses is defined as the last value prior to administration of investigational product on Day 1 (predose).

The following exploratory parameters will be analyzed in the same manner as the secondary efficacy variable: markers of liver biochemistry, liver function, liver inflammation, apoptosis, liver fibrosis, glycemic control, and bile acids. Additionally, descriptive statistics will be generated and will include change from baseline, percentage change from baseline, and estimates of LS means, standard errors, and 95% CIs presented by treatment group. Changes from baseline will be summarized for anthropometric measures. PK analysis will be done using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics. Only samples that have a confirmed fasting of approximately 8 hours or more before their visit will be included in the PK analysis. Further details regarding specific parameters and methods will be described in the Statistical Analysis Plan.

Safety Analyses:

All safety analyses will be based on the Safety Population. The incidence of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs) will be tabulated by system organ class and preferred term for each treatment group, and similarly by severity and relationship to treatment. The incidence of pre-treatment AEs and pre-treatment SAEs occurring after informed consent form signoff and before the first dosing of investigational product (OCA or placebo) will be tabulated in the same manner as above for all subjects participating in the washout period.

Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized.

LTSE Analyses:

Similar analyses to that which are described above will be conducted for the LTSE using the double-blind baseline value. Analyses based on the double-blind baseline will be performed using randomized treatment groups (placebo, OCA 5 mg, OCA 10 mg, or OCA 25 mg). Sensitivity analyses may be conducted using the last value prior to first dose in the LTSE for all subjects.

Sample Size Justification:

It is the intent of this study to characterize the components of LDL metabolism (cholesterol concentration, particle size, particle concentration) 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 LDL in the OCA 25 mg group without atorvastatin therapy after 16 weeks of treatment based on data from FLINT, a sample size of 20 subjects per group will provide greater than 97.3% power to demonstrate the statistically significant difference of LDL increase from baseline with a 2-sided type I error of 0.05.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this protocol.

Abbreviation or Specialist Term	Explanation
6-ECDCA	6α-ethyl-chenodeoxycholic acid
A1AT	alpha-1-antitrypsin
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ApoCII	apolipoprotein CII
ApoCIII	apolipoprotein CIII
ApoE	apolipoprotein E
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
BMI	body mass index
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
C4	7α-hydroxy-4-cholesten-3-one
CAC	Cardiovascular Adjudication Committee
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
COX-2	cyclooxygenase-2
CPK	creatine phosphokinase
CRA	Clinical Research Associate
CRF	case report form(s)
CRN	clinical research network
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Specialist Term	Explanation
DMC	Data Monitoring Committee
eCRF	electronic case report form(s)
ECG	electrocardiogram
EDC	electronic data capture
EOS	End of Study
ET	Early Termination
FGF-19	fibroblast growth factor-19
FLINT	Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment
FRS	Framingham Risk Score
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
glyco-OCA	glycine conjugate of OCA
GMP	Good Manufacturing Practice
HbA1c	hemoglobin-specific A1c fraction
HCC	hepatocellular carcinoma
HDL	high-density lipoprotein
HDLc	high-density lipoprotein cholesterol
HDPE	High-density polyethylene
HIV	human immunodeficiency virus
HMG	3-hydroxy-3-methyl-glutaryl
HOMA-β	homeostatic model assessment–beta-cell function
HOMA-IR	homeostatic model assessment – insulin resistance
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	investigational new drug
iNOS	inducible nitric oxide synthase

Abbreviation or Specialist Term	Explanation
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator site file
ITT	intent-to-treat
IWRS	interactive web response system
LCAT	lecithin cholesterol acyltransferase
LDL	low-density lipoprotein
LDLc	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
LS	least-square
LTSE	long-term safety extension
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
NAFLD	nonalcoholic fatty liver disease
NAS	nonalcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
NMR	nuclear magnetic resonance
OCA	obeticholic acid
PAI-1	plasminogen activator inhibitor-1
PBC	primary biliary cirrhosis (also known as primary biliary cholangitis
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamics(s)
PI	Principal Investigator
PK	pharmacokinetic(s)
PSC	primary sclerosing cholangitis
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	suspected adverse reaction
SREBP1c	sterol regulatory element binding protein
SUSAR	suspected unexpected serious adverse reaction

Abbreviation or Specialist Term	Explanation
T3	triiodothyronine
T4	thyroxine
tauro-OCA	taurine conjugate of OCA
TE	transient elastography
TEAE	treatment-emergent adverse event
TG	triglyceride
TNF-α	tumor necrosis factor-α
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VLDL	very low-density lipoprotein

5. INTRODUCTION

5.1. Overview of Nonalcoholic Steatohepatitis and Obeticholic Acid

Nonalcoholic fatty liver disease (NAFLD) is considered to be the hepatic manifestation of metabolic syndrome, a cluster of closely related clinical features linked to visceral obesity and characterized by insulin resistance, dyslipidemia, and hypertension (Chalasani 2012, Angulo 2011). NAFLD is the most common cause of chronic liver disease in the western hemisphere, and as the prevalence of obesity and metabolic syndrome rises, a parallel rise of NAFLD across the world is generally expected. NAFLD is thought to be represented by a spectrum of histological disease, which progresses from pure fatty liver (simple steatosis) to nonalcoholic steatohepatitis (NASH). While NAFLD itself is considered a relatively benign and reversible condition, up to one-third of patients in the spectrum of NAFLD develop NASH, a chronic, serious, life-threatening, inflammatory liver disease characterized by hepatocellular injury, inflammation, and progressive fibrosis. As opposed to simple steatosis, NASH is associated with significant morbidity and progression that, if left untreated, can progress to advanced fibrosis, cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related death (Vernon 2011).

Of all the histologic features of NASH, fibrosis is considered the strongest predictor of adverse clinical outcomes, including liver-related death (Younossi 2011, Ekstedt 2014). Patients with NASH develop progressive fibrosis over a period of 4 to 6 years (Pagadala 2012) and 21% to 26% of these patients develop cirrhosis in 8.2 years (Loomba 2013). In patients with NASH who have progressed to cirrhosis, it is estimated 38% to 45% have liver failure after 7 years to 10 years, and 2% to 5% of this population will develop HCC per year (Organisation 2012). Accumulating evidence suggests that patients with NASH can progress to HCC, even in the absence of apparent cirrhosis (Williams 2013, Ertle 2011).

There are currently no approved therapies for the treatment of NASH nor an accepted standard of care. The therapeutic options for NASH are largely limited to lifestyle modifications and treatment of concurrent conditions such as diabetes (Chalasani 2012, Neuschwander-Tetri 2003, Sanyal 2010, Belfort 2006), although practice guidelines from the American Association for the Study of Liver Diseases recommend the use of vitamin E as first line therapy for patients with NASH without diabetes.

In view of the serious nature of the disease, the increasing prevalence, the complications that arise from the disease, and the clear unmet medical need, evaluation of therapies for NASH is warranted.

Obeticholic acid (OCA) is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary bile acid chenodeoxycholic acid (CDCA). CDCA is the natural ligand for FXR, which is a nuclear receptor expressed at high levels in the liver, intestine, kidney, and adrenal glands. In the liver, FXR is expressed in hepatocytes, Kupffer cells, and endothelial cells, and at a low level in hepatic stellate cells. Nuclear receptors constitute a family of ligand-activated transcription factors that can either activate or repress a variety of target genes.

OCA is 100-fold more potent than the endogenous FXR agonist CDCA, which makes OCA an attractive novel therapeutic agent for NAFLD and NASH due to its multiple FXR-mediated effects, including an increase in insulin sensitivity, glucose and lipid metabolism; hepatocyte

protection against bile acid-induced cytotoxicity; anti-inflammatory effects in liver and vasculature; and prevention and reversal of liver fibrosis (Mudaliar 2013, Adorini 2012). Thus, there is strong rationale to advance OCA for the treatment of NASH based on its FXR-mediated hepatoprotective properties, and results that indicate OCA improves glycemia by increasing peripheral glucose uptake, enhances glucose-stimulated insulin secretion, and inhibits hepatic lipid synthesis and content while inducing lipid uptake by adipocytes.

5.2. NASH, Lipoprotein Metabolism, and Statins

NAFLD is the most common cause of incidental abnormal serum liver enzymes and is associated with dyslipidemia and high-risk of cardiovascular events. Statins have been shown to reduce the risk of major coronary and vascular events in NAFLD (Pastori 2015). There has been some concern that patients with underlying liver disease are at an increased risk of hepatotoxicity because the statins are hepatically cleared and can cause elevations in liver enzymes. However, there have also been studies that have shown that elevated serum transaminases secondary to comorbid conditions like NAFLD or NASH may be improved by statin treatment (Athyros 2010, Pastori 2015). Atherogenic hyperlipidemia, which is defined by increased triglycerides (TGs), decreased high-density lipoprotein (HDL), and the presence of small, dense low-density lipoprotein (LDL), is frequently associated with NAFLD, thus the treatment of dyslipidemia plays a critical role in the overall management of NAFLD and NASH.

In the Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) Trial conducted by the NASH Clinical Research Network (CRN) at the National Institute of Diabetes and Digestive and Kidney Diseases, subjects with non-cirrhotic NASH were randomized to either placebo or 25-mg OCA for 72 weeks (Neuschwander-Tetri 2014). Subjects in this study were representative of the NASH population with baseline total cholesterol and LDL cholesterol (LDLc) levels at the high end of normal, HDLc levels within the normal range, and TG levels borderline high. Approximately 50% of subjects were receiving antilipidemic agents at Baseline. Increases in total cholesterol, LDLc, and TG were observed in both treatment groups with OCA-treatment being associated with a somewhat greater percentage of subjects exhibiting increased concentrations of total cholesterol and LDLc. Similarly, decreases in HDL cholesterol (HDLc) were observed in both treatment groups with a higher percentage of OCA-treated subjects compared with placebo. While the OCA-related changes in lipids was modest and initial increases in total cholesterol and LDLc trended back towards baseline values with continued treatment, it is important to characterize the mechanism of OCA treatment on lipids in patients with NASH and the functionality of concomitant lipid therapies.

Using nuclear magnetic resonance (NMR) lipid profiling, it will be possible to characterize the effect of OCA on the actual concentration and sizes of the particles within each lipoprotein class. While a standard lipid panel measures the cholesterol or TG content of lipoproteins, it does not measure the actual particle concentration. The cholesterol and TG content of LDL, HDL, and very low-density lipoprotein (VLDL) particles is not constant, but varies widely among individuals and over time. Even within a given lipoprotein class, the sizes of the particles are not uniform as the relative amounts of cholesterol and TG carried in the core of a lipoprotein particle varies across individuals. Compositional differences also relate to plasma TG levels with LDL and HDL particles becoming more cholesterol-depleted and TG-rich as plasma TG levels increase. Thus, presentation of the same measured concentration of LDL in 2 patients may

represent significantly different numbers of LDL particles and, therefore, a different risk for cardiovascular disease (Jeyarajah 2006, Otvos 2006). The patient with the higher number of small, atherogenic LDL particles would be considered to be at higher cardiovascular risk. Thus, NMR lipid profiling, which allows differentiation of particle size and number, will provide a better understanding of the mechanistic impact of OCA treatment on lipids.

Recent evidence also suggests that HDL-mediated atheroprotection is largely governed through regulation of reverse cholesterol transport from macrophages within atherosclerotic plaques to HDL acceptor particles for ultimate return to the liver and biliary excretion (Rohatgi 2014). Thus, this study will also assess macrophage efflux and candidate components of this pathway to further elucidate the mechanism of OCA and atorvastatin treatment on lipids in the presence of NASH.

5.3. Mechanism of Action of Obeticholic Acid

CDCA is the principal natural ligand of FXR in humans. When cellular levels are high, the negative feedback pathway inhibits the further synthesis of bile. OCA is structurally related to CDCA and differs by the addition of a single ethyl group (the chemical name of OCA is 3α 7α-dihydroxy-6α-ethyl-5βcholan-24-oic acid. It is also referred to as 6α-ethyl-chenodeoxycholic acid, or (6-ECDCA) and as an agonist it is approximately 100-fold more potent than CDCA in vitro (Pellicciari 2002). OCA is also highly selective for FXR and does not bind other nuclear receptors, and with the exception of weakly activating the dedicated bile acid receptor TGR5, it does not activate any G-protein coupled receptors (CEREP 2008).

OCA is an attractive novel therapeutic agent for NAFLD and NASH due to its multiple FXR-mediated effects including an increase in insulin sensitivity, hepatocyte protection against bile acid-induced cytotoxicity, anti-inflammatory effects in liver and vasculature, and prevention and reversal of liver fibrosis (Adorini 2012, Mudaliar 2013). Specifically:

- FXR and other identified bile acid receptors, such as TGR5, play a role in regulating key aspects of carbohydrate and lipid metabolism; thus, serving as important mediators of energy expenditure and metabolic homeostasis.
- FXR agonists have been shown to suppress hepatic fatty acid and TG synthesis through down-regulation of sterol regulatory element binding protein (SREBP1c) and increase hepatic fatty acid oxidation through up-regulation of pyruvate dehydrogenase kinase 4 (Lefebvre 2009).
- FXR activation has insulin-sensitizing effects. In mice fed a high-fat diet, treatment with recombinant fibroblast growth factor-19 (FGF-19) improves indices of dyslipidemia, hepatic steatosis, hyperinsulinemia, hyperleptinemia, and insulin sensitivity, while reducing body weight and adiposity (Fu 2004). Studies in FXR knockout mice show that FXR is involved in the regulation of insulin signaling pathways and the receptor appears to have a beneficial role in decreasing insulin resistance (both hepatic and in skeletal muscle) and gluconeogenesis, as well as in regulating TG, free fatty acid, and lipid levels.

- Treatment of OCA at doses of 25 mg and 50 mg for 6 weeks resulted in increased insulin sensitivity and reduced markers of liver inflammation and fibrosis in subjects with NAFLD and type 2 diabetes mellitus (Mudaliar 2013).
- Treatment with OCA at a dose of 25 mg for 72 weeks was superior to placebo in improving not only the key histologic features important in the underlying pathophysiology of the disease (inflammation, ballooning, steatosis), but notably that OCA was superior to placebo in improving fibrosis, a strong predictor of liver-related death (Neuschwander-Tetri 2014).

The FXR-SHP cascade is postulated to mediate the links between lipid and glucose metabolism (Zhang 2008, Cariou 2006, Rizzo 2006, Ma 2006, Shulman 2005).

OCA induces lipid uptake by mouse adipocyte cell line (3T3-L1) and primary human adipocytes, which correlate with reduced hepatic and circulating lipid levels, together with increased insulin sensitivity (Rizzo 2009, Rizzo 2006). Moreover, OCA significantly enhances adiponectin and leptin secretion by mouse and human adipocytes, which can enhance insulin sensitivity in peripheral tissues. Pancreatic beta cells express FXR messenger ribonucleic acid (mRNA) and protein, and OCA significantly enhances insulin secretion by mouse β-TC6 cells and human pancreatic islets (Rizzo 2009).

Collectively, these results indicate that OCA improves glycemia by increasing peripheral glucose uptake, enhancing glucose-stimulated insulin secretion, and inhibiting hepatic lipid synthesis and content while inducing lipid uptake by adipocytes (Adorini 2012, Mudaliar 2013).

5.4. Nonclinical Experience with Obeticholic Acid

Nonclinical studies have shown several potentially beneficial properties of FXR agonism in NASH, including

Effects of OCA on glycemic, metabolic, and cardiovascular properties

- FXR plays a role in bile acid homeostasis, metabolism, and clearance (Zhang 2008, Ma 2006, Cariou 2006).
- FXR controls glucose metabolism through regulation of gluconeogenesis and glycogenolysis in the liver, as well as regulation of peripheral insulin sensitivity in striated muscle and adipose tissue (Mudaliar 2013, Zhang 2006).
- In nonclinical models, FXR agonism is associated with beneficial effects on body weight and composition (Xu 2009, Fu 2004).
- The absence of endogenous intact FXR signaling results in dyslipidemia and a hepatic phenotype similar to NASH patients (Zhang 2008). Conversely, FXR agonists lower plasma TGs by repressing hepatic sterol regulatory element binding protein 1-c (Watanabe 2004) and increased hepatic fatty acid oxidation (Savkur 2005).
- In addition, OCA and other FXR agonists are anti-atherogenic and cardioprotective in animal models (Hartman 2009, Miyazaki-Anzai 2010).

Anti-inflammatory and anti-fibrotic effects of OCA

- OCA exerts direct effects on serum-starved LX2 cells (an immortalized hepatic stellate cell line) to reduce the expression of key fibrotic genes (collagen I, alpha smooth muscle actin, transforming growth factor β-1 and matrix metalloproteinases; (Albanis 2005).
- In primary and cultured hepatocytes treated with pro-inflammatory mediators, OCA exerted direct effects to inhibit pro-inflammatory gene expression (eg, tumor necrosis factor-α [TNF-α], cyclooxygenase-2 [COX-2], and inducible nitric oxide synthase [iNOS]; (Wang 2008, Li 2007).
- FXR activation (with WAY-362450) reduced inflammatory cell infiltration and hepatic fibrosis in a mouse model of NASH (Zhang 2009).
- OCA improved portal hypertension in cirrhosis models (Mookerjee 2014).
- OCA inhibited gastrointestinal inflammation and preserves intestinal barrier function in models of inflammatory bowel diseases (Gadaleta 2011).

Effects of OCA on diabetic nephropathy

- OCA ameliorates TG accumulation by modulating fatty acid synthesis and oxidation in a murine model of diet-induced obesity (Wang 2009)
- In the same murine model of diet-induced obesity, OCA improves proteinuria, prevents podocyte loss, mesangial expansion, accumulation of extracellular matrix proteins, and increased expression of pro-fibrotic growth factors and fibrosis markers, and reduces inflammation and oxidative stress (Wang 2009)
- In a murine model of diabetes, OCA improves renal injury by decreasing proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis, and modulating renal lipid metabolism, macrophage infiltration, renal expression of SREBPs, pro-fibrotic growth factors, and oxidative stress enzymes (Wang 2010)

In summary, there is strong rationale to advance OCA for the treatment of NASH based on its FXR-mediated hepatoprotective properties and results indicating that OCA improves glycemia by increasing peripheral glucose uptake, enhances glucose-stimulated insulin secretion, and inhibits hepatic lipid synthesis and content while inducing lipid uptake by adipocytes.

5.5. Clinical Experience with Obeticholic Acid

OCA is under investigation for the treatment of multiple chronic liver diseases, including the treatment of NASH, primary biliary cirrhosis (PBC, also known as primary biliary cholangitis [Beuers 2015a, Beuers 2015b, Beuers 2015c]), primary sclerosing cholangitis (PSC), and biliary atresia. The clinical development program for OCA includes the following 3 studies conducted using subjects with NAFLD or NASH:

- Study 747-203: A proof-of-concept, Phase 2 study in subjects with type 2 diabetes and NAFLD to evaluate the effects of OCA on insulin sensitivity (Mudaliar 2013)

- FXR Ligand OCA in NASH Treatment (FLINT): A Phase 2 study conducted by the National Institute of Diabetes and Digestive and Kidney Diseases and the NASH CRN to evaluate the efficacy and safety of OCA in the treatment of NASH (Neuschwander-Tetri 2014)
- Study D8602001: A Phase 2 study conducted by Intercept's Asian development partner (Sumitomo Dainippon Pharma Co., Ltd) to evaluate the efficacy and safety of 3 doses of OCA versus placebo in NASH

Study 747-203 showed improved insulin sensitivity in subjects with type 2 diabetes and NAFLD, demonstrating the clinical relevance of the FXR agonist pathway and supporting the potential of OCA to treat NAFLD and/or NASH. With the exception of weight loss, OCA 25 mg appeared to be at least as effective as OCA 50 mg for the majority of endpoints evaluated.

The FLINT study demonstrated that OCA was superior to placebo in improving not only the key histologic features important in the underlying pathophysiology of the disease (inflammation, ballooning, steatosis), but notably that OCA was superior to placebo in improving fibrosis, a strong predictor of liver-related death. OCA treatment was also associated with improvement in markers of hepatocellular injury and some cardiometabolic features including weight and systolic blood pressure. Salutary effects on weight and blood pressure are important considerations since patients with NASH present with higher cardiovascular risk given the comorbidities of obesity and diabetes.

On average, LDL cholesterol demonstrated a significant increase in subjects treated with OCA compared to placebo; however, this increase was reversed and LDL cholesterol returned to below baseline levels in subjects who initiated statin therapy. The change in lipid profile, which was attenuated with continued treatment and reversed post-treatment, needs to be further investigated mechanistically and with respect to clinical management with standard of care statin therapy. With the exception of pruritus, which occurred more frequently in the OCA-treated subjects (23% OCA versus 6% placebo) and led to 1 discontinuation, the general adverse event (AE) profile was similar across both groups. There were 2 deaths in the FLINT study, both in OCA treatment groups (one from sepsis and congestive heart failure, and the other from cardiac ischemia or infarction (Neuschwander-Tetri 2014). The event of cardiac ischemia or infarction was assessed by the Investigator as possibly related to OCA while the event of sepsis was assessed as unrelated to OCA by the Investigator (Data on File).

Study D8602001 demonstrated a dose-dependent increase in the percentage of OCA-treated subjects compared to placebo subjects who achieved the primary endpoint ($p = 0.053$, not significant). The 40 mg OCA dose group achieved statistical significance for the primary endpoint compared to placebo ($p = 0.0496$). Dose-dependent trends not reaching statistical significance were also observed for several other pre-specified histologic endpoints, including the proportion of subjects with steatosis and inflammation improvement, ballooning resolution, and NASH resolution. In the completer analysis, similar dose-dependent effects were observed, with 51% of patients in the 40 mg dose group compared to 22% in the placebo group meeting the primary endpoint ($p = 0.0061$). With the exception of dose-dependent pruritus, OCA appeared to be generally safe and well tolerated. The number of pruritus-associated discontinuations were 0, 0, 2, and 5 subjects in the placebo, 10 mg, 20 mg, and 40 mg OCA groups, respectively. Changes in lipid parameters were directionally similar to those observed in the FLINT study.

No other meaningful differences in the rate of AEs between the OCA and placebo groups were noted.

Overall, the safety and efficacy profiles of OCA support a favorable benefit-risk ratio and demonstrate that OCA is a potentially important therapeutic option for patients with NASH, PBC, and other liver and gastrointestinal conditions. Pruritus is the most common dose-related AE associated with OCA treatment, especially in subjects with cholestasis. Other potential risks include liver toxicity and lipid profile abnormalities.

5.6. Rationale for Study Design, Doses of Investigational Product and Use of Atorvastatin

5.6.1. Rational for Study Design

As described in Section 5.1, the incidence of NASH is increasing and is likely to be the leading cause of liver transplant by 2020, highlighting the need for development of effective therapies that may improve steatohepatitis and resulting fibrosis, potentially delaying liver transplant or death. Given the atherosclerotic risk associated with elevations in LDL cholesterol, which are common in NASH, and also an observed effect of treatment with OCA, it is important to characterize the changes observed in circulating cholesterol associated with OCA treatment and the potential for management of those changes.

FXR has been shown to play an important role in lipid homeostasis and atherosclerosis with the potential to modulate circulating levels of both LDL and HDL cholesterol, which are components of cardiovascular prognosis in rodents (Gautier 2013, Zhang 2010, Nissen 2007). Similarly, the FLINT study demonstrated OCA-related changes in LDL and HDL cholesterol (Neuschwander-Tetri 2014). While the observed changes in LDL cholesterol in both rodents and humans run counter to changes that have been typically associated with improved cardiovascular health, animal data have consistently shown FXR agonism to be associated with reductions in atherosclerotic plaque formation. Rodent studies have shown that this anti-atherogenic effect with FXR agonism is possibly due to an increase in the hepatic clearance of excess cholesterol (Mencarelli 2009, Hartman 2009, Zhang 2010). It should be noted that the relevance of these findings to humans needs further evaluation due to differences in human and rodent lipid physiology.

In addition to cholesterol concentration, lipoprotein particle concentration and sizes have emerged as important factors in the evaluation of cardiovascular risk (Jeyarajah 2006). A recent Veterans Affairs study assessing LDL and HDL cholesterol concentrations, as well as particle size and numbers, in subjects treated with gemfibrozil demonstrated that these factors were stronger predictors of cardiovascular risk or benefit, respectively, than cholesterol concentrations (Otvos 2006). Consistently, examination of LDL and HDL cholesterol concentrations and particle concentration from the Framingham Offspring cohort (n = 3066), showed that LDL particle concentration was more predictive of cardiovascular risk (Cromwell 2007).

Given the complex role of FXR in lipid homeostasis, the observations of OCA on HDL and LDL concentrations in NAFLD and NASH, and the importance of evaluating the underlying function and composition of apolipoproteins, it is essential to evaluate the effect of OCA on these lipid-driven mechanisms of cardiovascular risk/benefit when considering OCA as a potential treatment for NASH. As such, this study, 747-209, will evaluate the effect of OCA on lipid

metabolism and the subsequent management of lipid changes with atorvastatin therapy. Evaluated parameters will include changes in cholesterol concentrations, lipoprotein particle size and number, apolipoprotein concentrations and the effects on reverse cholesterol transport in subjects with NASH.

5.6.2. Rationale for Placebo Control Group

The use of a randomized placebo control will provide the best scientific evidence of safety and efficacy of OCA in NASH subjects. As there is no approved or proven pharmacologic therapy for NASH, the use of a placebo arm for comparative analysis is desired for robust analysis of efficacy and safety data. As the intent of the present study is to assess the effects of multiple doses of OCA and the subsequent addition of atorvastatin on cholesterol metabolism as well as the safety and tolerability of OCA in subjects with NASH, it is important to include a placebo control group to understand the relationship to OCA of any changes observed. In addition, the combination of OCA and atorvastatin (or any other statin) has not been previously evaluated in clinical studies; thus, the placebo control group, which will be treated with atorvastatin, will provide comparative information regarding the safety and tolerability of the OCA and atorvastatin combination compared to atorvastatin alone.

5.6.3. Rationale for OCA Doses

The selection of OCA doses for the present study (5 mg, 10 mg, and 25 mg) was guided by the available safety and tolerability data from randomized, double-blind, placebo-controlled Phase 2 and Phase 3 studies in subjects with NAFLD, NASH, and PBC as described in Section 5.5 above.

In Study 747-203, subjects with type 2 diabetes and NAFLD were treated with placebo, OCA 25 mg, or OCA 50 mg for 6 weeks. Although both doses were similarly efficacious, there were clinically significant increases in the LDLc levels in both OCA dose groups, with a significant reduction in HDL observed in the OCA 50 mg treatment group. Similarly, OCA was efficacious and well-tolerated in the subsequent, Phase 2, randomized, double-blind FLINT study, which evaluated OCA 25 mg and placebo in subjects with NASH over a period of72 weeks. In this study, small but statistically significant changes in the levels of total cholesterol and LDLc levels (increase from Baseline), and HDL levels (decrease from Baseline) were observed with OCA treatment. Due to the similarity in efficacy and the observed lipoprotein changes in the two Phase 2 studies in subjects with NASH, OCA 25 mg will be the maximum dose in this study.

There was an increased incidence of mostly mild or moderate pruritus in OCA-treated subjects compared to placebo-treated subjects in the FLINT study. Pruritus was also the most common AE associated with OCA in PBC studies, and has been shown to be dose-related, warranting evaluation of lower doses as a potential strategy to improve tolerability. Phase 2 and Phase 3 studies evaluating OCA for the treatment of PBC have shown that the incidence and severity of pruritus with OCA treatment can be mitigated with lower OCA doses of 5 mg to 10 mg. Therefore, based on the therapeutic effect of 10 mg in PBC and to evaluate potential attenuation of the effect of OCA on pruritus and serum lipid levels, both 5 mg and 10 mg daily will be evaluated in the proposed NASH study in addition to the 25-mg dose.

5.6.4. Rationale for the Use of Atorvastatin

Subsequent to diet and lifestyle modification, statin therapy is recommended for the management of cholesterol to reduce cardiovascular risk globally (Perk 2012, NICE 2014, Stone 2014). Atorvastatin is one of the most commonly used statins worldwide (Jackevicius 2012). Historically, statin therapy has been contraindicated in subjects with elevations in liver aminotransferases. However, several studies have evaluated statin use in chronic liver diseases where cardiovascular risk is a significant concern and the consensus findings have not shown an increased risk of hepatotoxicity in subjects with elevated liver aminotransferases. Calderon et al reported that statin treatment is safe and can improve both liver aminotransferase levels and reduce cardiovascular morbidity (Calderon 2010, Tikkanen 2013, Athyros 2010).

The increase in LDL cholesterol levels in the OCA-treated NASH population observed in clinical studies may predispose these subjects to increased cardiovascular risk. Atorvastatin is one of the most widely prescribed statins for dyslipidemia in North America (Jackevicius 2012, Jackevicius 2013). The atorvastatin prescribing information suggests a starting dose of 10 mg, with dose adjustments every 2 to 4 weeks. In line with this recommendation, all subjects will be started at an atorvastatin dose of 10 mg at Week 4, titrating to 20 mg atorvastatin at Week 8 (if 10 mg daily is tolerated), and allowing for further dose adjustments at Week 12 based on clinical need and Investigator discretion.

In addition to mitigating the potential risk of statin use in this population by initiating treatment at the lowest indicated dose (10 mg once daily), subjects with excessive (>300 U/L) elevations in alanine aminotransferase (ALT), pre-existing cardiovascular disease, and those with elevated cardiovascular risk (eg, unstable hypertension) will be excluded. Finally, liver function, cholesterol levels, and vital signs will be monitored at all visits in this study, and investigational product will be withdrawn or its dosing interrupted in subjects who develop elevated levels of liver enzymes per protocol discontinuation criteria (see Section 8.4.1).

5.6.4.1. Rationale for Statin Withdrawal

The intent of this study is to assess the increase in LDL cholesterol with OCA and then to determine the extent to which this can be mitigated with appropriate use of statin therapy. Therefore, participating subjects need to either be statin-free or have washed off of their current statin therapy. Given the clear role of statins in reducing cardiovascular risk, it is imperative to minimize the potential risk associated with withdrawing statin therapy. These steps include minimizing the duration of statin withdrawal and exclusion of subjects for whom removal of statin therapy is of significant concern.

Duration of statin withdrawal

A statin withdrawal period of 5 weeks was selected and is similar to other recent studies in statin-using patients where a 4-week washout period was employed (Teramoto 2012, Teramoto 2014). The extra week in the present study allows for the assessment of LDL levels after 4 weeks of washout, and based on prior studies, assumes levels of LDL to be stable after 4 weeks, and enables the stratification of subjects at randomization on Day 1 by this value.

Following randomization, subjects will be treated with OCA or placebo for 4 weeks prior to the introduction of atorvastatin. Based on data in healthy subjects, PBC, and NAFLD, 4 weeks is

sufficient to observe peak changes in LDL and HDL cholesterol due to OCA alone in most subjects.

Overall, statin therapy will be withheld from subjects for a maximum of 9 weeks: 5 weeks prior to randomization on Day 1 and 4 weeks following randomization. This duration of statin withdrawal is less than the combined withdrawal period used in the Teramoto et al study, which included a group of subjects who had statin therapy withheld for a total of 16 weeks (4 week washout period followed by 12 weeks of placebo treatment) (Teramoto 2014). There was no appreciable difference in the safety profile of these patients compared to those who had statin therapy reintroduced after the washout period. Further support for the minimal impact of short-term discontinuation of statins is seen in follow-up analyses of the Treating to New Target study which showed that even in patients with stable coronary artery disease, that a 6-week interruption of statin therapy did not acutely impact cardiac events (McGowan 2004).

Exclusion of subjects at elevated risk

Subjects where the removal of a statin would be considered to be clinically concerning are excluded from participation in this study. At risk subjects include subjects with existing cardiovascular disease (including but not limited to stable or unstable angina, previous myocardial infarction or stroke or a previous peripheral or coronary revascularization procedure), significant dyslipidemia (as defined by LDLc ≥190 mg/dL) despite the use of statin therapy, unstable hypertension, and familial hypercholesterolemia.

Safety monitoring during the off-statin period

All subjects will have frequent safety assessments prior to and following the reintroduction of statin therapy. Following Screening Visit 1, subjects will have 4 visits to the study site over the 9-week period prior to initiation of atorvastatin: Screening Visit 2/Week -1, Randomization/Day 1, Week 2 and Week 4. During these visits AEs, vital signs, and safety labs will be assessed and monitored by the site staff.

5.6.5. Rationale for Duration of Treatment

In the clinical studies where healthy subjects and subjects with PBC were treated with OCA, changes in cholesterol were evident by 2 weeks of treatment. Accordingly, the effect of OCA on lipoprotein metabolism, prior to the introduction of atorvastatin, will be assessed at 2 and 4 weeks of treatment to evaluate the change in these parameters and the effect of sustained treatment with OCA; all subjects will then initiate atorvastatin therapy, in addition to their blinded treatment, and the effect on lipoprotein metabolism will be evaluated over an additional 12 weeks. The total duration of the double-blind phase of the study is 16 weeks, which is sufficient to evaluate the effect of atorvastatin on the OCA treatment-induced alterations in the lipoprotein profile of statin-naïve and statin-washed out NASH subjects.

Following the double-blind phase, subjects may volunteer to continue in a 2-year open-label long-term safety extension (LTSE) during which all subjects will receive OCA. During the LTSE, LDL cholesterol will be managed as clinically indicated. The LTSE will evaluate the long-term safety of OCA and atorvastatin treatment and the effect of OCA and atorvastatin on histological markers of NASH.

5.6.6. Rationale for Timing of Unblinding Process and Implications in LTSE

As Study 747-209 is a randomized, double-blind study, the double-blind data will not be unblinded until all double-blind data are final and the database is locked. Accordingly, all subjects continuing in the LTSE, Investigators, and the Sponsor will remain blinded to subjects' double-blind treatment regimen. Subjects who were receiving placebo or 5 mg OCA in the double-blind phase will be randomized to receive either OCA 10 mg or OCA 25 mg in the LTSE. Subjects who were receiving OCA 10 mg or OCA 25 mg in the double-blind phase will continue on the same dose throughout the LTSE. Using this approach, blinding of the trial will be maintained.

5.7. Summary of Known Potential Risks with Investigational Product

The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy subjects, with the highest frequency observed in subjects with PBC.

An increase in liver enzymes and hepatic AEs, including jaundice, were observed in subjects with liver disease at OCA doses between 10 mg and 50 mg. Elevated liver enzymes were observed in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies; however, these elevations were only considered to be of clinical concern at the maximum dose of 250 mg daily.

Changes in lipid profiles have also been observed with OCA dosing, including a decrease in HDL cholesterol and an increase in LDL cholesterol. The clinical significance of these lipid findings remains unclear and is being studied further. HDL levels have generally remained within normal limits in subjects treated with OCA. While LDLc levels increased with OCA treatment, the changes were modest, and trended toward baseline values with continued treatment through to 72 weeks.

Refer to the Investigator's Brochure (IB) for additional information regarding the known potential risks with the investigational product.

5.8. Summary of Known Potential Risks with Atorvastatin

Muscle complaints are the most frequent adverse reports among patients treated with statins with the most severe side effects including myopathy and rhabdomyolysis. The Statin Muscle Safety Task Force (Rosenson 2014) has provided a classification of the spectrum of statin-associated muscle AEs that may be seen in clinical practice and can be used in characterizing reports of muscle-related events.

a. Myalgia – unexplained muscle discomfort often described as "flu-like" symptoms
   - Muscle aches
   - Muscle soreness
   - Muscle stiffness
   - Muscle tenderness
   - Muscle cramps with or shortly after exercise (not nocturnal cramping)

b. Myopathy – muscle weakness (not attributed to pain and not necessarily associated with elevated CPK)
c. Myositis – muscle inflammation
d. Myonecrosis – muscle enzyme elevations or hyperCPKemia
   - Mild >3x baseline or ULN
   - Moderate ≥10x baseline or ULN
   - Severe ≥50x baseline or ULN
e. Clinical Rhabdomyolysis - Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine ≥0.5 mg/dL

There is no evidence that these muscle-related AEs are a continuum beginning with myalgia and progressing to more severe manifestations of myopathy; rather events occur independent of each other. Myalgia events, with frequencies ranging from 1% to 5% in clinical trials to 11% to 29% in observational cohorts, typically occur within 1 month of statin initiation and resolve within 2 weeks of statin cessation (Rosenson 2014). Retrospective analyses have suggested that patients who discontinue statins due to intolerance are able to tolerate statins long-term following re-challenge (Zhang 2013, Mampuya 2013).

Historically, statins have been associated with biochemical abnormalities of liver function, but available data suggest that increases in liver transaminases associated with statins are asymptomatic and generally reversible (Desai 2014). In the absence of liver disease, US guidelines (Stone 2013) recommend that baseline transaminase levels should be checked before initiating statin therapy and subsequent testing should only be done in the presence of symptoms suggestive of hepatic disease. As this study is being conducted in subjects with confirmed NASH, liver enzymes will be frequently monitored and Section 8.4.1.3, Section 8.4.2.2, and Appendix B provide detailed guidance for handling elevated liver biochemistry values.

Statins modestly increase the risk of type 2 diabetes mellitus in individuals with risk factors for diabetes. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines (American Diabetes Association 2013).

Confusion and memory loss have been reported with statins, but medical evidence supporting a causal effect is weak or nonexistent (Simic 2015). However, any reports of cognitive events should be appropriately evaluated, particularly in individuals whose symptoms persist despite statin discontinuation.

In this study, any AEs (including signs and symptoms described above) regardless of relationship to investigational product or study medication, must be documented appropriately (see Section 12).

If treatment with statins is initiated, women of childbearing potential must be informed that statin use is contraindicated during pregnancy. Methods of contraception should be reviewed and modified, if necessary, to ensure highly effective methods with failure rates <1% per year, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or history of vasectomy of partner are used.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of the study is:

- To evaluate the effect of OCA on LDL metabolism in subjects with biopsy-confirmed NASH and to assess the ability of atorvastatin to modulate this effect

6.2. Secondary Objectives

The secondary objectives of the study 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
  - HDL, VLDL, TGs, total cholesterol, and apolipoprotein concentrations
  - Components of the reverse cholesterol transport pathway

6.3. Exploratory Objectives

The exploratory objectives of the study 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, and waist and hip circumference measurements; and 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)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This Phase 2, double-blind, randomized, placebo-controlled, multicenter study, with an open-label LTSE, will evaluate the effect 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. 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.

Screening Period:

Subjects will have a screening period of up to 5 weeks prior to Randomization/Day 1.

Subjects using statins within 30 days of the initial Screening Visit (Screening Visit 1) are required to stop statin therapy immediately following this initial visit and must undergo a 4-week statin washout period prior to Screening Visit 2. At Screening Visit 2 these subjects will have a pre-randomization visit for assessment of their fasting LDL cholesterol levels. Subjects with fasting LDL cholesterol values >200 mg/dL at Screening Visit 2 will be excluded from the study and their dyslipidemia should be managed according to standard of care.

Subjects who are not using statin therapy at Screening Visit 1 are required to provide a fasting blood sample at Screening Visit 2, which can occur at any time prior to randomization but after signing of the ICF. Statin free subjects with fasting LDL cholesterol values >200 mg/dL at either Screening Visit will be excluded from the study and should be managed according to standard of care.

Double-Blind Phase:

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 fasted serum LDL cholesterol concentration (≤125 mg/dL or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4).

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 double-blind phase will occur at Week 16, after which subjects may continue into the open-label LTSE.

Subjects who discontinue investigational product or atorvastatin during the double-blind phase are still expected to attend scheduled study visits and are to be followed through the Week 16 Visit.

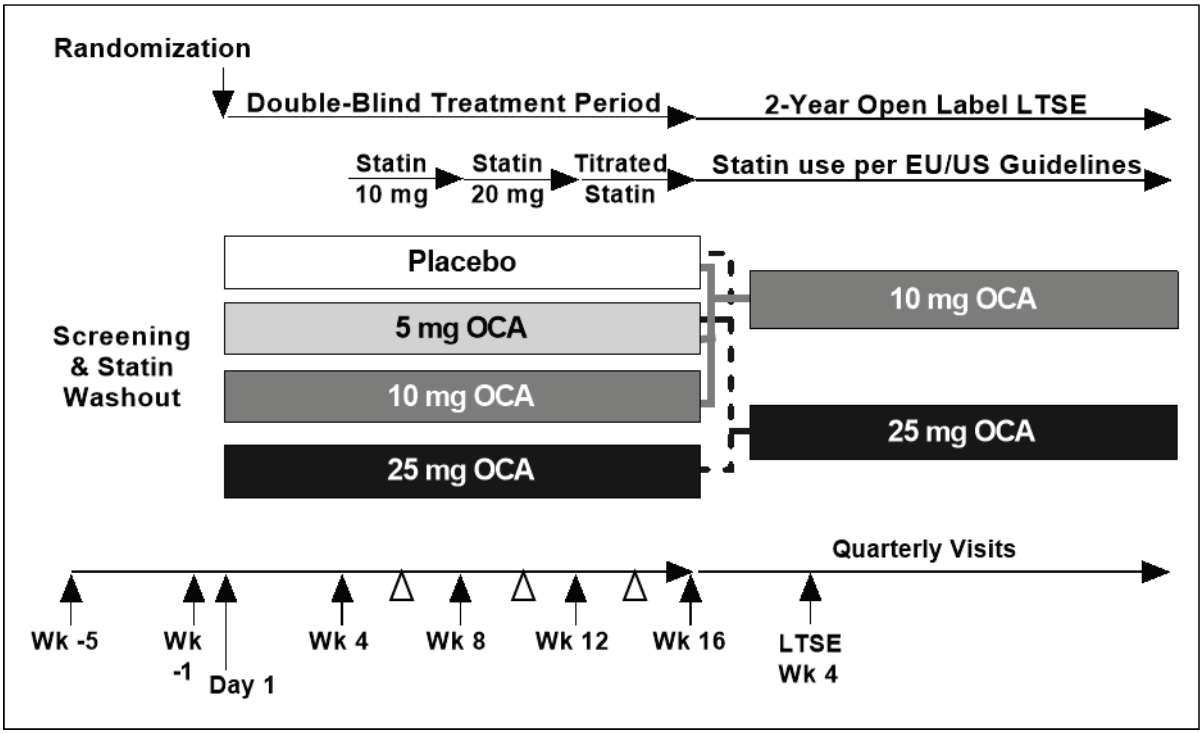
Subjects who discontinue atorvastatin during the double-blind phase are eligible to continue OCA during the double-blind phase and enroll into the LTSE at the discretion of the Investigator, provided they continue to meet the LDLc cutoff of exclusion criteria #4 (ie, LDLc <200 mg/dL).

LTSE Phase:

During the LTSE phase, all subjects will be treated with open-label OCA 10 mg or OCA 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 IB for possible treatment options. Subjects may continue, discontinue, or modify the atorvastatin therapy as clinically indicated.

7.1.1. Study Design

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

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures: Double-Blind Period

Study Visits	Screening Visit 1[a]	Screening Visit 2[b]	Randomi-zation/ Day 1	Wk 2	Wk 4	Wk 6 (Contact)	Wk8	Wk 10 (Contact)	Wk 12	Wk 14 (Contact)	Wk 16/ LTSE Day 1	ET/ EOS[c]
Week	-5 to -1	-1 to 1	1	2	4	6	8	10	12	14	16	
Visit Window (Days)	-35 to -7	-7 to -1		±4	±4	±4	±4	±4	±4	±4	±4	±7[c]
STUDY PROCEDURES												
Fast ≥8 h Prior to Visit		X	X	X	X		X		X		X	X
Informed Consent	X											
Medical History	X											
Inclusion/Exclusion Criteria	X	X	X									
Physical Exam	X										X	X
Vital Signs[d]	X		X	X	X		X		X		X	X
Anthropometric Measures[e]	X		X	X	X		X		X		X	X
12- Lead Electrocardiogram	X		X								X	X
AUDIT Alcohol Intake Questionnaire	X		X								X	X
Liver Biopsy[f]	X											
Transient Elastography[g]	X	X	X								X	X
AEs[h]	X[h]	X[h]	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Randomization/Treatment Assigned[i]			X[i]								X[i]	
Dispense/Administer Investigational Product[k]			X	X	X		X		X		X[j]	
Dispense/Administer Open-Label Atorvastatin[k]					X		X		X		X[j]	

Table 1: Schedule of Study Procedures: Double-Blind Period (Continued)

Study Visits	Screening Visit 1[a]	Screening Visit 2/ Wk -1[b]	Randomi-zation/ Day 1	Wk 2	Wk 4	Wk 6 (Contact)	Wk8	Wk 10 (Contact)	Wk 12	Wk 14 (Contact)	Wk 16/ LTSE Day 1	ET/ EOS[c]
Collect Bottles/Investigational Product Accountability/Compliance				X	X	X	X	X	X	X	X	X
Collect Bottles/Atorvastatin Accountability/Compliance							X	X	X	X	X	X
CLINICAL LABORATORY EVALUATIONS[k]												
Hepatitis B Virus and Hepatitis C Virus Tests	X											
Serum Chemistry[l, m] /Hematology/ Coagulation Parameters	X	X	X	X	X		X		X		X	X
Lipoprotein Analyses[n]			X	X	X		X		X		X	X
Reverse Cholesterol Transport Analytes[o]			X	X	X		X		X		X	X
PD Assessments			X		X		X		X		X	X
Markers of Inflammation, Fibrosis, and Apoptosis			X		X		X		X		X	X
Vitamin D			X		X		X		X		X	X
Markers of Glucose Metabolism Including C-peptide, Insulin, Fasting Plasma Glucose, and HbA1c[p]			X		X		X		X		X	X
Thyroid Function Tests: T3, T4, and TSH			X								X	X
Urinalysis	X		X								X	X
Pregnancy Test[q]	X[q]		X	X	X		X		X		X	X
Blood Sample for Future Exploratory Analysis[r]			X				X				X	X
PK Assessments[s]			X[s]								X[s]	

AE = adverse event; AUDIT = Alcohol Use Disorders Identification Test; β-hCG = beta human chorionic gonadotropin; BMI = body mass index; CPK = creatine phosphokinase; EOS = End of Study; ET = Early Termination; HbA1c = hemoglobin-specific A1c fraction; hs-CRP = high-sensitivity C-reactive protein; PD = pharmacodynamics; PK = pharmacokinetics; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; Wk = Week

Note: No study-related procedures, including Screening procedures, will be performed prior to obtaining informed consent from the subject. Historical procedures (eg, liver biopsy samples collected, FibroScan) completed as part of standard of care, may be used for screening analysis if collected within the allowed windows specified in the protocol.

[a] Subjects using statins within 30 days of Screening are required to stop administering statin therapy after Screening Visit 1, and must complete a 4-week statin washout prior to performing assessments at Screening Visit 2.

[b] Screening Visit 2 is required for all subjects. All subjects must have been fasting for at least 8 hours prior to the visit. The Randomization/Day 1 Visit may occur as soon as screening labs are available and eligibility is confirmed for all subjects. For subjects undergoing a 4-week washout period, Screening Visit 2 may occur on day 28 (±1) day of the washout period. For subjects not taking statins at Screening Visit 1, Screening Visit 2 can occur at any time within 28 days after Screening Visit 1. All Screening assessments must be completed ≤35 days prior to the Randomization/Day 1 Visit.

[c] The ET Visit will occur as soon as possible upon study discontinuation and as near as possible to last dose taken. The EOS Visit will occur ±1 week (7 days) relative to the EOS date announced by the Sponsor.

[d] Sitting heart rate, blood pressure, body temperature, and respiratory rate.

[e] Weight, waist and hip circumference (and height at Screening Visit 1). BMI and waist-to-hip ratio will be calculated via electronic data capture (EDC).

[f] Liver biopsy will be performed to histologically confirm NASH only if slides from historic biopsy (within 1 year of Day 1) are not available. A central reader designated by the Sponsor will perform all biopsy scoring; the results of which must be available prior to randomization on Day 1.

[g] Transient elastography (TE) will be conducted at selected trial sites where the FibroScan® TE device is available. TE is scheduled for Screening Visit 1; however, it may be performed any time after Screening Visit 1 and prior to randomization. In addition, if TE has been done within 3 months of Day 1 and a report/adequate data are available, a pretreatment TE at Day 1 is not required.

[h] AEs occurring after the signing of the informed consent form (ICF) must be entered on the AE eCRF.

[i] Only those subjects who were statin naive at Screening or who have successfully completed the washout period and meet all other inclusion criteria, and none of the exclusion criteria, may be randomized. Subjects randomized to placebo or OCA 5 mg during the double-blind period will be randomized to OCA 10 or 25 mg during the LTSE.

[j] Only applies to subjects continuing in LTSE.

[k] Blood samples for all analyses will be collected predose (before administering investigational product or atorvastatin) on indicated visit days.

[l] CPK will be assessed in all subjects at Screening Visit 2 and as clinically indicated, including anytime myopathy is suspected.

[m] Serum chemistry will include a basic lipid panel and also liver biochemistry panel (see Table 10).

[n] Serum and plasma samples will be collected for lipoprotein analysis, which will include cholesterol concentration in LDL, HDL, and VLDL, their particle concentration and sizes; concentrations of apolipoprotein (Apo)A1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a); and proprotein convertase subtilisin/kexin type 9 (PCSK9).

[o] Reverse cholesterol transport analysis will include following analytes: Pre-β1 HDL concentration, macrophage cholesterol efflux, lecithin cholesterol acyltransferase activity, and cholesterol ester transfer protein activity.

[p] The homeostatic model assessment–beta-cell function (HOMA-β) and homeostatic model assessment – insulin resistance (HOMA-IR) indexes will be calculated using fasting plasma glucose and serum insulin values.

[q] Serum pregnancy test will be administered if urine-based β-hCG pregnancy test is positive. Screening pregnancy tests will be serum-based tests.

[r] Includes markers of cardiovascular risk (adiponectin, plasminogen activator inhibitor-[(PAI-1], and B-type natriuretic peptide [BNP]).

[s] At selected investigational sites, subjects will have the option to provide blood samples for measurement of PK for OCA (Day 1 and Week 16), and for atorvastatin (Week 16). PK samples will be collected within 30 minutes prior to dosing and again 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.

Table 2: Schedule of Study Procedures: LTSE

		Annual Schedule (Year 1 through Study Termination)[b]				
Study Visits	**Month 1[a]**	**Month 3, Month 15**	**Month 6, Month 18**	**Month 9, Month 21**	**Month 12**	**EOS/ET[c]**
Visit Windows (weeks)	±1	±1	±1	±1	±1	±1/ N/A[c]
STUDY PROCEDURES						
Fast ≥8 h Prior to Visit	X	X	X	X	X	X
Physical Exam		X			X	X
12-Lead Electrocardiogram		X	X	X	X	X
Vital Signs[d]	X	X	X	X	X	X
Anthropometric Measures[e]		X	X	X	X	X
AUDIT Alcohol Intake Questionnaire			X		X	X
AEs	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X
Transient Elastography[f]					X	X
Dispense/Administer Investigational Product[g]		X	X	X	X	
Dispense/Administer Atorvastatin[g,h,i]		X	X	X	X	
Collect Bottles/Investigational Product Accountability/Compliance	X	X	X	X	X	X
Collect Bottles/Atorvastatin Accountability/Compliance	X	X	X	X	X	X
LABORATORY EVALUATIONS[g]						
Serum Chemistry[j,k]/Hematology/ Coagulation Parameters	X	X	X	X	X	X
Lipoprotein Analyses[l]		X	X	X	X	X
Reverse Cholesterol Transport Analysis[m]			X		X	X
PD Assessments		X	X	X	X	X
Markers of Inflammation, Fibrosis, and Apoptosis		X	X	X	X	X
Vitamin D		X	X	X	X	X
Markers of Glucose Metabolism Including C-peptide, Insulin, Fasting Plasma Glucose, HbA1c[n]	X	X	X	X	X	X
Thyroid Function Tests: T3, T4, and TSH					X	X
Urinalysis					X	X
Urine Based β-hCG Pregnancy Test[o]	X	X	X	X	X	X
Blood Sample for Future Exploratory Analysis[p]					X	X

AE = adverse event; AUDIT = Alcohol Use Disorders Identification Test; β-hCG = beta human chorionic gonadotropin; BMI = body mass index; CPK = creatine phosphokinase; EOS = End of Study; ET = Early Termination; HbA1c = hemoglobin-specific A1c fraction; PD = pharmacodynamics; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

[a] The first visit after start of LTSE (Month 1 Visit) is relative to Week 16 Visit of the double-blind phase (LTSE Day 1 Visit).

[b] After the Month 12 Visit, the procedures will be performed as listed for Month 3, Month 6, and Month 9 visits (at 15 months, 18 months, and 21 months, respectively, into the LTSE).

[c] The ET Visit will occur as soon as possible upon study discontinuation and as near as possible to last dose taken. The EOS Visit will occur ±1 week (7 days) relative to the EOS date announced by the Sponsor.

[d] Sitting heart rate, blood pressure, body temperature, and respiratory rate.

[e] Weight, waist and hip circumference. BMI and waist-to-hip ratio will be calculated via electronic data capture (EDC).

[f] Transient elastography (TE) will be conducted during the LTSE at selected trial sites where the FibroScan® TE device is available.

[g] Blood samples for all analyses will be collected predose (before administering investigational product) on indicated visit days.

[h] Atorvastatin may be continued or subjects may change or discontinue statins as clinically indicated.

[i] **NOTE**: Any time atorvastatin is up-titrated or re-initiated, a telephone safety contact must be conducted to assess AEs, concomitant medications, and atorvastatin compliance.

[j] CPK will be assessed in all subjects only as clinically indicated, including anytime myopathy is suspected, in subjects taking statins.

[k] Serum chemistry will include a basic lipid panel and liver biochemistry panel (see Table 10).

[l] Serum samples will be collected for lipoprotein analyses, which will include cholesterol concentration in LDL, HDL, and VLDL, their particle concentration and sizes; concentrations of apolipoprotein (Apo)A1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a); and proprotein convertase subtilisin/kexin type 9 (PCSK9).

[m] Reverse cholesterol transport analysis will include following analytes: Pre-β1 HDL concentration, macrophage cholesterol efflux, lecithin cholesterol acyltransferase activity, and cholesterol ester transfer protein activity.

[n] The homeostatic model assessment–beta-cell function (HOMA-β) and homeostasis model assessment – insulin resistance (HOMA-IR) indexes will be calculated using fasting plasma glucose and serum insulin values.

[o] Serum pregnancy test will be administered if urine-based β-hCG pregnancy test is positive.

[p] Blood sample for future exploratory analysis, including markers of cardiovascular risk (adiponectin, plasminogen activator inhibitor-[(PAI-1], and B-type natriuretic peptide [BNP]).

7.1.3. Study Duration

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 double-blind treatment phase, and a 2-year, open-label LTSE. The LTSE may be terminated earlier by the Sponsor if OCA becomes commercially available, or for other reasons as described in Section 8.4.3.

7.2. Number of Subjects

Approximately 80 subjects who meet the eligibility criteria, including biopsy-confirmed NASH and evidence of liver fibrosis, but no hepatic decompensation, will be included in this study. A maximum of 30% of subjects will have stage 4 fibrosis.

7.3. Treatment Assignment

Eligible subjects will be randomized into 4 groups in a 1:1:1:1 ratio to receive OCA 5 mg, OCA 10 mg, OCA 25 mg, or placebo during the double-blind phase of the study. Randomization will be stratified by LDL concentration (fasting serum LDL cholesterol at Screening Visit 2; ≤125 mg/dL or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4). All subjects will also receive atorvastatin starting at Week 4 at 10 mg daily, escalating to 20 mg at Week 8 (if 10 mg daily is tolerated), with further dose adjustments to be performed as clinically indicated at Week 12, and throughout the LTSE phase. Subjects will receive open-label OCA 10 mg or OCA 25 mg during the LTSE depending on their double-blind randomized dose (see Section 7.1). The study design schematic is shown in Figure 1.

7.4. Dose Adjustment Criteria

7.4.1. Investigational Product Dose Adjustments

Dose adjustments of investigational product are not permitted during the double-blind phase. Please refer to Section 8.4.4 for instructions regarding subject withdrawal if investigational product is discontinued.

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 re-randomized in a 1:1 ratio through IWRS to OCA 10 mg or OCA 25 mg upon entry into and throughout the LTSE phase. Subjects randomized to OCA 10 mg will continue to receive OCA 10 mg throughout the LTSE. Subjects randomized to OCA 25 mg will continue to receive OCA 25 mg throughout the LTSE. Subjects may continue with atorvastatin therapy as clinically indicated.

7.4.2. Atorvastatin Dose Adjustments

For all subjects, atorvastatin therapy will be initiated at a dose of 10 mg at Week 4. At Week 8 the dose will be increased to 20 mg (if 10 mg daily is tolerated), and following the Week 12 Visit, the dose can be adjusted to manage cholesterol as clinically indicated (Section 9 and Appendix A). During the LTSE, subjects may continue with atorvastatin therapy as clinically indicated.

If at any time during the double-blind or LTSE phases, serum chemistry results indicate LDLc<40 mg/dL, the subject should be brought back to the site within 1 to 2 weeks after the first result is obtained for an unscheduled (repeat) laboratory assessment. If LDLc<40 mg/dL is obtained on 2 consecutive visits, the subject may discontinue or reduce the dose of atorvastatin.

Subjects may also interrupt or discontinue atorvastatin due to tolerability issues including muscle-related symptoms (Section 5.8) and abnormal liver biochemistry. Any muscle-related complaints should be assessed per the ACC/AHA Guidelines (Appendix A) and statin dose adjusted accordingly:

- To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline prior to initiation of statin therapy.
- If mild to moderate muscle symptoms develop during statin therapy:
  - Discontinue the statin until symptoms can be evaluated.
  - Evaluate the patient for other conditions that might increase the risk for muscle symptoms.
  - If muscle symptoms resolve, and if no contraindication exists, re-challenge the subject with the same or a reduced dose of atorvastatin to establish a causal relationship between the muscle symptoms and statin therapy.
  - Once a low dose statin is tolerated, the dose may be gradually increased as tolerated and clinically indicated.
  - If after 2 months without statin treatment, muscle symptoms or elevated CPK levels do not completely resolve, consider other causes of muscle symptoms.
  - If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.
- If unexplained severe muscle symptoms or fatigue develop during statin therapy, discontinue the statin and address the possibility of rhabdomyolysis by evaluating CPK and serum creatinine, and performing urinalysis for myoglobinuria.

Elevations in liver biochemistry should be monitored per protocol subject withdrawal criteria (Section 8.4 and Appendix B).

Subjects who discontinue atorvastatin may continue on investigational product through the double-blind and LTSE phases, as deemed appropriate by the Investigator and Medical Monitor, and provided they continue to meet exclusion criteria #4 (LDLc <200 mg/dL).

7.4.3. Safety Criteria for Adjustment or Stopping of Doses of Investigational Product

The Data Monitoring Committee (DMC) will review safety data from this study as well as other ongoing OCA studies on a periodic basis (Section 13.8). Adjustments to or discontinuation of treatment may be considered based on DMC evaluation of OCA safety and tolerability. The criteria for study termination are described in Section 7.5.

7.5. Criteria for Study Termination

The Sponsor reserves the right to terminate the study at any time. It is normal procedure to review the emerging clinical and safety data. As a result of such a review or a recommendation by the DMC, it may be necessary to stop the study before all subjects have completed the study. In addition, the Sponsor may terminate the study at an investigational site, at any time (eg, Good Clinical Practice [GCP] noncompliance, poorly performing sites, as determined by the number of subjects enrolled or the quality of the study data).

The Investigator and/or the Sponsor (or designee) must notify the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of discontinuation of a site or the study and the reason(s) for doing so.

Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the End of Study (EOS) or Early Termination (ET) Visit.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

Approximately 80 subjects with biopsy-confirmed NASH without evidence of hepatic decompensation who meet eligibility criteria will be enrolled at approximately 30 investigational sites in the US. Prospective subjects will be identified primarily from the hospital and/or physician's database of patients with NASH, or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international NASH patient societies, forums, or networks. Subjects will be selected according to the inclusion and exclusion criteria below.

8.2. Subject Inclusion Criteria

Subjects must satisfy all of the following criteria to be eligible for enrollment:

1. Age ≥18 years of age
2. Histologic evidence of NASH, as assessed by central reading of a liver biopsy obtained no more than 1 year prior to randomization, defined by the presence of all 3 key histological features of NASH with a score of at least 1 for each and a combined score of 4 or greater out of a possible 8 points according to NASH CRN criteria.
3. Histologic evidence of fibrosis stage 1 to stage 4 (as defined by NASH CRN scoring of fibrosis) without any evidence of hepatic decompensation.
4. If subject has type 2 diabetes, is on stable dose of anti-diabetic medication (except thiazolidinediones [TZDs]) for ≥3 months prior to Day 1.
5. Is either not taking or is on stable doses of TZDs and/or Vitamin E for ≥6 months prior to Day 1
6. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of

investigational product. Effective methods of contraception are considered to be those listed below.

- Barrier method, ie, condom (male or female) with spermicide or diaphragm with spermicide
- Intrauterine device
- Vasectomy (partner)
- Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
- Abstinence (defined as refraining from heterosexual intercourse).

7. Must provide written informed consent and agree to comply with the study protocol, including adherence to protocol-described statin withdrawal and statin therapy.

8.3. Subject Exclusion Criteria

Subjects who satisfy any of the following exclusion criteria will be ineligible for enrollment:

1. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to Screening Visit 1 (significant alcohol consumption is defined as more than 2 units/day in females and more than 4 units/day in males, on average).
2. Prior intolerance to treatment with atorvastatin or other 3-hydroxy-3-methyl-glutaryl (HMG) Coenzyme A reductase inhibitors (including but not limited to rhabdomyolysis).
3. LDLc ≥190 mg/dL and already on statin therapy at Screening Visit 1.
4. LDL cholesterol >200 mg/dL at any Screening Visit in subjects who are not on statin therapy, or at Screening Visit 2 in statin washout subjects.
5. Planned change in diet or exercise habits during participation in the double-blind period, or a significant weight change of >5% in the prior 6 months.
6. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.
7. History of biliary diversion.
8. Uncontrolled diabetes defined as HbA1c ≥9.5% within 60 days prior to randomization (Day 1).
9. Administration of any of the following medications as specified below:
   - Prohibited 30 days prior to Day 1:
     - bile acid sequestrants (BAS) including cholestyramine and its derivatives, colesevelam, colestipol, or
     - omega-3 fatty acid containing dietary supplements

- Prohibited 3 months prior to Day 1:
  - nicotinic acid and derivatives, ezetimibe, or
  - any prescription or over-the-counter medication or herbal remedy with putative NASH efficacy (except Vitamin E or TZDs), or
  - ursodeoxycholic acid, or
  - fenofibrate or other fibrates, or
  - Any over-the-counter or health foods used to treat lipids including plant sterols and berberine
- Prohibited 6 months prior to Day 1:
  - azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate, mofetil, pentoxifylline; budesonide and other systemic corticosteroids; or
  - potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)
- Prohibited 12 months prior to Day 1:
  - antibodies or immunotherapy directed against interleukins, or
  - other cytokines or chemokines

10. Evidence of other forms of known chronic liver disease including but not limited to:
    - Positive test result at Screening for hepatitis B surface antigen
    - Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or history of positive HCV RNA test result
    - PBC, PSC, autoimmune hepatitis or overlap syndrome
    - Alcoholic liver disease
    - Wilson's disease or hemochromatosis or iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy
    - Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level less than normal; exclusion at the Investigator's discretion)
    - Prior known drug-induced liver injury within 5 years before Day 1
    - Known or suspected HCC
11. History of liver transplant, current placement on a liver transplant list, or current Model for End-Stage Liver Disease (MELD) score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (eg, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.

12. Presence of hepatic decompensation including:
    - Gastroesophageal varices
    - Ascites
    - Hepatic encephalopathy
    - Spontaneous bacterial peritonitis
    - Hepatorenal or hepatopulmonary syndromes
13. Total bilirubin ≥2x upper limit of normal (ULN) at any Screening Visit (subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >2x ULN if their conjugated bilirubin is <2x ULN)
14. Creatine phosphokinase (CPK) >5x ULN at Screening Visit 2
15. Serum creatinine ≥1.5 mg/dL at any Screening Visit
16. Serum ALT >300 U/L at any Screening Visit
17. Platelet count <75 000 /mm^3 at any Screening Visit
18. Known positivity for human immunodeficiency virus (HIV) infection
19. Subjects with recent history (within 1 year of randomization) of cardiovascular disease or with history or planned cardiovascular interventions to treat atherosclerotic cardiovascular disease, including:
    a) Peripheral or Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting)
    b) Coronary angioplasty, stenting, or carotid atherectomy
    c) Cardiac pacemaker or defibrillator (placement of cardiac pacemaker or defibrillator for reasons other than atherosclerotic cardiovascular disease [eg, for treatment of atrial fibrillation subsequent to nodal ablation] is not exclusionary)
    d) Prosthetic heart valves
    e) Myocardial infarct, unstable angina, or acute coronary syndrome
    f) Other clinically significant atherosclerotic cardiovascular disease
    g) Cerebrovascular accident (stroke), cerebrovascular ischemia, or transient ischemic attack
    h) Unstable hypertension
    i) Familial hypercholesterolemia or other genetic lipid abnormality
20. Other concomitant disease, malignancy, or condition likely to significantly decrease life expectancy to <5 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphocytic leukemia) and moderate to severe congestive heart failure.
21. Known substance abuse, including inhaled or injected drugs in the year before Screening

22. For female subjects: pregnancy, planned pregnancy, potential for pregnancy and unwillingness to use effective birth control during the study, or breastfeeding
23. Participation in a clinical research study with any investigational product being evaluated for the treatment of diabetes or NASH in the 6 months before Day 1
24. Receipt of any investigational product not being evaluated for the treatment of diabetes or NASH from Screening Visit 1 to Day 1, within 30 days prior to Day 1, or within 5 half-lives of the compound before Day 1 (whichever was longer)
25. Previous exposure to OCA
26. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
27. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
28. Any other condition which, in the opinion of the Investigator, would impede compliance or hinder completion of the study
29. Acute cholecystitis or acute biliary obstruction

8.4. Subject Withdrawal Criteria

8.4.1. Reasons for Mandatory Discontinuation of Investigational Product or Atorvastatin

8.4.1.1. Adverse Events ≥Grade 3 in Severity and Possibly, Probably, or Definitely Related to Investigational Product

If a subject experiences an AE that is ≥Grade 3 in severity (Section 12.1.4) that is considered possibly, probably, or definitely related to investigational product, the investigational product must be discontinued.

8.4.1.2. Pregnancy

Whenever the site is notified of a possible pregnancy, the subject should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female subject becomes pregnant, she must discontinue treatment with investigational product and atorvastatin immediately, but should continue with the study visit schedule and must be followed by the Investigator through pregnancy outcome. The mother (and infant) will be followed as considered appropriate by the Investigator and the Medical Monitor. As described in Section 12.1.8.1, pregnancy is not considered an AE for reporting purposes.

8.4.1.3. Severe Drug-Induced Liver Injury

If a subject develops signs and symptoms of a severe drug-induced liver injury, regardless of causality, investigational product and atorvastatin should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule. Subjects who develop significant drug-induced liver injury, which is considered to be causally

related to the investigational product or atorvastatin, should be discontinued from investigational product or atorvastatin, as appropriate and should not be rechallenged. Significant injury as described in Appendix B, and includes evidence of functional hepatic impairment as indicated by rising bilirubin or INR. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued.

Severe drug induced-liver injury that is not considered related to investigational product or atorvastatin must be discussed with the Sponsor before investigational product or atorvastatin is reinitiated. Follow-up procedures for subjects resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to this site. Results must be reported immediately to the site so the Investigator can determine if the subject is to be allowed to continue treatment. Subjects who discontinue due to significant drug-induced liver injury must be followed until the AE has resolved, stabilized, or is not of clinical concern.

8.4.1.4. Myonecrosis

Moderate myonecrosis as defined by creatine kinase ≥10x the untreated baseline levels or ULN. Muscle-related symptoms that do not necessitate mandatory discontinuation of investigational product or atorvastatin are detailed in Section 5.8.

8.4.2. Reasons for Mandatory Interruption of Investigational Product

8.4.2.1. Adverse Events ≥Grade 4 in Severity and Not or Unlikely Related to Investigational Product

If a subject experiences an AE categorized as ≥Grade 4 in severity and not or unlikely related to investigational product, at least a mandatory interruption of investigational product is required.

8.4.2.2. Suspected Mild or Moderate Drug-Induced Liver Injury

Because transient fluctuations of ALT or AST are common, and progression to severe drug-induced liver injury or acute liver failure is uncommon, automatic discontinuation of investigational product with an elevation of ALT or AST that is >3x ULN/baseline/nadir or total bilirubin >2x ULN/baseline/nadir, as described in Appendix B, may be unnecessary. If a subject develops signs of a mild or moderate event of drug-induced liver injury, regardless of causality, investigational product should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule. The subject may restart treatment after resolution of the event or return to baseline. Follow-up procedures, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject will be allowed to continue treatment.

8.4.3. Other Reasons for Study or Treatment Discontinuation of Subjects

A reasonable effort must be made to determine the reason(s) why a subject fails to return for his/her final visit or is discontinued from the study. This information and date must be recorded on the appropriate electronic case report form (eCRF). The following events are considered appropriate reasons for a subject to discontinue from the study:

- The subject decides that it is in his/her best interest. It is fully understood that all subjects volunteer for the study and that they may withdraw their consent to continue in the study at any time
- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject
- There is a major violation of the clinical study protocol
- Noncompliance of the subject
- An inability to provide plasma or urine samples

8.4.4. Subject Discontinuation Notification

The Investigator must notify the Sponsor as soon as possible if any subject prematurely discontinues from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. Subjects will be considered "lost to follow-up" only after reasonable, documented attempts to reach the subject prove unsuccessful. In all cases, a reasonable effort must be made to determine the reason(s) that a subject fails to return for required study visits or discontinues from the study. This information must be documented in the eCRF.

If a subject is withdrawn from the study early (regardless of the cause), all of the ET evaluations, with the exception of PK procedures, should be performed at the time of withdrawal, to the extent possible.

9. TREATMENT OF SUBJECTS

9.1. Investigational Product and Atorvastatin Treatment Regimen

While placebo, OCA, and atorvastatin are all study medications provided by the Sponsor, for the purposes of this protocol, investigational product refers to OCA or placebo, and study medication, where used, refers to atorvastatin.

Four treatment groups will be evaluated: placebo, OCA 5 mg, OCA 10 mg, and OCA 25 mg. Each dose will be made up of 1 tablet (ie, 1 placebo tablet, 1 OCA 5-mg tablet, 1 OCA 10-mg tablet, or 1 OCA 25-mg tablet). The list of excipients included in the tablets are provided in the IB.

Investigational product will be taken orally with water, once daily for the duration of the study. Subjects will be instructed to begin dosing on Day 1 and are to take investigational product at

approximately the same time each day. Subjects must be instructed to swallow the tablets whole with water; they must not chew, divide, or crush the tablets.

9.1.1. Double-Blind Period

Subjects enrolled in the study will be randomized to receive one of the following treatments: OCA 5 mg, OCA 10 mg, OCA 25 mg, or placebo, starting on Day 1.

At the Week 4 Visit, all subjects will also 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) at the Week 12 Visit as clinically indicated using the atorvastatin prescribing information and the guidance for lipid management (see Appendix A). Blinded treatment with investigational product and open-label atorvastatin will continue through the Week 16 Visit. Investigational product will be dispensed in bottles of 30 tablets.

9.1.2. LTSE

Subjects who complete the Week 16 Visit of the double-blind phase will be able to participate in an open-label LTSE. The Week 16 Visit of the double-blind phase will be Day 1 of the LTSE phase of the study.

Following completion of Week 16 Visit procedures, all subjects will be treated with open-label OCA 10 mg or OCA 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.

Investigational product during the LTSE period will be dispensed in bottles of 30 or 100 tablets, and subjects will be instructed to take one or more tablets per day per his/her OCA dose assignment. During the LTSE phase, the dose of atorvastatin may remain the same as during the double-blind phase or may be modified as clinically indicated per atorvastatin prescribing information and lipid management guidelines (Appendix A).

9.2. Concomitant Medications

Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 12 months of Day 1) and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study.

9.2.1. Medications with Potential NASH-Modifying Properties

Doses of TZDs and Vitamin E should be stable 6 months before Day 1 through Week 16. Ideally, subjects should generally remain on baseline TZDs and/or Vitamin E throughout both the double-blind and LTSE phases of the study unless the baseline therapy is no longer considered clinically appropriate by the Investigator.

9.2.2. Diabetes-Specific Therapy

All diabetes-specific therapies except TZDs should be at a stable dose for ≥3 months prior to Day 1 through Week 16. TZDs must be at a stable dose for ≥6 months prior to Day 1 through Week 16. Ideally, subjects should remain on Baseline diabetes-specific therapies through the end of the LTSE, but will be allowed to make changes if the Baseline therapy is no longer considered clinically appropriate by the Investigator.

9.2.3. Management of Changes in Cholesterol

During the double-blind phase of the study, the dose of atorvastatin administration should be as described in this protocol through Week 12 unless tolerability issues develop as referenced in Section 7.4.2. At the Week 12 Visit, Investigators may increase or decrease the dose of atorvastatin as clinically indicated.

During the LTSE, Investigators may add or change the management of treatment as clinically appropriate. Appendix A provides a general guidance for cholesterol management including monitoring, triggers for intervention, and treatment goals.

9.2.4. Prohibited Medications

The medications prohibited per the study enrollment exclusion criteria and or during the study are listed below and summarized in Table 3:

- Prohibited 30 days prior to Day 1:
  - BAS including cholestyramine, colesevelam, colestipol, or
  - omega-3 fatty acid containing dietary supplements
- Prohibited 3 months prior to Day 1 and throughout the double-blind period:
  - nicotinic acid and derivatives, ezetimibe, or
  - fenofibrate or other fibrates
  - any over-the-counter or health foods used to treat lipids including plant sterols and berberine
- Prohibited 3 months prior to Day 1 and throughout the double-blind period and LTSE:
  - any prescription or over-the-counter medication or herbal remedy with putative NASH efficacy (except Vitamin E or TZDs)
  - ursodeoxycholic acid
- Prohibited 6 months prior to Day 1 and throughout the double-blind period and LTSE:
  - azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate, mofetil, pentoxifylline; budesonide and other systemic corticosteroids;

  - potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)

- Prohibited 12 months prior to Day 1 and throughout the double-blind period:
  - antibodies or immunotherapy directed against interleukins or
  - other cytokines or chemokines
- Prohibited throughout the double-blind phase of the study:
  - weight loss drugs including appetite suppressants (eg, orlistat, lorcaserin)
  - medications contraindicated in the atorvastatin label, including HIV and Hepatitis C protease inhibitors, clarithromycin, and itraconazole (refer to atorvastatin prescribing information in Appendix E for complete list). These medications are also prohibited during the LTSE phase if the subject continues to receive atorvastatin during the LTSE.
- Prohibited during the double-blind and LTSE phases of the study:
  - medications historically associated with NAFLD including: amiodarone, tetracyclines, tamoxifen, estrogens (at doses greater than those used for hormone replacement), anabolic steroids

Table 3: Medications Prohibited Prior to Randomization and/or During Study Participation

	Use Prohibited Prior to Randomization				Use Prohibited During Study	
Medications	**-12 Months**	**-6 Months**	**-3 Months**	**-30 Days**	**Double-Blind Phase**	**LTSE**
Bile acid sequestrants including cholestyramine, colesevelam, colestipol				X		
Omega-3 fatty acid containing dietary supplements				X		
Nicotinic acid and derivatives			X	X	X	
Ezetimibe			X	X	X	
Fenofibrate or other fibrates			X	X	X	
Any over-the-counter or health foods used to treat lipids including plant sterols and berberine			X	X	X	
Any prescription or over-the-counter medication or herbal remedy with putative NASH efficacy (except Vitamin E or TZDs)			X	X	X	X
Ursodeoxycholic acid			X	X	X	X
Azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate, mofetil, pentoxifylline; budesonide and other systemic corticosteroids		X	X	X	X	X
Potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)		X	X	X	X	X

Table 3: Medications Prohibited Prior to Randomization and/or During Study Participation (Continued)

	Use Prohibited Prior to Randomization				Use Prohibited During Study	
Medications	**-12 Months**	**-6 Months**	**-3 Months**	**-30 Days**	**Double-Blind Phase**	**LTSE**
Antibodies or immunotherapy directed against interleukins	X	X	X	X	X	
Other cytokines or chemokines	X	X	X	X	X	
Weight loss drugs including appetite suppressants (eg, orlistat, lorcaserin)					X	
HIV and Hepatitis C protease inhibitors, clarithromycin, itraconazole					X	X
Medications historically associated with NAFLD including: amiodarone, tetracyclines, tamoxifen, estrogens (at doses greater than those used for hormone replacement), anabolic steroids					X	X

Note: For clarity, only prior months and study periods with prohibited use are indicated with "X"; other periods with no restrictions are shaded grey.

9.2.5. Standard of Care and Other Concomitant Medications

With the exception of Vitamin E, TZDs and other diabetes-specific therapy, allowed concomitant medications should be at a stable dose 30 days before Day 1. Concomitant medications will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). Relevant information about all concomitant medications taken before (ie, within 12 months of Day 1; Table 3) and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study.

Subjects taking BAS (including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigational product, ensuring at least 4 hours between doses of the BAS and/or antacids and the investigational product (ie, BAS should be administered 4 hours before or 4 hours after investigational product administration).

Taken concomitantly, OCA and warfarin may decrease INR, thus INR should be monitored and the dosage of warfarin adjusted, as needed, to maintain the target INR range.

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate, showed weak effect of OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.

9.3. Treatment Compliance

The Investigator should assess the subject's compliance with dosing of investigational product and open-label atorvastatin on an ongoing basis throughout the study and confirm by conducting drug accountability (ie, count of returned tablets) during subjects' onsite visits.

Subjects should be instructed to retain all bottles of investigational product and atorvastatin, even if empty, and to return them to the Investigator at the subsequent visit (refer to Table 1 and Table 2). The Investigator or designee should perform drug accountability and, if applicable, follow up with the subject to retrieve any investigational product and atorvastatin bottles that have not been returned.

If the Investigator has concerns about a subject's dosing compliance s/he should discuss this with the subject, assess the reasons for noncompliance and the likelihood that the subject will remain noncompliant, and notify the Sponsor accordingly. Continued study eligibility should be assessed based on the subject's compliance with investigational product and atorvastatin dosing and clinic visits.

9.4. Randomization and Blinding

The initial phase of the study will be conducted in a double-blind, placebo-controlled manner. Enrolled subjects will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups (OCA 5 mg, OCA 10 mg, OCA 25 mg, or placebo) based on a predefined randomization code (generated by Sponsor or designee) using an IWRS. The IWRS will serve as the investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide patient data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned and investigational product (OCA or placebo) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind. The subjects, Investigator, and study site staff will be blinded to the subjects' treatment allocation in the double-blind phase of the study until all subjects have completed the double-blind phase of the study and the database is locked.

In the LTSE phase, all subjects will be treated with open-label OCA 10 mg or OCA 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, and subjects randomized to OCA 10 mg or OCA 25 mg during the double-blind phase will continue on the same dose throughout the LTSE.

9.4.1. Stratification

In order to ensure that factors with the potential to affect treatment response are randomized in equal proportions to the different treatment groups, subjects will be stratified by LDL cholesterol concentration (Screening Visit 2 LDL cholesterol value for statin washout subjects or Screening LDL cholesterol value for statin-free subjects). Randomization will be stratified by the pre-randomization fasted serum LDL cholesterol concentration (≤125 mg/dl or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4).

9.4.2. Emergency Unblinding Procedures

Randomization codes and corresponding treatment assignments will be made available to the Investigator and the Medical Monitor for emergency use only through the IWRS system. When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document the case in the subject's source record. Subsequently, the Investigator should contact the Medical Monitor to explain any premature unblinding of treatment assignment (eg, accidental unblinding or unblinding due to a serious AE [SAE]). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. The Medical Monitor will document within study correspondence the rationale, circumstances, and the person(s) being informed about the unblinding.

The DMC (refer to Section 13.8) will have access to the IWRS and will be able to unblind individual subjects. The DMC will review aggregate data during closed sessions. The DMC will document details about any subject who was unblinded in the closed session DMC minutes, which will be made available to the Sponsor only after the double-blind database is locked and unblinded.

Access to randomization codes and corresponding treatment assignments will also be made available through the IWRS system to the appropriate, named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities.

9.5. Assignment of Site and Subject Numbers

9.5.1. Site Numbers

Each study site selected to participate in this study will be assigned a Site Number by the Sponsor. The Site Number will be used to categorize subject data and to identify the site and or Investigator within study documents. This number will be recorded in the eCRF.

9.5.2. Subject Numbers

Subjects will be identified by a unique 6-digit number. The first 3 digits will represent the site number and the last 3 digits, the Screening number, which will be assigned sequentially by the site.

9.6. Restrictions

9.6.1. Fasting Requirement at Study Visits

All subjects must have been fasting for at least 8 hours prior to Screening Visit 2 (Week -1 Visit) and all subsequent study visits, as all analytes will be assayed in fasting blood, serum, or plasma samples (Table 1 and Table 2). Water is permitted during the fasting period.

If the subject reports having eaten within 8 hours, the information will be documented accordingly in the source and eCRF and the subject will be reminded that at least 8-hour fasting is required prior to all study visits, but water is permitted. The blood sample will still be collected during the visit with the exception of Screening Visit 2, which will require rescheduling of the visit.

9.6.2. Grapefruit and Grapefruit Juice

Grapefruit and grapefruit juice consumption should be discouraged following initiation of atorvastatin due to possible increases in plasma concentration of atorvastatin (please refer to atorvastatin prescribing information [Appendix E]).

9.6.3. Diet and Exercise

Consistent with the exclusion criteria (Section 8.3), subjects should not make significant changes to their diet and exercise habits during the double-blind phase. This is not intended to override physician advice for lifestyle modification, and inclusion in the study should preferably be after lifestyle modifications have been made and are stable.

9.7. Visit Procedures

9.7.1. Visit Windows

All Screening assessments should occur ≤35 days prior to the Randomization/Day 1 Visit. Subjects who are taking statins at the time of screening or within 30 days of Screening Visit 1 are required to stop statin therapy for 4 weeks (28 (±1) days), and provide a fasting blood sample at Screening Visit 2 to confirm eligibility. Subjects who have not taken statins within 30 days of Screening Visit 1 are not required to enter into the washout period and may proceed to Screening

Visit 2 to provide a fasting blood sample. The Randomization/Day 1 Visit may occur as soon as all screening labs are available and eligibility is confirmed.

All visits during the double-blind phase will be relative to Day 1 (eg, if the Week 2 Visit occurs 4 days late, the Week 4 Visit should still be 4 weeks from Day 1), and should occur within ±4 days of the visit day. The timing of all study visits during the LTSE is relative to Week 16/LTSE Day 1. LTSE Visits should occur within ±1 week of the visit day.

The visit windows are summarized below:

Visit or Procedure	Visit Window and/or Interval
Screening Visit 1	Visit(s) are to occur ≤5 weeks (35 days) prior to Day 1.
Screening Visit 2 (Week -1)	±1 day
Randomization (Day 1)	This is the day of Randomization and the first day of dosing with investigational product. On-treatment visit scheduling should be calculated from this point going forward unless stated otherwise.
Week 2, Week 4, Week 8, and Week 12	±4 days; the visits during double-blind phase will be relative to Day 1 (ie, first dose of investigational product)
Week 6, Week 10, and Week 14 (Contact visits)	±4 days
Week 16 (LTSE Day 1)	±4 days
LTSE Visits: Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, and Month 21	±1 week (7 days); the LTSE visits are relative to LTSE Day 1 (ie, Week 16 of double-blind phase)
EOS	±1 week (7 days) relative to the EOS date announced by the Sponsor
ET	As soon as possible upon study discontinuation and as near as possible to last dose taken

EOS = End of Study; ET = Early Termination

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose possible risks and benefits of the study to the subject and will provide him/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject will be informed that participation is voluntary and that his/her future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information sheet and his/her signed and dated consent form). At selected study sites, subjects will have the option to consent to participate in an additional PK assessment. Subjects may also be required to sign a new consent form prior to entering the LTSE phase of the study. Subjects will be requested to provide blood samples for exploratory future analysis of analytes such as adiponectin, plasminogen activator inhibitor-1(PAI-1), and B-type natriuretic peptide (BNP; Table 10).

9.7.3. Screening Visit 1 Procedures

The Screening Visit assessments must be performed ≤5 weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study.

Subjects who are statin-free (ie, no statin use within 30 days of Screening) must return for fasted serum chemistry labs at Screening Visit 2, and may proceed to the Randomization/Day 1 Visit once screening labs are available and eligibility is confirmed; subjects who need to wash out statin therapy are required to return for Screening Visit 2 following the washout period.

Screening Visit procedures for all subjects are as follows:

- Review ICFs and obtain signatures before performing any study-related procedures, including Screening procedures.
- Collect medical history.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Perform a standard 12-lead electrocardiogram (ECG).
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference, and height.
- Determine alcohol consumption (using AUDIT questionnaire).
- Assess availability of liver biopsy samples: If >1 year since last biopsy, schedule pretreatment biopsy. Liver biopsies conducted within 1 year of Day 1, for which unstained slides can be obtained and submitted for central review, are considered adequate for study entry. All samples must be submitted for central read such that the report is available prior to Day 1.
- For participating sites only: TE is scheduled for Screening Visit 1; however, it may be performed any time between Screening Visit 1 and prior to Randomization (Day 1). In addition, if TE has been done within 3 months of Day 1 and a report/adequate data is/are available, a pretreatment TE at Day 1 is not required.
- Assess and record any pretreatment-emergent AEs (after the ICF has been signed).
- Record prior (if within 12 months of Day 1) and current concomitant medications.
- Obtain serum sample for hepatitis B surface antigen or hepatitis C antibody (and positive HCV ribonucleic acid [RNA]) testing to confirm study eligibility.
- Schedule laboratory visit for fasted blood samples for
  - Serum chemistry (includes basic lipid panel and liver biochemistry panel), hematology, and coagulation

- Obtain urine sample for urinalysis.
- Perform serum pregnancy test in females of childbearing potential.
- Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted).

Additional Screening Visit 1 procedure for subjects currently taking statins:

- Subjects who are currently taking statins, defined as statin use within 30 days of Screening, will be instructed to discontinue statin therapy following Screening Visit 1. After 4 weeks of statin washout, subjects will return for Screening Visit 2 to provide blood samples for fasted serum chemistry.

9.7.4. Screening Visit 2 Visit Procedures

All subjects will return for Screening Visit 2 to confirm eligibility criteria and provide blood samples for fasted serum chemistry.

For subjects who were receiving statin therapy at the time of screening:

- Verify that subjects have completed a 4-week washout period.

For all subjects:

- Review inclusion and exclusion criteria for eligibility.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, the visit should be rescheduled.
- Obtain blood samples for
  - Serum chemistry (will include basic lipid and liver biochemistry panel), hematology, and coagulation
  - CPK
- Assess and record pretreatment-emergent AEs.
- Assess and record new concomitant medications.
- For participating sites only: Perform TE if not done during Screening Visit 1 or a report/adequate data from a scan done within 3 months and Day 1 is/are not available.

9.7.5. Randomization/Day 1 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that at least 8-hour fasting is required prior to all study visits, but water is permitted.

- Review inclusion and exclusion criteria for eligibility.
- Perform a standard 12-lead ECG.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, and waist and hip circumference.
- Determine alcohol consumption (using AUDIT questionnaire).
- Assess and record any pretreatment-emergent AEs.
- Record prior (since Screening Visit 1) and current concomitant medications.
- For participating sites only: Perform TE if not done during Screening Visit 1 or Screening Visit 2, or if a report/adequate data from a scan done within 3 months and Day 1 is/are not available.
- Obtain blood samples for:
  - Serum chemistry (includes basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes
  - CPK, if myopathy suspected
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - Blood sample for future exploratory analysis of biomarkers adiponectin, PAI-1, and BNP
  - Thyroid Function Tests: TSH, T4, and T3
  - Possible analysis of conjugated and unconjugated bile acids
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Randomize the subject only if s/he meets all inclusion criteria and no exclusion criteria: Record the visit in IWRS along with the subject's Screening Visit 2 (Week -1) fasting LDL cholesterol value, randomize the subject to study treatment group, and dispense investigational product according to IWRS instructions.
- Administer the first dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s); s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

Additional Day 1 Procedures for PK Subjects

At participating investigational sites, subjects will have the option to consent to participate in an additional PK assessment. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study.

Following collection of the Day 1 fasted samples indicated above, subjects who are participating in the PK assessment will each receive a single dose of their assigned investigational product with water. Serial blood samples will be obtained for measurement of OCA and its conjugates 30 minutes prior to dosing 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. Meal will be provided following collection of the 1-hour PK sample, and will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance.

9.7.6. Week 2 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference.
- Assess and record AEs.
- Review and record concomitant medications.
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.
- Obtain blood samples for:
  - Serum chemistry (includes basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes

  - CPK, if myopathy suspected
- Perform a urine-based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Schedule the next visit, reiterate dosing instructions and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s); s/he will dose at the clinic
  - To fast overnight (at least 8 hours) prior to the next visit, but water is permitted

9.7.7. Week 4 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference.
- Assess and record AEs.
- Review and record concomitant medications.
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.
- Obtain blood samples for:
  - Serum chemistry (includes basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - CPK, if myopathy suspected
- Perform a urine-based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.

- Record the visit in IWRS and dispense investigational product and atorvastatin as instructed.
- Administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Administer the daily dose of atorvastatin at the study site. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product or atorvastatin on the morning of the next visit
  - To bring the investigational product and atorvastatin bottle(s); s/he will dose at the clinic
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.8. Week 6 Safety Contact

- This is a telephone contact with the subject to
  - Review and record AEs
  - Review and record concomitant medications
  - Assess investigational product and atorvastatin compliance

9.7.9. Week 8 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference
- Assess and record AEs.
- Review and record concomitant medications.
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.

- Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability.
- Obtain blood samples for:
  - Serum chemistry (includes basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - CPK, if myopathy suspected
  - Blood sample for future exploratory analysis of biomarkers adiponectin, PAI-1, and BNP
- Perform a urine-based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Record the visit in IWRS and dispense investigational product and atorvastatin as instructed.
- Administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Administer the daily dose of atorvastatin at the study site. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Reiterate dosing instructions and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product or atorvastatin on the morning of the next visit
  - To bring the investigational product and atorvastatin bottle(s); s/he will dose at the clinic
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.10. Week 10 Safety Contact

- This is a telephone contact with the subject to:
  - Review and record AEs
  - Review and record concomitant medications
  - Assess investigational product and atorvastatin compliance

9.7.11. Week 12 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference.
- Assess and record AEs.
- Review and record concomitant medications.
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.
- Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability.
- Obtain blood samples for:
  - Serum chemistry (includes basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - CPK, if myopathy suspected
- Perform a urine-based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Record the visit in IWRS and dispense investigational product and atorvastatin as instructed.
- Administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Administer the daily dose of atorvastatin at the study site. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Reiterate dosing instructions and advise the subject:
  - Take the investigational product at approximately the same time each day

- NOT to take investigational product or atorvastatin on the morning of the next visit
- To bring the investigational product and atorvastatin bottle(s); s/he will dose at the clinic
- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits; water is permitted.

9.7.12. Week 14 Safety Contact

- This is a telephone contact with the subject to:
  - Review and record AEs
  - Review and record concomitant medications
  - Assess investigational product and atorvastatin compliance

9.7.13. Week 16 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference.
- Perform a standard 12-lead ECG.
- Determine alcohol consumption (using AUDIT questionnaire).
- For participating sites only: perform TE
- Assess and record AEs.
- Review and record concomitant medications.
- Collect all used and unused bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.
- Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability.

- Obtain blood samples for:
  - Serum chemistry (includes basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - CPK, if myopathy suspected
  - Blood sample for future exploratory analysis of biomarkers adiponectin, PAI-1, and BNP
  - Thyroid Function Tests: TSH, T4, and T3
  - Possible analysis of conjugated and unconjugated bile acids
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Record the visit in IWRS and indicate if the subject is continuing into the LTSE.

9.7.13.1. Additional Week 16 Procedures for PK Subjects

At participating investigational sites, subjects will have the option to consent to participate in an additional PK assessment. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Week 16 Visit.

Following collection of the Week 16 fasted samples indicated above, subjects who are participating in the PK assessment will each receive a single dose of their assigned double-blind investigational product with water. Serial blood samples will be obtained for measurement of OCA and its conjugates, and atorvastatin and its metabolites, 30 minutes prior to dosing 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. The meal will be provided following collection of the 1-hour PK sample, and will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance.

9.7.14. Additional Procedures at Week 16/LTSE Day 1 Visit for Subjects Continuing into the LTSE

Subjects who continue into the LTSE phase after completing the procedures listed for the Week 16 Visit (Section 9.7.13) will undergo the following procedures after signing the LTSE-specific ICF:

- Record the visit in IWRS, randomize the subject to one of the open-label treatment groups, and dispense open-label investigational product according to IWRS instructions.
- If the subject is continuing with atorvastatin therapy, dispense (via IWRS) and provide dosing instructions as clinically indicated (Appendix A).
- Reiterate dosing instructions for investigational product and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product or atorvastatin on the morning of the next visit
  - To bring the investigational product and atorvastatin bottle(s); s/he will dose at the clinic
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.15. Early Termination/End of Study Procedures: Double-Blind Period

Subjects who terminate participation in the study prior to the Week 16 Visit should have an early termination (ET) Visit as soon as possible following the decision to discontinue therapy. If the study is terminated early by the Sponsor (Section 7.5), the subject will be asked to return to the site for ET/EOS procedures as soon as possible. The procedures to be performed at the double-blind phase ET/EOS Visit are as follows:

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference.
- Perform a standard 12-lead ECG.
- Determine alcohol consumption (using AUDIT questionnaire).
- For participating sites only: perform TE
- Assess and record AEs.
- Review and record concomitant medications.

- Collect used and unused bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.
- Collect used and unused bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability.
- Obtain blood samples for:
  - Serum chemistry (will include basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - CPK, if myopathy suspected
  - Blood sample for future exploratory analysis of biomarkers adiponectin, PAI-1, and BNP
  - Thyroid Function Tests: TSH, T4, and T3
  - Possible analysis of conjugated and unconjugated bile acids
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Obtain urine sample for urinalysis.
- Record the visit in the IWRS.

9.7.16. LTSE Visits

LTSE Visits should occur within ±1 week of the visit day and the timing of all visits should be relative to the double-blind Week 16 Visit (ie, the start of the LTSE; LTSE Day 1). For example, if the Month 6 Visit occurred 1 week late, the Month 9 Visit should still be approximately 9 months after the Week 16 Visit.

The first LTSE visit following LTSE Day 1 will occur at LTSE Month 1. The next visit will occur at LTSE Month 3 and every 3 months thereafter (eg, at Months 6, 9, and 12) for the duration of the LTSE. The quarterly visit procedures described below will repeat annually for the duration of the LTSE. For example, once a subject completes a year (Month 12 Visit) in the LTSE, their next visit should be 3 months later and the procedures described for the Month 3 LTSE Visit should be followed.

9.7.17. LTSE Month 1 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.

  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability. Following product accountability, redispense the same bottle of investigational product for use until the next visit.
- Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability. Following atorvastatin accountability, if the subject is continuing with the same dose of atorvastatin, redispense the same bottle for use until the next visit.
  - NOTE: If atorvastatin dose is up-titrated or re-initiated after dose interruption, a telephone safety contact must be conducted 2 weeks following the change in dose to assess for AEs, concomitant medications, and investigational product and atorvastatin compliance.
- Obtain blood samples for:
  - Serum chemistry (will include basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Markers of glucose metabolism
  - CPK, if myopathy suspected
- Perform a urine based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Reiterate dosing instructions for investigational product and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product or atorvastatin (if applicable) or on the morning of the next visit
  - To bring the investigational product and atorvastatin (if applicable) bottle(s); s/he will dose at the clinic
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.18. LTSE Month 3, Month 6, Month 9, Month 15, Month 18, and Month 21 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination (only at Month 3 and Month 15 Visits).
- Perform a standard 12-lead ECG.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference.
- Determine alcohol consumption (using AUDIT questionnaire [only at Month 6 and Month 18 Visits]).
- Assess and record AEs.
- Review and record concomitant medications.
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.
- Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability.
  - NOTE: If atorvastatin dose is up-titrated or re-initiated after dose interruption, a telephone safety contact must be conducted 2 weeks following the change in dose to assess for AEs, concomitant medications, and investigational product and atorvastatin compliance.
- Obtain blood samples for:
  - Serum chemistry (will include basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses
  - Reverse cholesterol transport analytes (only at Month 6 and Month 18)
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - CPK, if myopathy suspected

- Perform a urine based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Record the visit in IWRS and dispense investigational product and atorvastatin (if applicable) as instructed.
- Reiterate dosing instructions for investigational product and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product or atorvastatin (if applicable) or on the morning of the next visit
  - To bring the investigational product and atorvastatin (if applicable) bottle(s); s/he will dose at the clinic
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.19. LTSE Month 12 Visit Procedures

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference.
- Perform a standard 12-lead ECG.
- Determine alcohol consumption (using AUDIT questionnaire).
- Assess and record AEs.
- Review and record concomitant medications.
- For participating sites only: Perform TE
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.
- Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability.

- Obtain blood samples for:
  - Serum chemistry (will include basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - CPK, if myopathy suspected
  - Blood sample for future exploratory analysis of biomarkers adiponectin, PAI-1, and BNP
  - Thyroid Function Tests: TSH, T4, and T3
- Obtain urine sample for urinalysis.
- Perform a urine based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Record the visit in IWRS and dispense investigational product and atorvastatin (if applicable) as instructed.
- Reiterate dosing instructions for investigational product and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product or on the morning of the next visit, and
  - To bring the investigational product and atorvastatin (if applicable) bottle(s); s/he will dose at the clinic, and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.20. LTSE End of Study/Early Termination Procedures

When the LTSE concludes, subjects will be asked to return to the site for EOS procedures as soon as possible. Subjects who terminate participation in the study during the LTSE should have an ET Visit as soon as possible following the decision to discontinue therapy. If the study is terminated by the Sponsor (Section 7.5), the subjects will be asked to return to the site for the ET/EOS procedures as soon as possible. The procedures to be performed at the LTSE ET/EOS Visit are as follows

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.

  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required prior to all study visits, but water is permitted.

- Perform a physical examination.
- Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record anthropometric measures: body weight, waist and hip circumference.
- Perform a standard 12-lead ECG.
- Determine alcohol consumption (using AUDIT questionnaire).
- Assess and record AEs.
- Review and record concomitant medications.
- For participating sites only: Perform TE
- Collect used and unused bottles of investigational product, assess investigational product compliance, and perform investigational product accountability.
- Collect used and unused bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability.
- Obtain blood samples for:
  - Serum chemistry (will include basic lipid panel and liver biochemistry panel), hematology, and coagulation
  - Lipoprotein analyses and reverse cholesterol transport analytes
  - PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 10)
  - Vitamin D
  - CPK, if myopathy suspected
  - Blood sample for future exploratory analysis of biomarkers adiponectin, PAI-1, and BNP
  - Thyroid Function Tests: TSH, T4, and T3
- Obtain urine sample for urinalysis.
- Perform a urine based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.
- Record the visit in IWRS.

9.7.21. Unscheduled Safety Visits

The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted or requested by the Medical Monitor. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted.

An increase in aminotransferases (ALT or AST) to >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN) should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing (Appendix B). AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms.

As appropriate, the Medical Monitor should be contacted.

10. INVESTIGATIONAL PRODUCT AND STUDY MEDICATION

10.1. Investigational Product (OCA or Placebo)

Double-Blind Phase:

Investigational Product will be supplied as white, round, film-coated tablets containing OCA 5 mg, OCA 10 mg, OCA 25 mg, or placebo. All tablets will be debossed with "INT" on one side and "3547" on the other side, and will be of the same size and appearance. The tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The 25-mg tablet also contains silicon dioxide. The investigational product tablets will be provided in high-density polyethylene (HDPE) bottles with an induction seal and child-resistant caps. All investigational product will be manufactured according to Good Manufacturing Practice (GMP).

LTSE Phase:

10-mg and 25-mg OCA tablets for the LTSE Phase will be supplied as white tablets.

- White OCA tablets are round and debossed with "INT" on one side and "3547" on the other side.

The tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The 25-mg tablet also contains silicon dioxide. All investigational product will be provided as a tablet for oral administration and provided in HDPE bottles with an induction seal and child-resistant caps.

10.2. Investigational Product Packaging and Labeling

The packaging and labeling of investigational product supplies will be performed according to GMP standards by designated, qualified vendors. A designated vendor will also be responsible for the distribution of the investigational product and placebo to the clinical sites.

For the double-blind period, investigational product will be packaged and labeled as single bottles containing 30 OCA- or placebo-containing tablets, and should be dispensed to the subject

as instructed by the IWRS and according to the visit schedule in Table 1. Each bottle will be labeled with a unique bottle number. More than one bottle of investigational product may be dispensed to the subject at a visit to provide sufficient tablets for daily dosing until the next study visit.

For the LTSE period, investigational product will be packaged and labeled as single bottles containing 30 or 100 tablets of OCA and should be dispensed to the subject as instructed by the IWRS. Each bottle will be labeled with a unique bottle number. More than one bottle of investigational product may be dispensed to the subject at a visit to provide sufficient tablets for daily dosing until the next study visit.

10.3. Investigational Product Storage

Investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15°C to 25°C.

10.4. Investigational Product Administration

Subjects will begin dosing at the clinic following Randomization and will be instructed to take investigational product at approximately the same time each day with water. Subjects must be instructed to swallow one tablet whole; they must not chew, divide, or crush the tablet.

10.4.1. Investigational Product Dispensation

On Randomization/Day 1, after confirmation of subject eligibility, the Investigator or designee will dispense investigational product to the subject. Before leaving the clinic, study site staff will ensure that the subject fully understands the dosing instructions.

Investigational product will be dispensed at clinic visits after confirmation of continued subject compliance and eligibility. If necessary, in exceptional circumstances, and only after approval by the Sponsor, investigational product may be delivered to subjects by courier, with proper precautions and documentation of shipping.

10.4.2. Missed Doses

Subjects who miss a dose of investigational product should be instructed to take it later the same day, as soon as they remember. "Missed" doses should not be taken on a subsequent day (ie, the subject should not take more than the prescribed daily dose). Subjects will be asked to record the day they miss a dose.

10.5. Atorvastatin Tablets

Atorvastatin tablets for oral administration contain 10 mg, 20 mg, and 40 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

10.5.1. Atorvastatin Packaging and Labeling

Atorvastatin is commercially available and will be supplied as tablets in its commercial configuration, though all bottles will have an auxiliary label with study protocol number and bottle number for compliance. A designated vendor will be responsible for the distribution of atorvastatin to the Investigator.

Atorvastatin should be dispensed to the subject and dosed as instructed by the IWRS.

10.5.1.1. Atorvastatin Storage

Atorvastatin should be stored in the containers in which they are received from the Sponsor's supplier, at the manufacturer's recommended storage conditions.

10.5.2. Atorvastatin Administration

Subjects will be instructed to begin atorvastatin dosing on the day following their Week 4 Visit. The first dose will be administered at the study site during the subject's study visit (Table 1). Atorvastatin can be administered as a single dose with water at any time of the day, with or without food.

10.5.3. Atorvastatin Dispensation

At the subject's Week 4 Visit, the Investigator or designee will dispense a bottle containing atorvastatin 10-mg tablets to the subject. At the subject's Week 8 Visit, the Investigator or designee will dispense atorvastatin 10-mg tablets to the subject advising the subject to take 2 tablets for a total dose of atorvastatin 20 mg. At subsequent visits, atorvastatin will be dispensed as clinically indicated. For doses higher than 20 mg, subject may take multiple atorvastatin tablets for a total dose of 40 mg or 80 mg, as clinically indicated. Before leaving the clinic, study site staff will ensure that the subject fully understands the dosing instructions.

Upon confirmation of continued subject compliance and eligibility, atorvastatin will be dispensed using IWRS inventory management during study visits.

10.5.4. Missed Doses of Atorvastatin

Subjects who miss a dose of atorvastatin should be instructed to take it later the same day, as soon as they remember. "Missed" doses should not be taken if it has been more than 12 hours since when they would normally take it; the next dose should be taken when they would normally dose. Subjects should be instructed not to take 2 doses at the same time. Subjects should be asked to record the day they miss a dose.

10.5.5. Atorvastatin Overdose

There is no specific treatment for an overdose of atorvastatin. In the event of an overdose, the subject should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

10.6. Investigational Product and Atorvastatin Accountability and Disposal

The Sponsor's representative will ship investigational product and atorvastatin to the study site under appropriate storage conditions. All shipments of investigational product and atorvastatin should be unpacked and the contents reviewed immediately upon receipt. If it is not possible to verify the contents immediately, they must be stored under the appropriate storage conditions until verification of the contents is possible (ideally, within 1 business day from receipt). The pharmacist or designee should verify the investigational product and atorvastatin against the shipment documentation. The pharmacist or designee should contact the Sponsor immediately to report any concerns regarding the shipment.

All investigational product and atorvastatin will be provided for use only in this study and is not to be used for any other purpose. The Investigator or designee will maintain a full record of investigational product and atorvastatin accountability, including records of individual subject dispensing and final return or disposition (as directed by the Sponsor).

The study monitor, also known as the Clinical Research Associate (CRA), will review accountability records against dispensed and in stock investigational product and atorvastatin during onsite monitoring visits, at study completion, and in the event of premature study termination. The CRA will retrieve documentation detailing and confirming the return or destruction of investigational product and atorvastatin.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1. Efficacy Assessments

An overview of parameters supporting primary, secondary, and exploratory objectives of the study are summarized in Table 4. Samples for the assessment of efficacy variables will be collected according to the schedule of study procedures for the double-blind period (Table 1) and LTSE (Table 2). For a complete list of variables, please refer to Appendix A.

Table 4: List of Planned Assessments

The efficacy assessments supporting the primary, secondary, and exploratory objectives of the study are as follows:

	Parameters
Primary Endpoints	
LDL metabolism	LDL cholesterol concentration, particle size, and particle concentration
Secondary Endpoints	
Lipoprotein metabolism	HDL cholesterol concentration, particle size and particle concentration; VLDL cholesterol concentration, particle size and particle concentration; TG and total cholesterol concentrations; ApoA1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a) concentrations; PCSK9 concentration
Reverse cholesterol transport	Pre-β1 HDL concentration, macrophage cholesterol efflux; LCAT activity; CETP activity
Exploratory Endpoints	
Liver biochemistry and markers of liver function[a]	Albumin, ALP, ALT (isoenzymes), AST, direct bilirubin, GGT, INR, total bilirubin
Markers of liver inflammation	IL-6, hs-CRP, and TNF-α
Marker for hepatic apoptosis and fibrosis	CK-18-M30 and CK-18-M65
Glycemic Control[b]	Glucose, insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR
OCA pharmacokinetics	OCA, tauro-OCA, glyco-OCA, total OCA, potentially other conjugates or metabolites not yet identified
Atorvastatin bioanalytical concentrations	Atorvastatin and its metabolites
Anthropometric measures[c]	Height, weight, and waist and hip circumference measurements; and BMI, and waist-to-hip ratio calculations
Pharmacodynamics	C4 (7α-hydroxy-4-cholesten-3-one) and FGF-19; possible analysis of conjugated and unconjugated bile acids
Noninvasive radiological liver fibrosis measurements	By TE (where available)
Cardiovascular risk scores	FRS and Reynolds scores

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; ApoCII = apolipoprotein CII; ApoCIII = apolipoprotein CIII; ApoE = apolipoprotein E; AST = aspartate aminotransferase; BMI = body mass index; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope M30; CK-18-M65 = cytokeratin-18 neoepitope M65; CTEP = cholesterol ester transfer protein; ECG = electrocardiogram; FGF-19 = fibroblast growth factor-19; FRS = Framingham Risk Score; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin-specific A1c fraction; HDL = high-density lipoprotein; HOMA-β = homeostatic model assessment–beta-cell function, HOMA-IR = homeostatic model assessment – insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; LCAT = lecithin cholesterol acyltransferase; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9;TE = transient elastography; TEAE = treatment-emergent adverse event; TG = triglycerides; TNF-α = tumor necrosis factor-α; VLDL = very low-density lipoprotein

[a] Liver biochemistry panel will be included in the serum biochemistry (see Table 10).
[b] HOMA-IR is calculated from fasting plasma glucose and fasting serum insulin values.
[c] Height will be measured at Screening only. BMI and waist-to-hip ratio will be calculated via EDC from waist and hip circumference measurements.

Please note that there are 2 distinct lipid assessments: the assessment of lipoprotein metabolism and the safety lipids assessment measured as part of serum chemistry. The latter will be used for randomization and safety assessments and the lipoprotein analysis samples will be used for the efficacy assessment.

11.1.1. Efficacy Laboratory Assessments

The complete list of planned laboratory assessments supporting primary, secondary, and exploratory objectives of the study is shown in Table 4, and includes parameters related to LDL metabolism, lipoprotein metabolism, reverse cholesterol transport, liver biochemistry and markers of liver function, markers of inflammation, glycemic control, OCA PD markers, and NASH disease severity markers CK-18-M30 and CK-18-M65.

Fasting (8 hours) blood samples are required for efficacy analyses. During each visit, the Investigator or designee will verify that the subject has fasted for at least 8 hours and record fasting status in the source and eCRF. If the subject reports having eaten (water is permitted) within 8 hours, the Investigator or designee will document accordingly in the source and eCRF and remind the subject that fasting is required prior to onsite visits.

Blood samples will be collected at visits indicated in the Schedule of Study Procedures (Table 1 and Table 2).

11.1.2. Liver Biopsy

Liver biopsy will be scheduled at Screening Visit 1 for confirmation of NASH (inclusion criteria) if no biopsy slides or tissue collected within 1 year of the Screening Visit 1 is available for central read. No other biopsy sample will be collected during the double-blind or LTSE phase of the study.

Biopsies should be at least 2 cm in length. All biopsies will be read centrally by a Sponsor-designated central reader.

11.1.2.1. Central Reading of Liver Histology

Full instructions concerning the number and type of samples to be collected at each visit, the sample collection methods, sample processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual.

All biopsy assessments, including determination of study eligibility based on NASH diagnosis and fibrosis staging during Screening, will be performed centrally by an independent pathologist. The central pathologist must confirm histological presence of NASH and a minimum NAS of 4 with a score of at least 1 in each component of NAS. Key features of NASH (ie, steatosis, lobular inflammation, and hepatocellular ballooning) will be graded in accordance with the NASH CRN criteria for scoring (Kleiner 2005) as summarized in Table 5. Fibrosis staging for eligibility will also be performed in accordance with NASH CRN criteria for fibrosis staging.

Table 5: NASH CRN Scoring System for Determining Eligibility and Primary Histological Endpoint Assessment

NAFLD Activity Score (NAS)		Fibrosis Staging	
Parameter	Scoring Criteria	Parameter	Staging Criteria
Steatosis	0 = <5% 1 = 5% - 33% 2 = >33% - 66% 3 = >66%	Stage 0	No Fibrosis
Lobular Inflammation	0 = No Foci 1 = <2 Foci per 200 × field 2 = 2 - 4 Foci per 200 × field 3 = >4 Foci per 200 × field	Stage 1 Stage 1a Stage 1b Stage 1c	Perisinusoidal or Periportal Mild, zone 3, perisinusoidal Moderate, zone 3, perisinusoidal Portal / periportal
Ballooning	0 = None 1 = Few balloon cells 2 = Many cells / prominent ballooning	Stage 2	Perisinusoidal and portal / periportal
		Stage 3	Bridging fibrosis
		Stage 4	Cirrhosis

In addition to the primary scoring system of NASH CRN, biopsy samples will also be scored based on modified Ishak scoring (Ishak 1995) for all subjects. Any extra biopsy tissue may undergo exploratory histological evaluations.

11.1.3. Noninvasive Radiological Liver Fibrosis Measurements

Liver stiffness will be assessed during LTSE using a noninvasive radiological method TE at study sites where available.

11.1.4. Blood Samples for Future Analysis

Blood samples for exploratory future analysis may be assessed for analytes such as adiponectin, plasminogen activator inhibitor-1(PAI-1), and B-type natriuretic peptide (BNP; Table 10). Blood samples may also be used to assess other disease or investigational product characteristics. The samples will be stored for up to 1 year after the end of the study and destroyed if not analyzed.

11.2. Pharmacokinetic and Pharmacodynamic Assessments

Parent OCA and its major conjugates (glyco-OCA and tauro-OCA), C4, and FGF-19 concentrations will be determined for OCA PK and FXR activity in OCA-treated subjects. Concentrations of atorvastatin and its metabolites will be assessed in PK sampled subjects. Samples will be obtained for possible assessment of conjugated and unconjugated bile acids.

11.2.1. Pharmacodynamic Assessments

PD assessments will be collected according to the Schedule of Study Procedures (Table 1 and Table 2) from all subjects to measure C4, FGF-19, and possibly conjugated and unconjugated bile acids (dependent on the results of the C4 and FGF-19 assessments).

11.2.2. Pharmacokinetic Assessments

Subjects who opt to participate in the PK assessment will provide blood samples for the measurement of OCA and its conjugates, and atorvastatin and its metabolites. The first sample should be collected within 30 minutes prior to administration of investigational product (predose) on Day 1 and prior to administration of investigational product or atorvastatin at the Week 16 Visit. Subjects will then receive a single dose of investigational product with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates, and atorvastatin and its metabolites, 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 after the 1-hour sample is collected. A meal will be provided following collection of the 1-hour PK sample; the meal will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance.

11.3. Anthropometric Assessments

Anthropometric measures include height (measured at Screening Visit 1 only), weight, and waist and hip circumference measurements. Waist-to-hip ratio will be calculated by the electronic data capture (EDC) system and will be calculated as ([Waist Circumference in Centimeters] / [Hip Circumference in Centimeters]). Height will also be collected at Screening Visit 1. Anthropometric measures will be performed during the visits indicated in Table 1 and Table 2.

11.3.1. BMI

BMI will be calculated as (Weight in Kilograms / [Height in Meters × Height in Meters]). Instructions for measuring body weight and waist and hip circumference are described below. All three measures are to be obtained after the subject has fasted for at least 8 hours.

11.3.2. Body Weight

Body weight should be obtained with the subject wearing a hospital gown or similar light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study. The floor surface on which the scale rests must be hard rather than carpeted or covered with other soft material. The subject should stand in the center of the platform. The weight is to be read and recorded to the first decimal point (eg, 97.1 kg) by study staff.

11.3.3. Waist and Hip Circumference:

The subject should be wearing little clothing and standing upright during the measurements, with arms relaxed at the side, feet close together, and body weight evenly distributed. Waist circumference should be measured at the end of several consecutive natural breaths, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid-axillary line. Hip circumference should be measured at the largest circumference of the buttocks. Both measurements should be made with a Sponsor-provided measuring tape that is wrapped snugly around the subject, but not to the point that the tape is constricting. The tape must be level and parallel to the floor at the point of measurement. Each measurement should be repeated twice; if

the measurements are within 1 cm of one another, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

12. ASSESSMENT OF SAFETY

Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. Refer to Section 17.1 for AE reporting procedures.

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definitions

12.1.1.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of the investigational product in humans, whether or not considered related to investigational product. An AE can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with any use of the investigational product, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose. For this study, investigational product refers to OCA or placebo, and study medication refers to atorvastatin.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the subject or asking about the occurrence of any specific symptom. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms "sudden numbness, dizziness, and difficulty speaking." The AE medical term of "stroke or cerebrovascular accident" should be recorded as it more accurately describes the AE.

12.1.1.2. Treatment-Emergent Adverse Event

A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.

12.1.1.3. Serious Adverse Event

An AE is considered 'serious' if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is immediately life threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Events **not** considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE;
- Elective treatment for a pre-existing condition that did not worsen;
- Respite care or observation when there is no AE associated with the hospitalization.

12.1.2. Relationship to Investigational Product or Study Medication

The Investigator will document her/his opinion of the relationship of the AE to treatment with investigational product and study medication (atorvastatin) using the criteria outlined in Table 6. Each AE will be assessed for relationship to investigational product and atorvastatin independently. An AE for which there is a "reasonable possibility" that either investigational product or atorvastatin caused the AE is otherwise referred to as a suspected adverse reactions (SARs). "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and/or atorvastatin and the AE.

If the relationship between a SAE and the investigational product is determined to be "definite," "probable," or "possible," the event will be considered to be related to the investigational product for the purpose of assessing expedited regulatory reporting.

If the relationship between an SAE and the atorvastatin is determined to be "definite," "probable," or "possible," the event will be considered to be related to atorvastatin for the purpose of assessing expedited safety reporting and reporting to the manufacturer.

Table 6: Relationship of Adverse Events to Investigational Product or Study Medication

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the investigational product or study medication in which the investigational product or study medication level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected investigational product or study medication;; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product or study medication, and reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from administration of the investigational product or study medication; that follows a known or expected response pattern to the suspected investigational product or study medication; that is confirmed by stopping or reducing the dosage of the investigational product or study medication; and that could not be reasonably explained by the known characteristics of the subject's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the investigational product or study medication; that follows a known or expected response pattern to the suspected investigational product or study medication; but that could readily be produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from administration of the investigational product or study medication; that does not follow a known or suspected response pattern to the suspected investigational product or study medication; and that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Relationship to Liver Biopsy

The Investigator will document her/his opinion of the relationship of the AE to liver biopsy using the criteria outlined in Table 7.

Table 7: Relationship of Adverse Events to Liver Biopsy

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from the liver biopsy, and that follows a known or expected response pattern to the liver biopsy.
Not Related	Any event that does not meet the above criteria.

12.1.4. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity) using Common Terminology Criteria for Adverse Events (CTCE) Version 4.03 (Appendix C). A severity category of mild, moderate, severe, life-threatening, or death as defined in Table 8, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE. When reporting AEs, reference should be made to the CTCAE manual for guidance on appropriate grading.

Table 8: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
2 = Moderate	Minimal, local or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living.[a]
3 = Severe	Medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living.[b]
4 = Life-Threatening	Urgent intervention indicated
5 = Death	Death related to AE

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.1.4.1. Severity of Pruritus (as an AE)

Pruritus was the most common AE seen in the Phase 2 PBC studies of OCA and thus may occur in this study.

To ensure consistency in reporting, the following guidelines for assessing severity of pruritus should be used for AE reporting. As pruritus is a subjective symptom, clinical judgment should be used to determine its severity and management (Table 9).

Table 9: Severity of Pruritus

Pruritus Grade	Clinical Description of Severity for Pruritus and Medical Intervention
1 = Mild	Generally localized; causing no limitation of usual activities or minimal sleep disturbance; the subject may experience slight discomfort. Medicinal intervention is not indicated.
2 = Moderate	Intense or widespread; causing some limitation of usual activities or sleep disturbance; the subject may experience annoying discomfort. Medicinal intervention may be indicated.
3 = Severe	Intense or widespread and interfering with activities of daily living, ie, causing inability to carry out usual activities, or severe sleep disturbance; the subject may experience intolerable discomfort. Medicinal intervention is typically indicated.

Since pruritus is a subjective symptom and the occurrence and magnitude of which are not readily measured by objective tools, clinical judgment needs to be applied in the management of each subject. Managing OCA-related pruritus may help improve tolerance in those subjects who experience problematic pruritus and may otherwise discontinue from the study prematurely. General guidance for the management of subjects experiencing significant pruritus includes:

- Drug holiday: A drug holiday is defined as an Investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (ie, non-daily dosing does not constitute a drug holiday). Details of drug holidays and/or nondaily dosing regimens should be recorded in the CRF. Per Section 8.4.1.1, subjects with pruritus ≥Grade 3 in severity and possibly, probably, or definitely related to investigational product must discontinue investigational product.
- Prescribe BAS. Subjects taking BAS (including colestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) should be instructed to stagger their dosing of investigational product, ensuring at least 4 hours between doses of the BAS and investigational product.
- Other therapies may be tried as deemed clinically appropriate.
- Less frequent dosing of investigational product (eg, on alternate days) may be tried, after which subjects may return to their original daily dose as soon as tolerated.

12.1.5. Reporting of Adverse Events and Serious Adverse Events

12.1.5.1. Reporting of Adverse Events

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

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice and in the eCRF in the EDC system. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product or study medication.

12.1.5.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor. Immediate reporting implies within 24 hours of becoming aware of the occurrence of an SAE.

All SAEs must be reported to the Sponsor. SAEs are reported by entering the SAE data into the study specific EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may be reported by:

- E-mail to the SAE email address: sae@interceptpharma.com
- Fax using a paper SAE report form: +1 800 497 8521
- Telephone: +1 844 250 6396

If an SAE is reported by telephone or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible. At a minimum, the following information should be provided at the time of the initial report:

- Subject number
- Event term
- At least 1 criterion classifying the event as serious
- Name and title of the reporting individual
- Causal relationship to the investigational product or study medication

The Investigator will assess whether the event is causally related to the investigational product or study medication. The Sponsor will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) Safety Reports/Expedited Safety Reports that occur during the study within the time frames required by each regulatory agency.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the Sponsor in the same manner as described above for the initial SAE report. Any supporting source documentation should be faxed to +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.

The Investigator is responsible for submitting information on IND Safety Reports/Expedited Safety Reports received from the Sponsor to her/his local IRB/IEC, as directed by the local country requirements.

Documentation of the submissions to IRBs/IECs must be retained in the appropriate study file(s). As instructed by the Sponsor, IND Safety Reports/Expedited Safety Reports should be retained in the appropriate investigative site study files, or with the IB.

12.1.6. Additional Investigator Responsibilities for SAEs

The safety data recorded in the EDC represent the official record of all AEs and SAEs reported in the study. The Investigator should comply with requests by the Medical Monitor or other Sponsor personnel to record the SAE on the subject's AE eCRF in the EDC. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Sponsor, the Investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow-up and closure of the SAE report.

The Investigator and supporting personnel responsible for subject care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments must be reported to the Medical Monitor.

12.1.7. Notification of Post-Study SAEs

If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours).

All SAEs that occur within 30 days following the cessation of investigational product or study medication, whether or not they are related to the study, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.5.2.

12.1.8. Follow-Up of Adverse Events and Serious Adverse Events

All AEs must be followed during the course of the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the subject is lost to follow-up.

AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the subject or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented in the EDC. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

All subjects showing possible drug-induced liver injury should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the CRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.

12.1.8.1. Pregnancy and Follow-Up

Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue treatment with investigational product and atorvastatin immediately (see Section 8.4.1.1) and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy eCRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to sae@interceptpharma.com or faxed to +1-800-497-8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and the Sponsor.

Women who discontinue the study due to pregnancy may not re-enroll in the study at any point, but should continue with the study visit schedule and must be followed by the Investigator through pregnancy outcome. Similarly, if a subject's pregnancy is terminated early (planned or unplanned), the subject will also be removed from the study.

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE if an AE/SAE has occurred related to or concurrent with the pregnancy. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 17.1 must also be followed.

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history will be obtained from the subject at Screening Visit 1. Alcohol consumption history will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Table 1 and Table 2). This includes height, which is only measured and recorded at Screening Visit 1. The physical examination must include the following:

- General appearance
- Height (Screening Visit 1 only)
- Weight (and BMI, if applicable)
- Skin
- Head, eyes, ears, nose, and throat
- Neck
- Lymph nodes
- Chest/Respiratory system
- Cardiovascular system
- Abdominal region
- Extremities
- Musculoskeletal system
- Mental status
- Neurological system

12.2.3. Vital Signs

Vital signs will be assessed at indicated visits (Table 1 and Table 2). Vital signs include body temperature, sitting heart rate, respiratory rate, and sitting blood pressure. When taking heart rate, respiratory rate, and blood pressure readings, subjects should be seated quietly for a minimum of 3 minutes before the readings are taken.

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the visits specified in Table 1 and Table 2. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any

clinically significant abnormalities on ECGs recorded after Randomization/Day 1 will also be documented as AEs and entered on the AE page of the eCRF, whereas abnormalities on ECGs up to Randomization/Day 1, prior to administration of the investigational product, will be recorded as pre-treatment AEs.

Investigative sites must retain a copy of all 12-lead ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Subject ID number, date, and time. Full instructions will be provided for forwarding the 12-lead ECGs for central reading.

12.2.5. Alcohol Consumption

Information about the subject's alcohol consumption will be collected during the visits indicated in Table 1 and Table 2 using the Alcohol Use Disorders Identification Test (AUDIT). AUDIT is a 10-item questionnaire that uses the domains of alcohol consumption, drinking behavior, and alcohol-related problems (Saunders 1993).

12.2.6. Laboratory Assessments

Except for Screening Visit 1, subjects will be instructed to attend each study visit in a fasted state, and subjects should remain fasted until their blood samples have been collected. For visits that require fasting, the Investigator or designee will verify that the subject has fasted for at least 8 hours and record fasting status in the source and eCRF. If the subject reports having eaten (water is permitted) within the past 8 hours, the Investigator or designee will document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits (see Section 9.6.1).

Blood, and urine samples for laboratory assessments will be collected at the visits specified in Table 1 and Table 2. Full instructions concerning the number and type of samples to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a separate procedural manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.

The list of laboratory analytes to be tested is shown in Table 10.

Table 10: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
All Subjects	
Serum chemistry	Albumin, BUN, creatinine, conjugated (direct) bilirubin, total bilirubin, AST, ALT, ALP (isoenzymes), GGT, creatine phosphokinase, electrolytes (calcium, chloride, magnesium, phosphorus, potassium, sodium), total protein, bicarbonate, free fatty acids; and blood lipids (total cholesterol, LDL, HDL, and VLDL fractions and TGs)
Hematology	Hemoglobin, hematocrit, white blood count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets, red blood cell count (including MCV, MCH, MCHC)
Urinalysis	pH, specific gravity, protein, glucose, ketones, bilirubin, blood, microscopic exam
Coagulation	PT, PTT, INR
Glycemic control measures	Fasting plasma glucose, insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR
Lipoprotein analysis[a]	LDL, HDL, VLDL, total cholesterol, triglycerides, ApoA1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a), PCSK9
Reverse Cholesterol Transport	Pre-β HDL, macrophage cholesterol efflux, LCAT and CETP
Markers of Inflammation	IL-6, hs-CRP, and TNF-α
Markers of fibrosis and apoptosis	CK-18-M30 and CK-18-M65
Vitamin D levels	Vitamin D
Thyroid function tests	T3, T4, TSH
PD Assessment	C4 and FGF-19; possible analysis of conjugated and unconjugated bile acids
Blood sample for future analysis, including markers of cardiovascular risk	Adiponectin, PAI-1, BNP
Pregnancy Test (female subjects of childbearing potential)	β-hCG
Virus screening tests	Hepatitis B surface antigen, hepatitis C antibody, and HCV ribonucleic acid [RNA]
Subset of Subjects	
PK analytes	OCA, tauro-OCA, glyco-OCA, and possible other conjugates or metabolites not yet identified Atorvastatin and its metabolites

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; ApoCI = apolipoprotein CI; ApoCII = apolipoprotein CII; ApoE = apolipoprotein E; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; C4 = 7α-hydroxy-4-cholesten-3-one; CETP = cholesterol ester transfer protein; CK -18-M30 = cytokeratin-18 neoepitope M30; CK-18-M65 = cytokeratin-18 neoepitope M65; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin-specific

A1c fraction; HDL = high-density lipoprotein; HOMA-β = homeostatic model assessment–beta-cell function; HOMA-IR = homeostatic model assessment – insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; INR = international normalized ratio; LCAT = lecithin cholesterol acyltransferase; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PAI-1 = plasminogen activator inhibitor-1; PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; Pre-β-HDL = pre-β-high-density lipoprotein; TGs = triglycerides; T3 = triiodothyronine; T4 = thyroxine; TNF-α = tumor necrosis factor-α; TSH = thyroid-stimulating hormone; VLDL = very low-density lipoprotein

[a] NMR-based panel will be used for LDL, HDL, and VLDL cholesterol concentrations, particle sizes, and particle concentrations. ApoA1, ApoB, ApoE, ApoCII, ApoCIII Lp(a), and PCSK9 concentrations will be measured using appropriate methods at central or specialty laboratories. Serum chemistry panel will be used for LDL, HDL, VLDL, TG, and total cholesterol concentration.

All subjects with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product related AE, is identified; or until further follow-up is deemed medically unnecessary.

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed for female subjects of childbearing potential at the visits specified in Table 1 and Table 2. If a urine pregnancy test is positive, a serum pregnancy test must be performed to confirm the result (Table 1, Table 2, and Section 9.7). If positive, the Sponsor must be notified and the subject will be followed, as outlined in Section 12.1.8.1 through pregnancy outcome.

International normalized ratio (INR) will be calculated based on prothrombin time value by the central laboratory. HOMA-IR values will be calculated based on fasting plasma glucose and insulin concentrations. Total OCA will be calculated based on OCA, tauro-OCA, and glyco-OCA concentrations.

13. STATISTICS

13.1. Analysis Sets

The following subject populations will be used for presentation and analysis of data:

- Intent-to-Treat (ITT) Population: All randomized subjects who receive any amount of investigational product will be included in the ITT Population. Treatment assignment will be based on the randomized treatment allocation.
- Safety Population: The Safety Population will include all subjects who receive any amount of investigational product. Treatment assignment will be based on the treatment actually received. The Safety Population will be used for the analysis of all safety data.
- Efficacy Evaluable Population: All subjects who complete the double-blind phase according to the indicated doses of investigational product and atorvastatin without

any significant protocol deviations. The Efficacy Evaluable Population will be the primary population used for efficacy analyses.

- Pharmacokinetic Populations: The OCA PK Population will include all OCA subjects who consent to participate in the PK assessments and have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours before the visit and must not have any major protocol deviations that potentially affect exposure levels. The Atorvastatin PK Population will include all subjects who consent to participate in the PK assessments and have at least one confirmed fasted analyzable sample.
- LTSE Population: All subjects who receive any amount of investigational product as part of the LTSE will be included in the LTSE Population.

13.2. Determination of Sample Size

It is the intent of this study to characterize the components of LDL metabolism (cholesterol concentration, particle size, particle concentration) 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, 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 FLINT, 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.

13.3. General Statistical Considerations

A Statistical Analysis Plan (SAP), providing details about the specific planned analyses and statistical tests for both the double-blind phase and the LTSE phase, will be prepared and approved by the Sponsor and its designees prior to study database lock.

13.4. Handling of Dropout and Missing Data

Primary analysis of efficacy endpoints will be done using observed data only; missing values will not be imputed. A sensitivity analysis using a last observation carried forward approach may be considered.

13.5. Subject Population and Demographic Characteristics

Approximately 80 subjects with a confirmed diagnosis of NASH will be randomized to receive investigational product. Demographic characteristics including age, gender, race, and ethnicity will be summarized descriptively.

13.6. Efficacy Analysis

All efficacy analyses will be conducted using the Efficacy Evaluable Population. In addition, the ITT Population will be used for sensitivity analysis of the primary analyses.

The baseline value for efficacy analyses is defined as the last value prior to administration of investigational product on Day 1 (predose).

13.6.1. Primary Efficacy Analysis

The primary efficacy analysis, changes in LDL cholesterol, particle size and particle concentration at Week 16 (end of double-blind phase) compared to Baseline will be summarized by treatment group.

Analyses of observed values will be carried out using an analysis of covariance (ANCOVA) model at each visit 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.

Descriptive statistics of the values will be summarized by treatment group and visit. The results, change from baseline, and percentage change from baseline values as well as estimates of least-square (LS) means, standard errors, and 95% confidence intervals (CIs) will be presented by treatment group.

The comparison of LDLc change from baseline and percentage change from baseline values between each active treatment group and placebo group will be performed as exploratory analysis. Estimates of the LS mean difference between each active treatment group and placebo group, the standard error of the difference, and 95% CI of the difference will be presented.

Sensitivity analysis for primary efficacy analysis will be performed using the ITT Population.

13.6.2. Secondary Efficacy Analysis

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, and estimates of LS means, standard errors, and 95% CIs presented by treatment group.

The secondary parameters related to lipoprotein metabolism include HDL cholesterol concentration, particle size and particle concentration; VLDL cholesterol concentration, particle size and particle concentration; TG and total cholesterol concentrations; and ApoA1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a) concentrations.

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, and proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme levels.

13.6.3. Additional Exploratory Efficacy Analyses

13.6.3.1. Liver Biochemistry, Hepatobiliary Damage, and Liver Function

The following laboratory parameters will be summarized by treatment group: ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total and conjugated (direct) bilirubin, albumin, INR, and platelets.

Analyses of observed laboratory values will be carried out using an ANCOVA model at each visit 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.

Descriptive statistics 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, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between each active treatment group and placebo group, the standard error of the difference, and 95% CI of the difference will be presented.

13.6.3.2. Markers of Inflammation, Fibrosis, and/or Apoptosis

Markers of hepatic fibrosis, inflammation, and/or apoptosis include IL-6, hs-CRP, TNF-α, and CK-18-M30 and CK-18-M65. These biomarkers will be summarized by treatment group using descriptive statistics at Baseline and at each post-Baseline visit. The absolute and percentage change from baseline will be 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 a Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.

13.6.3.3. Glycemic Control Measures

Glycemic control measures include fasting glucose, fasting insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR. These measures will be summarized by treatment group using descriptive statistics at Baseline and at each on-study evaluation. The change from baseline will also be summarized. Baseline is defined as the last fasting assessment prior to treatment. Treatment groups will be compared using an ANCOVA model at each visit 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. Estimates of LS means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between each active treatment group and placebo group, the standard error 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 factor from the ANCOVA model.

13.6.3.4. Anthropometric Measures and Blood Pressure

Anthropometric measures include height (measured and recorded only at Screening Visit 1), body weight, and waist and hip circumference measurements; and BMI and waist-to-hip ratio calculations. Anthropometric and blood pressure measures will be summarized by treatment group using descriptive statistics at Baseline and at each on-study evaluation. The change from Baseline will also be summarized. Baseline is defined as the last assessment prior to treatment. Treatment groups will be compared using an ANCOVA model at each visit 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. Estimates of LS means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between each active treatment group and placebo group, the standard error 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 factor from the ANCOVA model. Subgroup analyses of blood pressure will also be presented by use of antihypertensive medications.

13.6.3.5. Noninvasive Radiological Liver Fibrosis Measurements

Noninvasive radiological methods to assess liver stiffness will be conducted at selected centers where the devices are available. These assessments include TE. Measurements (based on available data) will be summarized by treatment group using descriptive statistics at Baseline and at each post-Baseline Visit. The proportion of fibrosis improvement based on TE measurement will be summarized by treatment group at Week 16 of the double-blind phase, and year 1 and year 2 of the LTSE phase. The correlation with histological assessment based on biopsy at Baseline will also be assessed.

13.6.3.6. Pharmacodynamic Analysis

C4, FGF-19, conjugated and unconjugated bile acids, and total bile acids will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline Visit. The absolute change from baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment.

13.6.3.7. Pharmacokinetic Analysis

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, atorvastatin and its metabolites, and potentially other analytes not yet identified. PK analysis will be conducted using standard non-compartmental methodologies.

For the analysis of OCA and its conjugates, values will be summarized by active treatment group using descriptive statistics. Only samples that have a confirmed fasting of approximately 8 hours or more before their visit will be included in the analysis.

Further details regarding the methods for calculating PK and the specific parameters to be reported will be described in the SAP.

13.6.3.8. Cardiovascular Risk Scores

The cardiovascular risk score includes the FRS and Reynolds scores. 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. These markers will be summarized by treatment group using descriptive

statistics at Baseline and at each on-study evaluation. The change and percentage change from Baseline will also be summarized.

13.6.4. LTSE Analyses

Similar analyses to that which are described above will be conducted for the LTSE using the double-blind baseline value. Analyses based on the double-blind baseline will be performed using randomized treatment groups (placebo, OCA 5 mg, OCA 10 mg, or OCA 25 mg). Sensitivity analyses may be conducted using the last value prior to first dose in the LTSE for all subjects.

13.7. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population. The evaluation of safety data will be conducted for both the end of double-blind phase and final analyses at the end of the LTSE.

13.7.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). Summary tables of TEAEs will be provided. The incidence of TEAEs and SAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided. The incidence of pre-treatment AEs and pre-treatment SAEs occurring after ICF signoff and before the first dosing of investigational product (OCA or placebo) will be tabulated in the same manner as above for all subjects participating in the washout period.

13.7.2. Clinical Laboratory Evaluations

Laboratory parameters will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline Visit. The absolute change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations (using fasting blood sample values for lipids and glucose) prior to treatment.

In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post-Baseline Visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline Visit will be provided for hematology, coagulation, and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation.

13.7.3. Lipoprotein Evaluations

Serum chemistry based assessments are the standard safety tool for monitoring subjects' serum lipids. Baseline is defined as the last fasting assessment prior to treatment. This analysis will only include samples that have a confirmed fasting of approximately 8 hours or more prior to the visit at which they were collected. Further analyses of lipoprotein analytes will be specified in the SAP.

Subgroup analyses will also be presented by use of statin medication.

13.7.4. Additional Safety Analysis

13.7.4.1. Vital Signs

The results and change from baseline to each on-study evaluation visit will be summarized for body temperature, sitting heart rate, and respiratory rate.

13.7.4.2. Electrocardiograms

The ECG data analysis will be conducted based on methodology recommended in the International Conference on Harmonisation (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. Descriptive statistics of ECG parameters (time between 2 consecutive R waves [RR], PR, QRS, QT, and QT interval corrected by Fridericia's formula [QTcF]) at baseline and at each post-baseline timepoint will be summarized by treatment group; absolute changes from baseline will also be summarized.

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

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

13.7.5. Adjudicated Cardiovascular Events

Adjudicated cardiovascular events include core major adverse cardiovascular events (MACE; cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes are defined in Appendix D and will be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. Undetermined cause of death will be classified as a cardiovascular death by the CAC.

Summaries of adjudicated cardiovascular events will include the incidence of TEAEs and the incidence of serious TEAEs. All summaries of incidence will include the associated exact binomial 95% CI.

13.8. Data Monitoring Committee

An independent DMC that includes hepatologists, pharmaceutical physicians, epidemiology/cardiology expert(s), and statistician(s) not involved in the study as Investigators, or consultants. The DMC will have oversight over the study conduct as defined by the DMC charter. All members will have considerable experience with clinical study conduct and DMCs. Any candidate found to have a conflict of interest or whose name is listed on the FDA debarment

list will not be offered membership. Conflicts of interest will be assessed regularly, and if members are found to have a new conflict of interest they would be replaced.

The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review safety and efficacy data. Based on review of these data, the DMC will advise the Sponsor on the validity and scientific merit of continuing the study.

Written minutes of both the open and closed DMC sessions will be prepared. The closed minutes will be made available to the appointed Sponsor representatives only after the double-blind database is locked and unblinded.

Data listings provided to the DMC do not contain individual subject treatment information; however, the DMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all subjects and separate treatment columns with fake labels, ie, the actual treatment groups are used, but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA coded AEs, and AEs leading to early withdrawal of investigational product. At each meeting, detailed narratives of interval SAEs (including events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs.

The DMC may agree to adjust meeting frequency based upon actual and projected safety and efficacy data availability.

All Investigators and responsible IRBs/IECs will be informed of any decisions made by the Sponsor based on recommendations from the DMC relating to subject safety that alter the conduct of this study. The Investigators will inform the subjects of such actions and the protocol, patient information sheet, and ICF will be revised, as appropriate.

13.9. Adjudication Committees

All suspected MACE, and drug-related hepatic injury events that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The 2 committees and event types they are responsible for adjudicating are as follows:

- Cardiovascular Adjudication Committee (CAC): Adjudicates all suspected MACE (Appendix D), including all deaths
- Hepatic Safety Committee: Adjudicates all suspected drug-related hepatic injury events

Each adjudication committee will have a charter that documents the reporting of events by the study site; definition of the suspected events to be adjudicated; supply of source documentation to the committee; and the entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.

The adjudication committee members will include experts with relevant adjudication experience; they will not be involved in the study as Investigators, DMC members, or consultants. Any candidate found to have a conflict or whose name is listed on the FDA debarment list will not be

offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The adjudication of suspected events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any individual subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Study records at each site will be monitored at regular intervals by a representative of the Sponsor, the CRA. The role of the CRA is to aid the Investigator in the maintenance and documentation of complete, accurate, legible, well organized and easily retrievable data. In addition, the CRA will ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational product and will ensure an understanding of the protocol, reporting responsibilities and the validity of the data. This will include ensuring that full and appropriate essential documentation is available.

In order to perform this role, the CRA must perform source data verification and as such, must be given access to the subject's primary source documentation (eg, paper or electronic medical records such as consent to participate in the study, visit dates, screening and randomization numbers, demographic information, medical history, disease history, physical examination, vital signs, laboratory assessments [copy of laboratory reports], AEs, concomitant medications, dates of dispensing investigational product, ECGs, etc) that support data entries in the eCRF. The eCRF must be completed promptly after each visit to allow the progress and results of the study to be closely followed by the Medical Monitor.

The Investigator may exercise judgment in allowing the CRA access to particular sections of the subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC and/or a regulatory agency to conduct one or more site audits during or after the study and agrees to allow access to all study-related documentation and information and be available for discussion about the study.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the eCRF or ultimately transferred into the database to ensure accuracy and completeness.

Training sessions, regular monitoring of the study at the study site by the Sponsor or designated personnel (eg, CRA), instruction manuals, data verification, cross-checking and data audits will

be performed to ensure quality of all study data. Investigators' meetings and/or onsite study initiations will be performed to prepare Investigators and other study site personnel for appropriate collection of study data.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject information, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written IRB/IEC approval to the Sponsor before he or she can enroll any subject into the study. The Investigator is responsible for providing the IB and any other available safety information and information about payments and compensation available to study subjects to the ethics committee for review.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. A favorable opinion on substantial amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of SARs will be provided to the IRB/IEC according to local regulations and guidelines. Investigators or the Sponsor or its designee will provide reports to the IRB/IEC as requested, as a minimum annually, and after the study is complete.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Sponsor's policies.

16.3. Written Informed Consent

The Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the ICF must be given to the subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All reports and communications relating to subjects in this study that are disclosed to an authorized third party will identify subjects only by protocol and assigned number and will be shared in a secure manner. All data shall be secured against unauthorized access.

The Investigator will maintain a list of subject names and identifying information (eg, subjects' hospital numbers, unique subject numbers). This list will not be collected by the Sponsor.

The written information sheet will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by the Sponsor or designee will be identified by unique subject number/randomization code/site number, only.

When personal subject data are stored or processed by computer, the data must be protected to prevent their disclosure to unauthorized third parties. The pertinent sections of the data protection laws in which the country is being conducted will be complied with in full.

The written information sheet and ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may require direct access to parts of the hospital or study site records relevant to the study, including subject medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects for the duration of the study. If the Investigator is not present at the study site during the assessment, he or she will leave instructions for the study site staff and a telephone number where he or she can be reached.

Named physician(s) will be responsible for the medical follow-up of subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject or discovered by any other means during the study. In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor.

17.2. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee). Only the Sponsor may amend the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol amendment to implement the change and obtain regulatory approval. The only exception is when the Investigator considers a subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

The following regulatory documentation must be completed or provided, and maintained:

- Approved Patient Information Sheets and ICF (all versions)
- IRB/IEC approvals (of protocol/amendments, subject questionnaires, etc.)
- Form FDA 1572
- Current medical license of Principal Investigators
- Curriculum vitae of Principal Investigators
- Laboratory certification and reference ranges
- Financial disclosure forms

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. Archiving and Record Retention

The Investigator should retain all correspondence relating to this study in the Investigator Site File (ISF). Any study documents stored elsewhere should have their location referenced in the ISF.

All documents relating to the study including the ISF itself, source documents and subject medical files, completed study subject log and confidential subject identification list will be retained by the Investigator in accordance with regulations. US Federal regulations require that records of drug disposition, eCRFs, source documents, and all reports of this investigation shall be retained by the Investigator for a minimum of 2 years following notification by the Sponsor that the regulatory authorities have been notified of the study's termination, or 2 years following approval of the marketing application. If the Investigator is unable to retain the study documents for the required amount of time, the Sponsor must be notified of the individual who will be assuming this responsibility. In the event that storage of records becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor prior to the destruction of any records. The Investigator will notify the Sponsor if ownership of documents or responsibility for the study site is transferred. The Sponsor will inform Investigators should it become aware of any changes in storage requirements.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for clinical studies that are appropriate for this study. Key issues include the following:

- Clinical Study Registries (eg, clinicaltrials.gov): A description of the study and relevant design elements (eg, basic design, objectives and endpoints, sample size, study population, and key inclusion/exclusion criteria) and results (when available) will be published online in a manner consistent with applicable regulatory guidelines.
- Overview: Investigators, reviewers, and editors will have the right to audit the data to verify its accuracy.
- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and the analyses conducted.
- Data Management: The Sponsor will establish data management and the SAP. The Investigators will have the opportunity to provide input into the plans. The Investigators will have the right to review the audit reports and data resolution decisions before the establishment of a clean file. The Investigators will have the right to appoint appropriately qualified auditors, with GCP experience, to audit the Sponsor's data before the establishment of a clean file. The Investigators must provide adequate notice (at least 2 months) to the Sponsor of their intention to audit a study. The audit should be conducted in a timely manner to allow the resolution of discrepancies before a clean file is established. The Investigators will bear all the costs for the conduct of audits that they initiate, except those related to the resolution of data queries which the Sponsor will bear. Such audits must be conducted in such a manner as to minimize the time to create the clean file.
- Authorship: The Sponsor, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
- Single Center Publication and Additional Publications: This is a multicenter study and is designed to be published with complete data from all the study sites. Single center publications are therefore not considered appropriate. Any such publications should clearly state that the data are "extracted" from a multicenter study and that the

study was not intended, or statistically powered, for data presentation by a single study site.

- Intercept Review of External Manuscripts: Consistent with this, Investigators must submit any drafts of any publications or presentations that may arise from this study to the Sponsor for review and approval and to ensure consistency with the policy in this protocol at least 30 days before submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies, or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit (eg, protocol and amendments, data tabulations, etc). Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

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APPENDIX A. AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION GUIDANCE FOR THE USE OF STATINS

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 63, No. 25, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.11.002

PRACTICE GUIDELINE

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults☆

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

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This document was approved by the American College of Cardiology Board of Trustees and the American Heart Association Science Advisory and Coordinating Committee in November 2013. The Academy of Nutrition and Dietetics affirms the value of this guideline.

The American College of Cardiology requests that this document be cited as follows: Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934.

This article is copublished in *Circulation*.

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Preamble and Transition to ACC/AHA Guidelines to Reduce Cardiovascular Risk

The goals of the American College of Cardiology (ACC) and the American Heart Association (AHA) are to prevent cardiovascular diseases; improve the management of people who have these diseases through professional education and research; and develop guidelines, standards, and policies that promote optimal patient care and cardiovascular health. Toward these objectives, the ACC and AHA have collaborated with the National Heart, Lung, and Blood Institute (NHLBI) and stakeholder and professional organizations to develop clinical practice guidelines for assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, management of blood cholesterol in adults, and management of overweight and obesity in adults.

In 2008, the NHLBI initiated these guidelines by sponsoring rigorous systematic evidence reviews for each topic by expert panels convened to develop critical questions (CQs), interpret the evidence, and craft recommendations. In response to the 2011 report from the Institute of Medicine on the development of trustworthy clinical guidelines (1), the NHLBI Advisory Council recommended that the NHLBI focus specifically on reviewing the highest-quality evidence and partner with other organizations to develop recommendations (2,3). Accordingly, in June 2013 the NHLBI initiated collaboration with the ACC and AHA to work with other organizations to complete and publish the 4 guidelines noted above and make them available to the widest possible constituency. Recognizing that the Expert Panels/Work Groups did not

consider evidence beyond 2011 (except as specified in the methodology), the ACC, AHA, and collaborating societies plan to begin updating these guidelines starting in 2014.

The joint ACC/AHA Task Force on Practice Guidelines (Task Force) appointed a subcommittee to shepherd this transition, communicate the rationale and expectations to the writing panels and partnering organizations, and expeditiously publish the documents. The ACC/AHA and partner organizations recruited a limited number of expert reviewers for fiduciary examination of content, recognizing that each document had undergone extensive peer review by representatives of the NHLBI Advisory Council, key federal agencies, and scientific experts. Each writing panel responded to comments from these reviewers. Clarifications were incorporated where appropriate, but there were no substantive changes because the bulk of the content was undisputed.

Although the Task Force led the final development of these prevention guidelines, they differ from other ACC/AHA guidelines. First, as opposed to an extensive compendium of clinical information, these documents are significantly more limited in scope and focus on selected CQs on each topic, based on the highest-quality evidence available. Recommendations were derived from randomized trials, meta-analyses, and observational studies evaluated for quality and were not formulated when sufficient evidence was not available. Second, the text accompanying each recommendation is succinct, summarizing the evidence for each question. The Full Panel/Work Group Reports include more detailed information about the evidence statements that serve as the basis for recommendations. Third, the format of the recommendations differs from other ACC/AHA guidelines. Each recommendation has been mapped from the NHLBI grading format to the ACC/AHA Classification of Recommendation/Level of Evidence (COR/LOE) construct (Table 1) and is expressed in both formats. Because of the inherent differences in grading systems and the clinical questions driving the recommendations, alignment between the NHLBI and ACC/AHA formats is in some cases imperfect. Explanations of these variations are noted in the recommendation tables, where applicable.

In consultation with NHLBI, the policies adopted by the writing panels to manage relationships of authors with industry and other entities (RWI) are outlined in the methods section of each panel report. These policies were in effect when this effort began in 2008 and throughout the writing process and voting on recommendations, until the process was transferred to ACC/AHA in 2013. In the interest of transparency, the ACC/AHA requested that panel authors resubmit RWI disclosures as of July 2013. Relationships relevant to this guideline are disclosed in Appendix 1. None of the ACC/AHA expert reviewers had relevant RWI (Appendix 2). See Appendix 3 for a list of abbreviations used in the guideline.

Systematic evidence reports and accompanying summary tables were developed by the expert panels and NHLBI. The guideline was reviewed by the ACC/AHA Task Force and approved by the ACC Board of Trustees, and the AHA Science Advisory and Coordinating Committee. In addition, ACC/AHA sought endorsement from other stakeholders, including professional organizations. It is the hope of the writing panels, stakeholders, professional organizations, NHLBI, and Task Force that the guidelines will garner the widest possible readership for the benefit of patients, providers, and the public health.

These guidelines are meant to define practices that meet the needs of patients in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by that patient. As a result, situations might arise in which deviations from these guidelines may be appropriate. These considerations notwithstanding, in caring for most patients, clinicians can employ the recommendations confidently to reduce the risks of atherosclerotic cardiovascular disease (ASCVD) events.

See Tables 1a and 1b for an explanation of the NHLBI recommendation grading methodology.

1. Introduction

1.1. Organization of the Panel

The Blood Cholesterol Expert Panel (Expert Panel) was originally convened as the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV) appointed by the NHLBI. The Expert Panel was composed of 13 members and 3 ex-officio members, which included primary care physicians, cardiologists, endocrinologists, and experts in clinical lipidology, clinical trials, cardiovascular epidemiology and nutrition, and guideline development. The Expert Panel chair asked all panel members to disclose any conflict-of-interest information to the full panel in advance of the deliberations; members with conflicts were asked to recuse themselves from voting on any aspect of the guideline for which a conflict might exist. All 16 members of the NHLBI Adult Treatment Panel IV Panel transitioned to the ACC/AHA guideline Expert Panel. Independent contractors performed the systematic review with the assistance of the Expert Panel and provided methodological guidance to the Expert Panel.

1.2. Document Review and Approval

A formal peer review process was initially completed under the auspices of the NHLBI and included 23 expert reviewers and representatives of federal agencies. This document was also reviewed by 4 expert reviewers nominated by the ACC and the AHA when the management of the guideline transitioned to the ACC/AHA. The ACC and

Table 1. Applying Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test: COR III: No benefit — Not Helpful; COR III: Harm — Excess Cost w/o Benefit or Harmful Treatment: No Proven Benefit; Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even when randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

AHA reviewers' RWI information is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and AHA and endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease.

1.3. Scope of Guideline

This guideline is based on the Full Panel Report, which is provided as an online-only data supplement to the guideline. The Full Panel Report contains background and additional material related to content, methodology, evidence synthesis, rationale, and references and is supported by the NHLBI Systematic Evidence Review, which can be found at http://www.nhlbi.nih.gov/guidelines/cholesterol/ser/. Table 2 provides an overview to facilitate understanding what is new in the present guideline.

The Expert Panel was charged with using data from randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs to update the clinical practice recommendations for the treatment of blood cholesterol levels to reduce ASCVD risk. For this guideline, ASCVD includes coronary heart disease (CHD), stroke, and peripheral arterial disease, all of presumed atherosclerotic origin. These recommendations are intended to provide a

Table 1a. NHLBI Grading of the Strength of Recommendations

Grade	Strength of Recommendation*
A	**Strong recommendation** There is high certainty based on evidence that the net benefit† is substantial.
B	**Moderate recommendation** There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate.
C	**Weak recommendation** There is at least moderate certainty based on evidence that there is a small net benefit.
D	**Recommendation against** There is at least moderate certainty based on evidence that there is no net benefit or that risks/harms outweigh benefits.
E	**Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends.")** Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
N	**No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting.")** Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

*In most cases, the strength of the recommendation should be closely aligned with the quality of the evidence; however, under some circumstances, there may be valid reasons for making recommendations that are not closely aligned with the quality of the evidence (e.g., strong recommendation when the evidence quality is moderate, such as smoking cessation to reduce cardiovascular disease risk or ordering an ECG as part of the initial diagnostic work-up for a patient presenting with possible MI). Those situations should be limited and the rationale explained clearly by the Work Group.
†Net benefit is defined as benefits minus risks/harms of the service/intervention.
ECG indicates electrocardiogram; MI, myocardial infarction; and NHLBI, National Heart, Lung, and Blood Institute.

Table 1b. NHLBI Quality Rating of the Strength of Evidence

Type of Evidence	Quality Rating*
• Well-designed, well-executed† RCT that adequately represent populations to which the results are applied and directly assess effects on health outcomes. • Meta-analyses of such studies. Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect.	High
• RCT with minor limitations‡ affecting confidence in, or applicability of, the results. • Well-designed, well-executed nonrandomized controlled studies§ and well-designed, well-executed observational studies‖. • Meta-analyses of such studies. Moderately certain about the estimate of effect. Further research may have an impact on our confidence in the estimate of effect and may change the estimate.	Moderate
• RCT with major limitations. • Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results. • Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). • Physiological studies in humans. • Meta-analyses of such studies. Low certainty about the estimate of effect. Further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.	Low

*In some cases, other evidence, such as large all-or-none case series (e.g., jumping from airplanes or tall structures), can represent high- or moderate-quality evidence. In such cases, the rationale for the evidence rating exception should be explained by the Work Group and clearly justified.
†"Well-designed, well-executed" refers to studies that directly address the question; use adequate randomization, blinding, and allocation concealment; are adequately powered; use intention-to-treat analyses; and have high follow-up rates.
‡Limitations include concerns with the design and execution of a study that result in decreased confidence in the true estimate of the effect. Examples of such limitations include but are not limited to: inadequate randomization, lack of blinding of study participants or outcome assessors, inadequate power, outcomes of interest that are not prespecified for the primary outcomes, low follow-up rates, and findings based on subgroup analyses. Whether the limitations are considered minor or major is based on the number and severity of flaws in design or execution. Rules for determining whether the limitations are considered minor or major and how they will affect rating of the individual studies will be developed collaboratively with the methodology team.
§Nonrandomized controlled studies refer to intervention studies where assignment to intervention and comparison groups is not random (e.g., quasi-experimental study design).
‖Observational studies include prospective and retrospective cohort, case-control, and cross-sectional studies.
NHLBI indicates National Heart, Lung, and Blood Institute; and RCT, randomized controlled trials.

strong, evidence-based foundation for the treatment of cholesterol for the primary and secondary prevention of ASCVD in women and men.

Because RCT data were used to identify those *most likely to benefit* from cholesterol-lowering statin therapy, the recommendations will be of value to primary care clinicians as well as specialists concerned with ASCVD prevention. Importantly, the recommendations were designed to be easy to use in the clinical setting, facilitating the implementation of a strategy of risk assessment and treatment focused on the prevention of ASCVD. The present guideline is intended to address treatment of adults (≥21 years of age) to complement the NHLBI cardiovascular health risk-reduction guideline for children and adolescents (4).

The members of the Expert Panel acknowledge the important contributions arising from decades of genetic and biochemical studies, observational epidemiological and ecological studies, and in vitro and animal experiments that associated higher low-density lipoprotein cholesterol (LDL-C) levels with greater ASCVD risk. These studies provided the rationale for RCTs, which in turn demonstrated that lowering cholesterol levels reduced ASCVD events and thereby established a central, causal role of atherogenic cholesterol-containing lipoprotein particles, particularly LDL, in the genesis of CHD and ASCVD.

Other strategies for using drug therapy to reduce ASCVD events have been advocated, including treat-to-cholesterol target, lowest-is-best, and risk-based treatment approaches. However, only 1 approach has been evaluated in multiple RCTs—the use of fixed doses of cholesterol-lowering drugs to reduce ASCVD risk. Because the overwhelming body of evidence came from statin

Table 2. What's New in the Guideline?*

1	***Focus on ASCVD Risk Reduction: 4 Statin Benefit Groups*** 1. This guideline is based on a comprehensive set of data from RCTs from which 4 statin benefit groups were identified that focus efforts to reduce ASCVD events in secondary and primary prevention. 2. This guideline identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention.
2	***A New Perspective on LDL-C and/or Non–HDL-C Treatment Goals*** 1. The Expert Panel was unable to find RCT evidence to support continued use of specific LDL-C or non–HDL-C treatment targets. 2. The appropriate intensity of statin therapy should be used to reduce ASCVD risk in *those most likely to benefit.* 3. Nonstatin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.
3	***Global Risk Assessment for Primary Prevention*** 1. This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women. 2. By more accurately identifying higher-risk individuals for statin therapy, the guideline focuses statin therapy on *those most likely to benefit.* 3. It also indicates, on the basis of RCT data, those high-risk groups that might not benefit. 4. This guideline recommends a discussion between clinicians and patients before initiation of statin therapy.
4	***Safety Recommendations*** 1. This guideline used RCTs to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk. 2. Using RCTs to determine statin adverse effects facilitates understanding of the net benefit from statin therapy. 3. This guideline provides expert guidance on management of statin-associated adverse effects, including muscle symptoms.
5	***Role of Biomarkers and Noninvasive Tests*** 1. Treatment decisions in selected individuals who are not included in the 4 statin benefit groups may be informed by other factors as recommended by the Risk Assessment Work Group and Blood Cholesterol Expert Panel.
6	***Future Updates to the Blood Cholesterol Guideline*** 1. This is a comprehensive guideline for the evidence-based treatment of blood cholesterol to reduce ASCVD risk. 2. Future updates will build on this foundation to provide expert guidance on the management of complex lipid disorders and incorporate refinements in risk stratification based on critical review of emerging data. 3. RCTs comparing alternative treatment strategies are needed in order to inform future evidence-based guidelines for the optimum ASCVD risk-reduction approach.

*See Appendix 5, for an expanded discussion of what's new in the guideline.
ASCVD indicates atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and RCT, randomized controlled trial.

RCTs, the Expert Panel appropriately focused on these statin RCTs to develop evidence-based guidelines for the reduction of ASCVD risk. We recognize that this represents a significant departure from current strategies. This should not come as a surprise to clinicians. The recent guideline on heart failure has changed long-standing paradigms on the basis of the evidence, and this guideline does as well (5). Future RCTs will be needed to determine the optimal treatment strategy to provide the greatest reduction in ASCVD events with best margin of safety.

The Expert Panel acknowledges that our process did not provide for a comprehensive approach to the detection, evaluation, and treatment of lipid disorders as was done in the prior Adult Treatment Panel III Report (6). However, the present guideline was never intended to be a comprehensive approach to lipid management for purposes other than ASCVD risk reduction. A limited number of expert opinion recommendations were made only when RCT evidence was not present and after a thorough consideration of what the Expert Panel had learned from the RCTs. For the many questions about complex lipid disorders that are beyond the scope of our systematic evidence review, or for which little or no RCT data are available, it is anticipated that clinicians with lipid expertise can contribute to their management.

1.4. Methodology and Evidence Review

Although the Expert Panel was convened before the Institute of Medicine reports on practice guidelines, our evidence-based process followed most of the standards from the Institute of Medicine report, "Clinical Practice Guidelines We Can Trust" (1). The systematic review was limited to RCTs with ASCVD outcomes and systematic reviews and meta-analyses of RCTs with ASCVD outcomes. Observational studies and those with <18 months (CQ1 and CQ2) or <12 months (CQ3) of follow-up were excluded. Support was provided by a methodology contractor and a systematic review and general support contractor and included the following steps:

- The Expert Panel constructed CQs relevant to clinical practice.
- The Expert Panel identified (a priori) inclusion/exclusion criteria for each CQ.
- An independent contractor developed a literature search strategy, based on inclusion/exclusion criteria, for each CQ.
- An independent contractor executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ. The date range for the overall literature search was January 1, 1995, through December 1, 2009. However, RCTs with hard ASCVD outcomes of myocardial infarction (MI), stroke, and cardiovascular death published after that date range were eligible for consideration until the Expert Panel began deliberations on relevant recommendations.
- RCTs that met the inclusion criteria and were independently graded as fair or good quality were included in the evidence tables for the consideration of the Expert Panel. RCTs that were graded as poor quality were excluded.
- With the assistance of independent methodologists, this evidence base was used to develop a series of evidence statements graded on the level of the evidence (high, medium, or low).
- The Expert Panel then synthesized the evidence statements into treatment recommendations/summaries

graded as A (strong), B (moderate), C (weak), D (recommend against), E (expert), and N (no recommendation).

- The final evidence statements and treatment recommendations were approved by at least a majority of voting members of the Expert Panel.
- Guideline implementability appraisals, planned and coordinated by the NHLBI Implementation Work Group, were performed to identify and address barriers to guideline implementation.

In addition, the Expert Panel was able to include major RCTs and meta-analyses of RCTs published through July 2013 in our discussion and as part of the process of determining ACC/AHA grading of the NHLBI expert-level recommendations.

2. Overview of the Guideline

The RCTs identified in the systematic evidence review indicated a consistent reduction in ASCVD events from 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) therapy in secondary- and primary-prevention populations, with the exception of no ASCVD event reduction when statin therapy was initiated in those with New York Heart Association class II to IV heart failure or those receiving maintenance hemodialysis. The RCTs either compared fixed doses of statins with placebo or untreated controls, or compared fixed doses of higher-intensity statins with moderate-intensity statins. These trials were not designed to evaluate the effect of titrated (dose-adjusted) statin treatment to achieve prespecified LDL-C or non–HDL-C goals.

Therefore, the Expert Panel was unable to find RCT evidence to support titrating cholesterol-lowering drug therapy to achieve target LDL-C or non–HDL-C levels, as recommended by Adult Treatment Panel III (6–8). Notably, the Expert Panel did find RCT evidence that use of therapy (e.g., niacin) to additionally lower non–HDL-C, once an LDL-C target was achieved, did not further reduce ASCVD outcomes (9). The Expert Panel also found extensive RCT evidence that the appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit. The work of the Expert Panel was informed by the reports of the Lifestyle Management (10) and Risk Assessment Work Groups (11) (Figure 1). A summary of the major recommendations for the treatment of cholesterol to reduce ASCVD risk is provided in Table 3.

2.1. Lifestyle as the Foundation for ASCVD Risk-Reduction Efforts

It must be emphasized that lifestyle modification (i.e., adhering to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a crucial component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol-lowering drug therapies. Healthy diet or lifestyle modifications were recommended as background therapy for the RCTs of cholesterol-lowering drug therapy. See the "2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk" (10) for lifestyle recommendations for healthy adults. Drug therapy for lifestyle-related risk factors such as hypertension is often needed and smoking should be avoided.

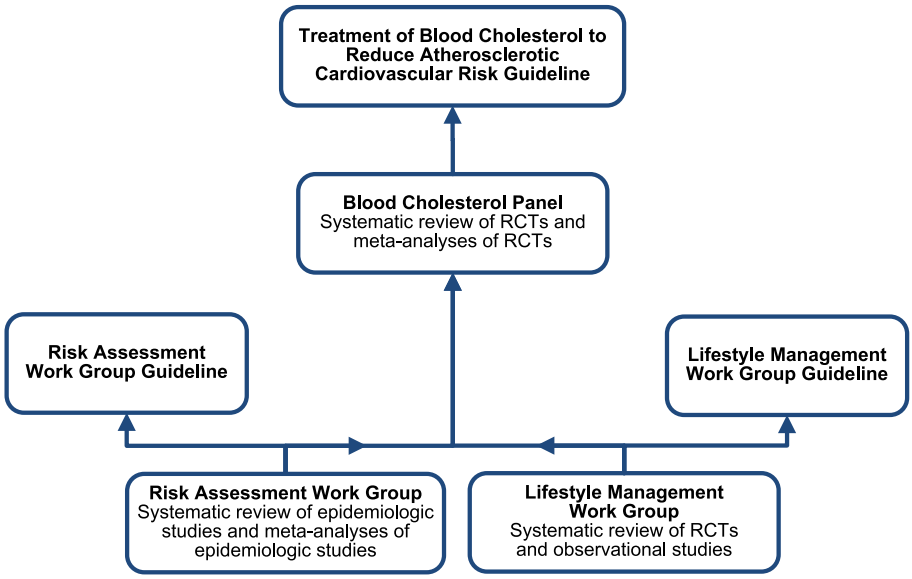

Figure 1. Overview of the Expert Panel's Guideline

RCTs indicates randomized controlled trials.

Table 3. Summary of Key Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults (See Tables 4, 8, 9, and 10 for the complete recommendations; and Table 5 for definition of statin intensity)

Recommendations	ACC/AHA COR	ACC/AHA LOE
A. Heart-healthy lifestyle habits should be encouraged for all individuals		
B. The appropriate intensity of statin therapy should be initiated or continued:		
1. Clinical ASCVD*		
a. Age ≤75 y and no safety concerns: High-intensity statin	I	A
b. Age >75 y or safety concerns: Moderate-intensity statin	I	A
2. Primary prevention – Primary LDL-C ≥190 mg/dL		
a. Rule out secondary causes of hyperlipidemia (Table 6)	I	B
b. Age ≥21 y: High-intensity statin	I	B
c. Achieve at least a 50% reduction in LDL-C	IIa	B
d. LDL-C lowering nonstatin therapy may be considered to further reduce LDL-C	IIb	C
3. Primary prevention—Diabetes 40–75 years of age and LDL-C 70–189 mg/dL		
a. Moderate-intensity statin	I	A
b. Consider high-intensity statin when ≥7.5% 10-y ASCVD risk using the Pooled Cohort Equations†	IIa	B
4. Primary prevention – No diabetes 40–75 years of age and LDL-C 70–189 mg/dL		
a. Estimate 10-y ASCVD risk using the Risk Calculator based on the Pooled Cohort Equations† in those NOT receiving a statin; estimate risk every 4–6 y	I	B
b. To determine whether to initiate a statin, engage in a clinician-patient discussion of the potential for ASCVD risk reduction, adverse effects, drug–drug interactions, and patient preferences	IIa	C
c. Re-emphasize heart-healthy lifestyle habits and address other risk factors		
i. **≥7.5% 10-y ASCVD risk**: Moderate- or high-intensity statin	I	A
ii. **5 to <7.5% 10-y ASCVD risk**: Consider moderate-intensity statin	IIa	B
iii. **Other factors may be considered**‡: LDL-C ≥160 mg/dL, family history of premature ASCVD, hs-CRP ≥2.0 mg/L, CAC score ≥300 Agaston units, ABI <0.9, or lifetime ASCVD risk	IIb	C
5. Primary prevention when LDL-C <190 mg/dL and age <40 or >75 y, or <5% 10-y ASCVD risk	IIb	C
a. Statin therapy may be considered in selected individuals‡		
6. Statin therapy is not routinely recommended for individuals with NYHA class II-IV heart failure or who are receiving maintenance hemodialysis		
C. Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments		
1. Assess adherence, response to therapy, and adverse effects within 4–12 wk following statin initiation or change in therapy	I	A
a. Measure a fasting lipid panel	I	A
b. Do not routinely monitor ALT or CK unless symptomatic	IIa	C
c. Screen and treat type 2 diabetes according to current practice guidelines. Heart-healthy lifestyle habits should be encouraged to prevent progression to diabetes	I	B
d. Anticipated therapeutic response: approximately ≥50% reduction in LDL-C from baseline for high-intensity statin and 30% to <50% for moderate-intensity statin	IIa	B
i. Insufficient evidence for LDL-C or non–HDL-C treatment targets from RCTs		
ii. For those with unknown baseline LDL-C, an LDL-C <100 mg/dL was observed in RCTs of high-intensity statin therapy		
e. Less than anticipated therapeutic response:		
i. Reinforce improved adherence to lifestyle and drug therapy	I	A
ii. Evaluate for secondary causes of hyperlipidemia if indicated (Table 6)	I	A
iii. Increase statin intensity, or if on maximally-tolerated statin intensity, consider addition of nonstatin therapy in selected high-risk individuals§	IIb	C
f. Regularly monitor adherence to lifestyle and drug therapy every 3–12 mo once adherence has been established. Continue assessment of adherence for optimal ASCVD risk reduction and safety	I	A
D. In individuals intolerant of the recommended intensity of statin therapy, use the maximally tolerated intensity of statin.	I	B
1. If there are muscle or other symptoms, establish that they are related to the statin	IIa	B
2. For specific recommendations on managing muscle symptoms (Table 8)		

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

†Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations (http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx).

‡These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; hs-CRP ≥2 mg/L; CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ABI <0.9; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

§High-risk individuals include those with clinical ASCVD, an untreated LDL-C ≥190 mg/dL suggesting genetic hypercholesterolemia, or individuals with diabetes 40 to 75 years of age and LDL-C 70 to 189 mg/dL.

ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ALT, alanine aminotransferase, a test of hepatic function; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CK, creatine kinase, a test of muscle injury; COR, Class of Recommendation; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; RCTs, randomized controlled trials; and TIA, transient ischemic attack.

2.2. Initiation of Statin Therapy

The Expert Panel found extensive and consistent evidence supporting the use of statins for the prevention of ASCVD in many higher-risk primary- and all secondary-prevention individuals without New York Heart Association class II–IV heart failure who were not receiving hemodialysis. In the RCTs reviewed, initiation of moderate-intensity therapy (lowering LDL-C by approximately 30% to <50%) or high-intensity statin therapy (lowering LDL-C by approximately ≥50%) is a critical factor in reducing ASCVD events. Moreover, statin therapy reduces ASCVD events across the spectrum of baseline LDL-C levels ≥70 mg/dL. In addition, the relative reduction in ASCVD risk is consistent for primary and secondary prevention and for various patient subgroups. Of note, the absolute reduction in ASCVD events is proportional to baseline absolute ASCVD risk. Therefore, statin therapy is recommended for individuals at increased ASCVD risk who are most likely to experience a net benefit in terms of the potential for ASCVD risk reduction and the potential for adverse effects (Table 3; Figure 2).

On the basis of this large and consistent body of evidence, 4 major statin benefit groups were identified for whom the ASCVD risk reduction clearly outweighs the risk of adverse events based on a strong body of evidence. These are 1) secondary prevention in individuals with *clinical* ASCVD, 2) primary prevention in individuals with primary elevations of LDL-C ≥190 mg/dL, 3) primary prevention in individuals with diabetes 40 to 75 years of age who have LDL-C 70 to 189 mg/dL, and 4) primary prevention in individuals without diabetes and with estimated 10-year ASCVD risk ≥7.5%, 40 to 75 years of age who have LDL-C 70 to 189 mg/dL. Moderate evidence supports the use of statins for primary prevention in individuals with 5% to <7.5% 10-year ASCVD risk, 40 to 75 years of age with LDL-C 70 to 189 mg/dL. Selected individuals with <5% 10-year ASCVD risk, or <40 or >75 years of age may also benefit from statin therapy. Clinicians and patients should engage in a discussion of the potential for ASCVD risk-reduction benefits, adverse effects, drug–drug interactions, and consider patient preferences for treatment. This discussion also provides the opportunity to re-emphasize healthy-lifestyle habits and address other risk factors.

Clinical ASCVD is defined by the inclusion criteria for the secondary-prevention statin RCTs (acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin). For primary prevention in individuals without clinical ASCVD or diabetes who have an LDL-C 70 to 189 mg/dL, the estimated absolute *10-year risk* of ASCVD (defined as nonfatal MI, CHD death, or nonfatal and fatal stroke) should be used to guide the initiation of statin therapy. The 10-year ASCVD risk should be estimated with the Pooled Cohort Equations (Section 4.7). For the primary prevention of ASCVD in individuals with diabetes (diabetes mellitus type 1 and type 2), estimated 10-year ASCVD risk can also be used to guide the intensity of statin therapy. For those with *clinical* ASCVD or with LDL-C ≥190 mg/dL who are already in a statin benefit group, it is not appropriate to estimate 10-year ASCVD risk. In primary prevention, additional factors may influence ASCVD risk in those for whom a risk-based decision is unclear. These include a primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, high-sensitivity C-reactive protein ≥2 mg/L, coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx.), ankle-brachial index <0.9, and elevated lifetime risk of ASCVD.

The findings support the use of statins to prevent both nonfatal and fatal ASCVD events. Such an approach can reduce the large burden of disability from nonfatal stroke (for which women are at higher risk than men) and nonfatal CHD events. Primary and secondary prevention of ASCVD with statins can positively impact rising healthcare costs. In addition, a high level of evidence was found that statins reduce total mortality in individuals with a history of prior ASCVD events (e.g., secondary-prevention settings). In individuals with no prior history of ASCVD events (e.g., primary-prevention settings), there is moderate evidence that statins reduce total mortality in individuals at increased ASCVD risk. It should be noted that 2 meta-analyses published after the completion of the Expert Panel's systematic review provide strong evidence that statins reduce total mortality in primary prevention (12,13).

3. Critical Questions and Conclusions

3.1. Identification of CQs

Although limited to 3 CQs, these questions were considered the most important to answer in order to identify whom to treat and with what treatment(s) and to consider how intensively the treatments should be used. The first 2 CQs evaluated the evidence for LDL-C and non–HDL-C goals for the secondary and primary prevention of ASCVD with cholesterol-lowering drug therapy. Titration to specific LDL-C goals has been considered a fundamental therapeutic strategy in deciding on the adequacy of cholesterol-lowering therapy for secondary and primary prevention. Therefore, a comprehensive systematic review

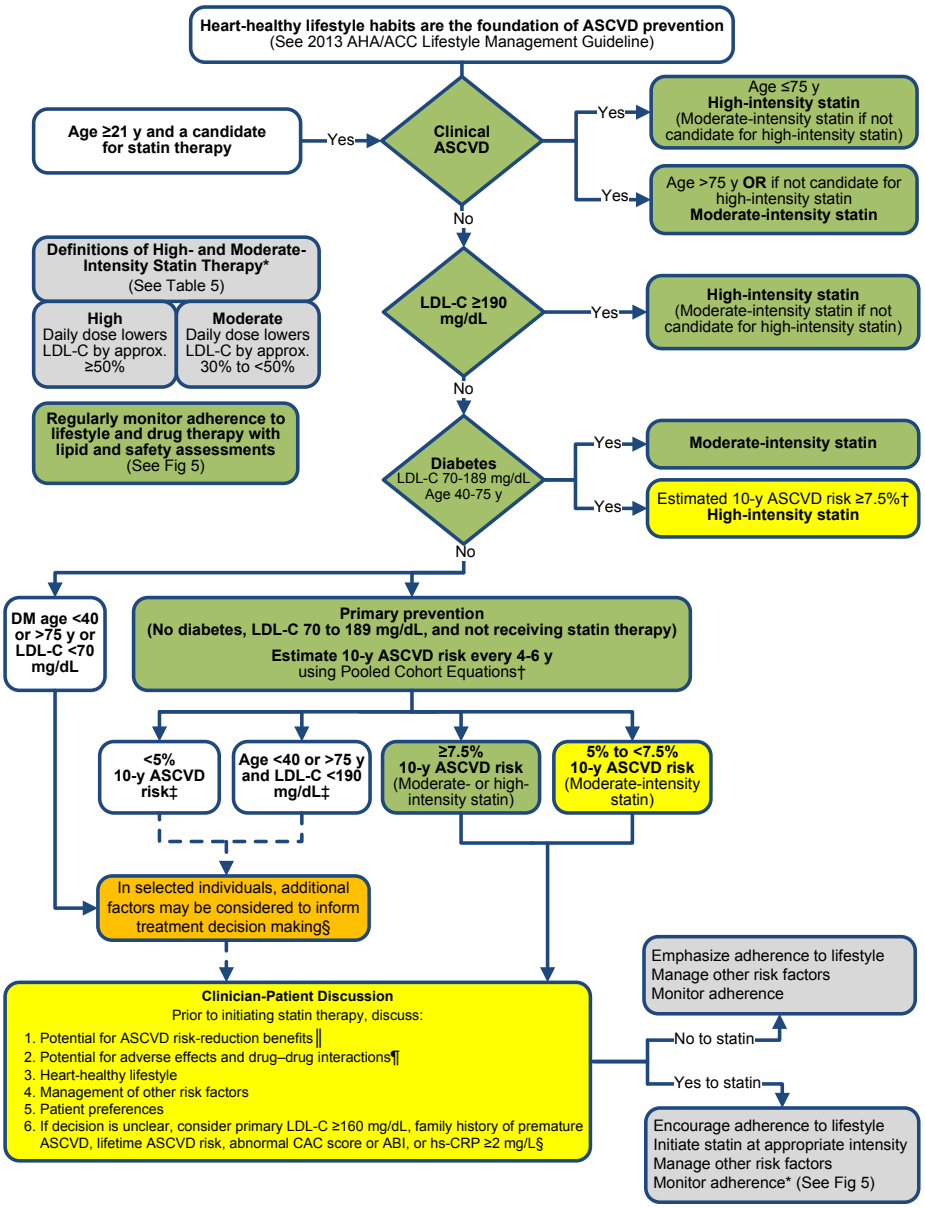

Figure 2. Summary of Statin Initiation Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults (See Figures 3, 4, and 5 for More Detailed Management Information)

Colors correspond to the Classes of Recommendation in Table 1. Assessment of the potential for benefit and risk from statin therapy for ASCVD prevention provides the *framework* for clinical decision making incorporating patient preferences.

*Percent reduction in LDL-C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal.

†The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. The estimator within this application should be used to inform decision making in primary prevention patients not on a statin.

‡Consider moderate-intensity statin as more appropriate in low-risk individuals.

§For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, hs-CRP ≥2 mg/L, CAC score ≥300 Agatston units, or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.

‖Potential ASCVD risk-reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative-risk reduction from the intensity of statin initiated (~30% for moderate-intensity statin or ~45% for high-intensity statin therapy). The net ASCVD risk-reduction benefit is estimated from the number of potential ASCVD events prevented with a statin, compared to the number of potential excess adverse effects.

¶Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In RCTs, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated (see Table 8, Safety Recommendation 8).

ABI indicates ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and RCT, randomized controlled trial.

of the evidence base supporting this concept was essential. The third CQ had several objectives:

- Identify groups of patients who will benefit from pharmacological treatment,
- Define the pharmacological treatment(s) for which there is the best evidence of net benefit, and
- Provide guidance on the appropriate intensity of pharmacological treatment to reduce ASCVD risk.

3.1.1. CQ1: LDL-C and Non–HDL-C Goals in Secondary Prevention

CQ1: What is the evidence for LDL-C and non–HDL-C goals for the secondary prevention of ASCVD?

The Expert Panel reviewed 19 RCTs to answer CQ1. Although CQ1 is supported conceptually by an extrapolation of observational studies and observational data from RCTs, no data were identified for treatment or titration to a specific LDL-C goal in adults with clinical ASCVD. The majority of studies confirming the efficacy of cholesterol reduction in improving clinical outcomes in patients with clinical ASCVD used a single fixed-dose statin to lower LDL-C levels. In the 4S trial, 37% had the dose of simvastatin raised from 20 mg/d to 40 mg/d to achieve a total cholesterol level <200 mg/dL (16). The Expert Panel was unable to find any RCTs that evaluated titration of all individuals in a treatment group to specific LDL-C targets <100 mg/dL or <70 mg/dL, nor were any RCTs comparing 2 LDL-C treatment targets identified. No statin RCTs reporting on-treatment non–HDL-C levels were identified. (In CQ3, statin-nonstatin combination therapy was evaluated.)

3.1.2. CQ2: LDL-C and Non–HDL-C Goals in Primary Prevention

CQ2: What is the evidence for LDL-C and non–HDL-C goals for the primary prevention of ASCVD?

The Expert Panel reviewed 6 RCTs. The 4 studies confirming the efficacy of cholesterol reduction in improving clinical outcomes in patients without ASCVD used fixed-dose statin therapy to lower LDL-C levels. In the AFCAPS-TEXCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trial (17), in 50% of participants, the lovastatin dose was raised from 20 mg to 40 mg to achieve an LDL-C level <110 mg/dL. In the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) trial (18), the dose of pravastatin could be uptitrated from 10 mg to 20 mg to achieve a total cholesterol level <220 mg/dL. The Expert Panel did not find any RCTs that evaluated titration of all individuals in a treatment group to specific LDL-C targets <100 mg/dL or <70 mg/dL, nor were any RCTs comparing 2 LDL-C treatment targets identified. No trials reported on-treatment non–HDL-C levels.

3.1.3. CQ3: Efficacy and Safety of Cholesterol-Lowering Medications

CQ3: For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

The populations examined included primary-prevention adult patients who could not have a diagnosis of CHD or cardiovascular disease. Interventions included pharmacotherapy with single-drug therapies or combination-drug therapies with any drug therapy used for treating blood cholesterol, including statins, fibrates (fenofibrate, gemfibrozil), nicotinic acid (niacin in immediate-, slow-, or extended-release form), bile acid sequestrants, ezetimibe, omega-3 fatty acids (also called marine fatty acids, including eicosapentaenoic acid alone, docosahexanoic acid alone, eicosapentaenoic acid plus docosahexanoic acid, and alpha-linolenic acid). There were no ASCVD outcomes identified for plant sterols, sterol esters, stanols, or stanol esters. A single ASCVD outcomes trial (19) used Xuezhikang, an extract from red yeast Chinese rice, which was not available in the United States during the timeframe for evidence review, so no recommendations were made regarding its use.

The recommendations synthesize the evidence retrieved for answering CQ3, along with the evidence from the trials included in CQ1 and CQ2, to guide the use of cholesterol-lowering drugs for secondary or primary prevention of ASCVD.

4. Statin Treatment: Recommendations

For each recommendation, the grades of the recommendation by both the NHLBI and ACC/AHA methods are provided. Major treatment recommendations are listed in Table 4, and statin intensities are defined in Table 5. The safety (statin and nonstatin) recommendations are in Section 5. A complete listing of the evidence statements supporting each recommendation, along with the references, is provided in Appendix 4.

4.1. Intensity of Statin Therapy in Primary and Secondary Prevention

The Expert Panel defines the intensity of statin therapy on the basis of the average expected LDL-C response to a specific statin and dose. “High-intensity,” “moderate-intensity,” and “low-intensity” statin therapy definitions were derived from the systematic reviews for CQ1 and CQ2. The basis for differentiation among specific statins and doses arose from the RCTs included in CQ1, where there was a high level of evidence that high-intensity statin therapy with atorvastatin 40 mg to 80 mg reduced ASCVD risk more than moderate-intensity

Table 4. Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults—Statin Treatment (High, Moderate, and Low Statin Intensities are Defined in Table 5)

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Treatment Targets				
1. The Expert Panel makes no recommendations for or against specific LDL-C or non–HDL-C targets for the primary or secondary prevention of ASCVD.	N (No recommendation)	1–4	—	—
Secondary Prevention				
1. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have *clinical ASCVD**, unless contraindicated.	A (Strong)	1,6–8,10–23,26–28	I	A
2. In individuals with *clinical ASCVD** in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated† or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (Table 8 for Safety of Statins, Recommendation 1).	A (Strong)	13–22,24,27,28	I	A
3. In individuals with *clinical* ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.	E (Expert Opinion)	—	IIa	B (16,20–43)
Primary Prevention in Individuals ≥21 Years of Age With LDL-C ≥190 mg/dL				
1. Individuals with LDL-C ≥190 mg/dL or triglycerides ≥500 mg/dL should be evaluated for secondary causes of hyperlipidemia (Table 6).	B (Moderate)	75	I‡	B (44,45)
2. Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): • Use high-intensity statin therapy unless contraindicated. • For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.	B (Moderate)	6,19,28,33–35,37,38	I§	B
3. For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction.	E (Expert Opinion)	—	IIa	B (20,46–50)
4. For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions, and consider patient preferences.	E (Expert Opinion)	—	IIb	C (51)
Primary Prevention in Individuals With Diabetes and LDL-C 70–189 mg/dL				
1. Moderate-intensity statin therapy should be initiated or continued for adults 40–75 years of age with diabetes.	A (Strong)	19,29–34,40	I	A
2. High-intensity statin therapy is reasonable for adults 40–75 years of age with diabetes with a ≥7.5% estimated 10-year ASCVD risk‖ unless contraindicated.	E (Expert Opinion)	—	IIa	B (49,52)
3. In adults with diabetes, who are <40 years of age or >75 years of age, or with LDL <70 mg/dL it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects and drug–drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.	E (Expert Opinion)	—	IIa	C (53–62)

Continued on the next page

Table 4. Continued

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Primary Prevention in Individuals Without Diabetes and With LDL-C 70–189 mg/dL				
1. The Pooled Cohort Equations should be used to estimate 10-year ASCVD‖ risk for individuals with LDL-C 70–189 mg/dL without *clinical ASCVD** to guide initiation of statin therapy for the primary prevention of ASCVD.	E (Expert Opinion)	—	I	B (11)
2. Adults 40–75 years of age with LDL-C 70–189 mg/dL, without *clinical* ASCVD* or diabetes, and with an estimated 10-year ASCVD‖ risk ≥7.5% should be treated with moderate- to high-intensity statin therapy.	A (Strong)	28,34–36,38,42–44, 47,49–56,76	I	A
3. It is reasonable to offer treatment with a moderate-intensity statin to adults 40–75 years of age, with LDL-C 70–189 mg/dL, without *clinical* ASCVD* or diabetes, and with an estimated 10-year ASCVD‖ risk of 5% to <7.5%.	C (Weak)	28,34–36,38,42–44, 47,49–56,76	IIa	B
4. Before initiation of statin therapy for the primary prevention of ASCVD in adults with LDL-C 70–189 mg/dL without *clinical* ASCVD* or diabetes, it is reasonable for clinicians and patients to engage in a discussion that considers the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions, as well as patient preferences for treatment.	E (Expert Opinion)	—	IIa	C (63)
5. In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk-based treatment decision is uncertain, additional factors¶ may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluation of the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions and consider patient preferences.	E (Expert Opinion)	—	IIb	C (11,13)
Heart Failure and Hemodialysis				
1. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.	N (No Recommendation)	71,72	—	—

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

†Contraindications, warnings, and precautions are defined for each statin according to the manufacturer's prescribing information (64–70).

‡Individuals with secondary causes of hyperlipidemia were excluded from RCTs reviewed. A triglyceride level ≥500 mg/dL was an exclusion criterion for almost all RCTs. Therefore, ruling out secondary causes is necessary to avoid inappropriate statin therapy.

§No RCTs included only individuals with LDL-C ≥190 mg/dL. However, many trials did include individuals with LDL-C ≥190 mg/dL, and all of these trials consistently demonstrated a reduction in ASCVD events. In addition, the Cholesterol Treatment Trialists meta-analyses have shown that each 39-mg/dL reduction in LDL-C with statin therapy reduced ASCVD events by 22%, and the relative reductions in ASCVD events were consistent across the range of LDL-C levels. Therefore, individuals with primary LDL-C ≥190 mg/dL should be treated with statin therapy.

‖Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, coronary heart disease death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.

¶These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein ≥2 mg/L; CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ABI <0.9; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; COR, Class of Recommendation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; RCTs, randomized controlled trials; TIA, transient ischemic attack; and —, not applicable.

statin therapy with atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20 mg to 40 mg twice daily. Classifying specific statins and doses by the percent reduction in LDL-C level is based on evidence that the relative reduction in ASCVD risk from statin therapy is related to the degree by which LDL-C is lowered. However, no variation in the relative reduction in ASCVD risk was observed after the data were adjusted for LDL-C reduction. Furthermore, there is no differentiation between the specific statins and doses used in primary- and secondary-prevention RCTs, according to a high level of evidence that statins reduce ASCVD risk similarly in both populations.

Percent reductions in LDL-C for a specific statin and dose were calculated for the RCTs included in individual meta-analyses conducted by the Cholesterol Treatment Trialists (CTT) in 2010 (20), in which statin therapy reduced ASCVD events. High-intensity statin therapy on average lowers LDL-C by approximately ≥50%, moderate-intensity statin therapy lowers LDL-C by approximately 30% to <50%, and lower-intensity statin therapy lowers LDL-C by <30% (Table 5).

4.2. LDL-C and Non–HDL-C Treatment Goals

The Expert Panel did not find evidence to support titrating cholesterol-lowering drug therapy to achieve optimal

Table 5. High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg	**Atorvastatin 10 (*20*) mg**	*Simvastatin 10 mg*
Rosuvastatin 20 (*40*) mg	**Rosuvastatin (*5*) 10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg‡	**Lovastatin 20 mg**
	Pravastatin 40 (*80*) mg	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

Boldface type indicates specific statins and doses that were evaluated in RCTs (16–18,46–49,64–75,77) included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3 (20). All of these RCTs demonstrated a reduction in major cardiovascular events. *Italic type* indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.
*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study (47).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.
BID indicates twice daily; CQ, critical question; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

LDL-C or non–HDL-C levels because the clinical trials were essentially fixed-dose trials (CQ1 and CQ2). Dosage increases did occur in a few RCTs with the intent of maximizing statin therapy. Therefore, these were not truly tests of defining optimal goals for LDL-C in primary and secondary prevention because not all individuals in the statin treatment groups received drug therapy titrated to achieve a specific LDL-C or non–HDL-C goal, nor were specific treatment targets compared. One RCT in CQ3 was identified that showed no additional ASCVD event reduction from the addition of nonstatin therapy to further lower non–HDL-C levels once an LDL-C goal had been reached. In AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes), the additional reduction in non–HDL-C levels (as well as further reductions in apolipoprotein B, lipoprotein[a], and triglycerides in addition to HDL-C increases) with niacin therapy did not further reduce ASCVD risk in individuals treated to LDL-C levels of 40 to 80 mg/dL (9).

Therefore, given the absence of data on titration of drug therapy to specific goals, no recommendations are made for or against specific LDL-C or non–HDL-C goals for the primary or secondary prevention of ASCVD.

4.3. Secondary Prevention

Women and men with clinical ASCVD (defined from the RCT inclusion criteria as acute coronary syndromes; history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin) arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin are at increased risk for recurrent ASCVD and ASCVD death. An extensive body of evidence demonstrates that high-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy (Table 4) in individuals with clinical ASCVD.

High-intensity statin therapy should be initiated for adults ≤75 years of age with clinical ASCVD who are not receiving statin therapy, or the intensity should be increased in those receiving a low- or moderate-intensity statin, unless they have a history of intolerance to high-intensity statin therapy or other characteristics that could influence safety (Section 5). This is consistent with RCT data. In 2 trials, patients were previously treated with a moderately intensive statin (46,47), and in 2 trials, 75% to 97% of patients had not received prior statin therapy (48,78). The high-intensity statins atorvastatin 80 mg and rosuvastatin 20 mg daily reduce LDL-C ≥50% on average and have been shown to reduce ASCVD events in RCTs.

Although atorvastatin 40 mg reduces LDL-C by approximately ≥50%, this dose was used in only 1 RCT if the participant was unable to tolerate atorvastatin 80 mg/dL. Whether an individual receiving atorvastatin 40 mg should be uptitrated to atorvastatin 80 mg should be based on the potential for an ASCVD risk-reduction benefit and the potential for adverse effects, drug–drug interactions, and consider patient preferences.

In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, either when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option, if tolerated (Section 5). In the relatively few individuals >75 years of age who were included in RCTs of high- versus moderate-intensity statin therapy, there was no clear evidence of an additional reduction in ASCVD events from high-intensity statin therapy. In contrast, individuals >75 years of age did experience a reduction in ASCVD events in the trials of mostly moderate-intensity statin therapy, as compared with control. Therefore, moderate-intensity statin therapy should be considered for individuals >75 years of age with *clinical* ASCVD. However, in acknowledgment that older participants in RCTs were likely to be healthier than many older individuals in the general population, the use of statin therapy should be individualized

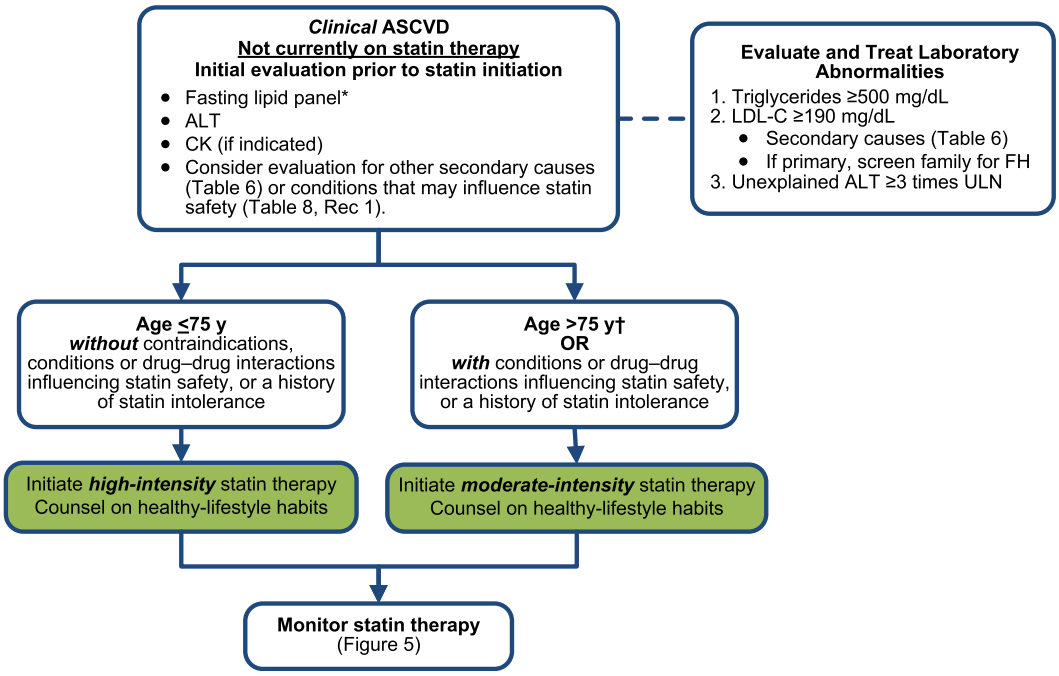

Figure 3. Initiating Statin Therapy in Individuals With Clinical ASCVD

Colors correspond to the Classes of Recommendation in Table 1.
*Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C level ≥220 mg/dL could indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.
†It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, and to consider patient preferences, in initiating or continuing a moderate- or high-intensity statin in individuals with ASCVD who are >75 years of age.
ALT indicates alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CK, creatine kinase; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and ULN, upper limit of normal.

in persons >75 years of age with *clinical* ASCVD, according to the potential for ASCVD risk-reduction benefits, adverse effects, drug–drug interactions, and consider patient preferences. The Expert Panel considers it reasonable to continue statin therapy in persons >75 years of age who have *clinical* ASCVD and are tolerating statin therapy.

The flow diagram for the initiation and management of statin therapy in individuals with *clinical* ASCVD is provided in Figure 3.

4.4. Primary Prevention in Individuals ≥21 Years of Age With LDL-C ≥190 mg/dL

This guideline recognizes that individuals ≥21 years of age with primary, severe elevations of LDL-C (≥190 mg/dL) have a high lifetime risk for ASCVD events. This is due to their lifetime exposure to markedly elevated LDL-C levels arising from genetic causes. Thus, at age 21, these individuals should receive statin therapy if they have not already been diagnosed and treated before this age. Although in most clinical trials individuals with LDL-C ≥190 mg/dL were not included because of their need for treatment, extensive evidence shows that each 39-mg/dL reduction in LDL-C by statin therapy reduces ASCVD risk by about 20%. Patients with primary elevations of LDL-C ≥190 mg/dL require even more substantial reductions in their LDL-C levels and intensive management

Table 6. Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice

Secondary Cause	Elevated LDL-C	Elevated Triglycerides
Diet	Saturated or *trans* fats, weight gain, anorexia nervosa	Weight gain, very-low-fat diets, high intake of refined carbohydrates, excessive alcohol intake
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
Diseases	Biliary obstruction, nephrotic syndrome	Nephrotic syndrome, chronic renal failure, lipodystrophies
Disorders and altered states of metabolism	Hypothyroidism, obesity, pregnancy*	Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy*

Adapted with permission from Stone et al (80).
*Cholesterol and triglycerides rise progressively throughout pregnancy (80); treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.
LDL-C indicates low-density lipoprotein cholesterol.

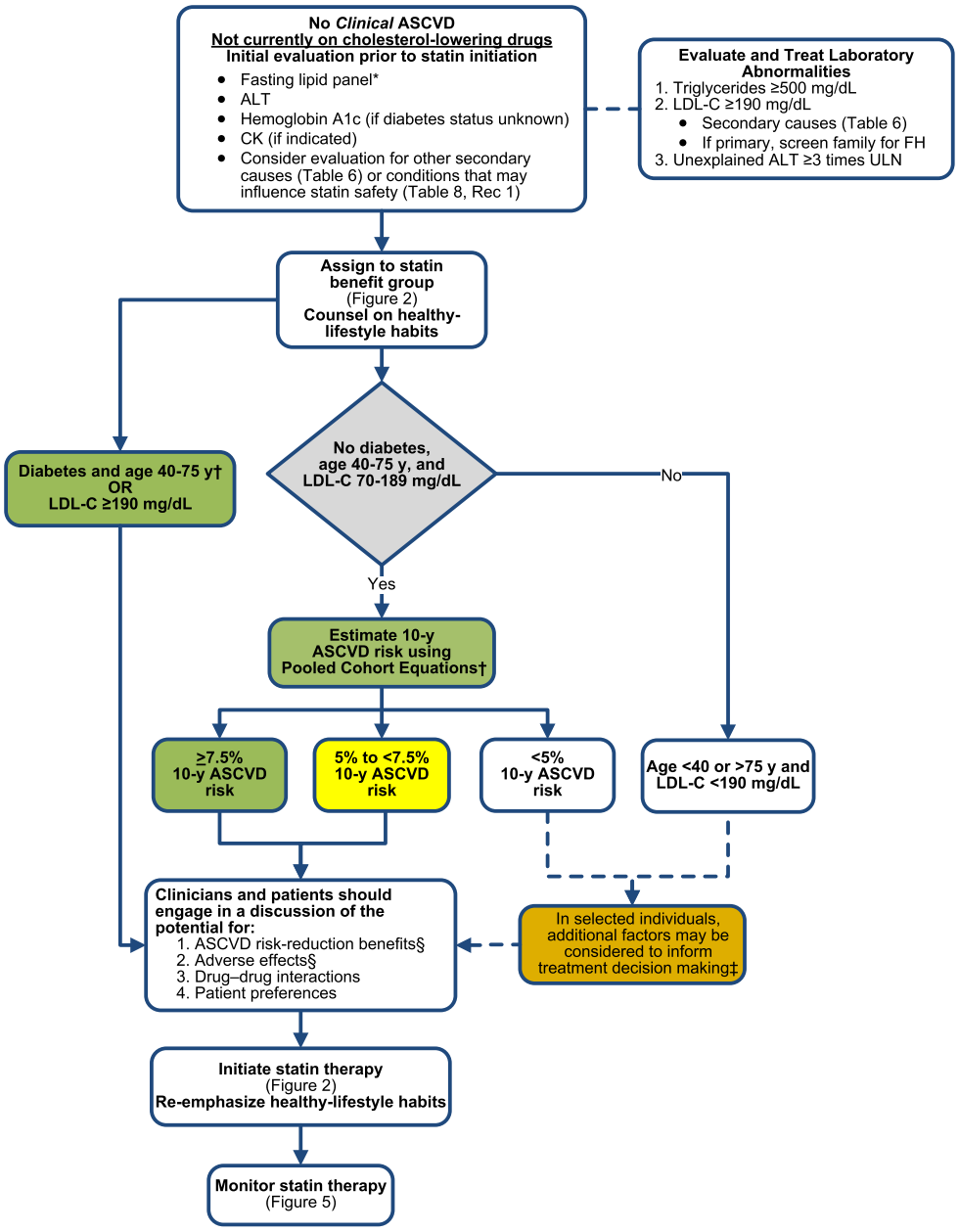

Figure 4. Initiating Statin Therapy in Individuals Without *Clinical* ASCVD

Colors correspond to the Classes of Recommendation in Table 1.

*Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C level ≥220 mg/dL could indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.

†The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes.

A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a Web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx.

‡For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, high-sensitivity C-reactive protein ≥2 mg/L; CAC ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ABI <0.9; or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment could be identified in the future.

§1) Potential ASCVD risk-reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative-risk reduction from the intensity of statin initiated (~30% for moderate-intensity statin or ~45% for high-intensity statin therapy). The net ASCVD risk-reduction benefit is estimated from the number of potential ASCVD events prevented with a statin, compared to the number of potential excess adverse effects. 2) Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In RCTs, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated (see Table 8, Safety Recommendation 8).

ABI indicates ankle-brachial index; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CK, creatine kinase; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RCT, randomized controlled trial; and ULN, upper limit of normal.

of other risk factors to reduce their ASCVD event rates. Therefore, it is reasonable to use high-intensity statin therapy to achieve at least a 50% reduction. It is recognized that maximal statin therapy might not be adequate to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C. In addition to a maximally tolerated dose of statin, nonstatin cholesterol-lowering medications are often needed to lower LDL-C to acceptable levels in these individuals. Because the hypercholesterolemia in these high-risk individuals is often genetically determined, family screening is especially important in this group to identify additional family members who would benefit from assessment and early treatment.

Secondary causes of severe elevations of LDL-C ≥190 mg/dL and triglycerides ≥500 mg/dL often contribute to the magnitude of the hyperlipidemia and should be evaluated and treated appropriately. For guidance, we note that in a lipid specialty clinic, the most frequently encountered secondary conditions were excessive alcohol intake, uncontrolled diabetes, and overt albuminuria (79). Table 6 focuses on secondary causes of hyperlipidemia most likely encountered in clinical practice (80). Management of individuals with fasting triglycerides ≥500 mg/dL has been addressed in an AHA statement (45).

The flow diagram for the initiation and management of statin therapy in individuals with LDL-C ≥190 mg/dL is provided in Figure 4.

4.5. Primary Prevention in Individuals With Diabetes

A high level of evidence supports the use of moderate-intensity statin therapy in persons with diabetes who are 40 to 75 years of age. The only trial of high-intensity statin therapy in primary prevention was performed in a population without diabetes. However, a high level of evidence existed for event reduction with statin therapy in individuals with a ≥7.5% estimated 10-year ASCVD risk (Section 4.6) who did not have diabetes to recommend high-intensity statin therapy preferentially for individuals with diabetes and a ≥7.5% estimated 10-year ASCVD risk (Section 4.7). This consideration for those with diabetes who are 40 to 75 years of age recognizes that these individuals are at substantially increased lifetime risk for ASCVD events and death. Moreover, individuals with diabetes experience greater morbidity and worse survival after the onset of clinical ASCVD. In persons with diabetes who are <40 years of age or >75 years of age, or whose LDL-C is <70 mg/dL, statin therapy should be individualized on the basis of considerations of ASCVD risk-reduction benefits, the potential for adverse effects and drug–drug interactions, and patient preferences (Figure 4).

4.6. Primary Prevention in Individuals Without Diabetes and With LDL-C 70 to 189 mg/dL

In individuals 40 to 75 years of age with LDL-C 70 to 189 mg/dL who do not have clinical ASCVD or diabetes,

Table 7. Rationale for the Expert Panel Approach to Primary-Prevention Guidelines

1. Cholesterol-lowering medications, particularly statins, are efficacious and effective for reducing risk of initial cardiovascular events.
2. Statins are associated with similar *relative risk reductions* for cardiovascular events across the majority of primary-prevention patient groups studied.*
3. The extent of *relative risk reduction* for ASCVD is proportional to the degree of LDL-C lowering observed on statin therapy. Therefore, more intensive statin therapy could reduce risk more than moderate- or lower-intensity statin therapy.
4. According to consistent findings, the *absolute* benefit in ASCVD risk reduction is proportional to the baseline risk of the patient group or individual and to the intensity of statin therapy.
5. Patients or groups at higher baseline *absolute* risk, therefore, will derive greater *absolute* benefit from initiation of statin therapy over a period of 5 to 10 years.
6. The *absolute* risk for adverse outcomes, including a small excess in cases of newly diagnosed diabetes, also appears to be proportional to the intensity of statin therapy. However, the adverse outcome of incident (or earlier diagnosis of) diabetes must be weighed in the context of the potentially fatal or debilitating occurrence of MI or stroke that could be prevented by statin therapy.
7. The Expert Panel emphasizes that the occurrence of a major ASCVD event (MI or stroke) represents a much greater harm to health status than does an increase in blood glucose leading to a diagnosis of diabetes. The *net absolute benefit* of statin therapy can be considered as a comparison of the *absolute risk reduction* for ASCVD with the absolute excess risks, including that for diabetes. Benefit also could be understood as a comparison of the number of statin-treated patients that would result in the prevention of 1 case of major ASCVD (NNT) with the number of statin-treated patients that would result in 1 excess case of diabetes (NNH).
8. Because the absolute benefit in terms of ASCVD risk reduction depends on the baseline *absolute* risk for ASCVD, the *absolute benefit* from initiation of statin therapy is lower and would approach the risk for adverse effects in patients with lower baseline levels of predicted ASCVD risk.
9. Available RCT evidence indicates a clear net absolute benefit of initiation of moderate-to-intensive statin therapy at a baseline estimated 10-year ASCVD risk of ≥7.5%.
10. Available RCT evidence indicates that when baseline ASCVD risk is 5.0% to <7.5%, there is still *net absolute* benefit with moderate-intensity statin therapy. However, the tradeoffs between the ASCVD risk-reduction benefit and adverse effects are less clear. Thus, a clinician-patient discussion is even more important for individuals with this range of ASCVD risk. The net benefit of high-intensity statin therapy may be marginal in such individuals.

Conclusion

On the basis of the above tenets and its review of the evidence, this guideline recommends initiation of moderate or intensive statin therapy for patients who are eligible for primary ASCVD prevention and have a predicted 10-year "hard" ASCVD risk of ≥7.5%. This guideline recommends that initiation of moderate-intensity statin therapy be considered for patients with predicted 10-year "hard" ASCVD risk of 5.0% to <7.5%.

*Available evidence suggests that initiation of statin therapy might not achieve a significant reduction of CVD risk in patients with higher classes of NYHA heart failure or who are receiving maintenance hemodialysis.

ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; NYHA, New York Heart Association; and RCT, randomized controlled trial.

initiation of statin therapy based on estimated 10-year ASCVD risk is recommended, regardless of sex, race, or ethnicity (Section 4.7). Point estimates of statin-associated reductions in the relative risk of ASCVD in primary prevention are similar for both women and men. There also is no evidence that the ASCVD risk-reduction benefit or adverse-effect profiles differ by race.

To better identify those individuals without ASCVD who would most benefit from statin therapy to reduce ASCVD risk, data were used from the 3 exclusively primary-prevention RCTs that included individuals with LDL-C levels <190 mg/dL, almost all of whom had LDL-C levels ≥70 mg/dL (17,18,49). From these trials, an estimate of the expected 10-year ASCVD event rates was derived from the placebo groups. The rates of excess adverse events in the statin treatment groups were obtained from meta-analyses of statin RCTs. A high level of evidence for an ASCVD risk-reduction benefit from initiation of moderate- or high-intensity statin therapy in individuals 40 to 75 years of age with ≥7.5% estimated 10-year ASCVD risk was found (Section 4.7). The reduction in ASCVD risk clearly outweighs the potential for adverse effects (Table 7). Thus, it is recommended that individuals 40 to 75 years of age, who are not already candidates for statin therapy on the basis of the presence of clinical ASCVD, diabetes, or LDL-C ≥190 mg/dL, receive statin therapy if they have a ≥7.5% estimated 10-year risk for ASCVD and LDL-C 70 to 189 mg/dL. Although only 1 exclusively primary-prevention RCT included individuals with LDL-C 70 to <100 mg/dL, the Cholesterol Treatment Trialists 2010 meta-analysis found a relative reduction in ASCVD events of similar magnitude across the spectrum of LDL-C levels ≥70 mg/dL (20). Given that the relative risk reduction is similar across the range of LDL-C 70 to 189 mg/dL, the absolute benefit of statin therapy in primary prevention is determined by the global risk estimate using all the risk factor information and is reflected in the estimated 10-year ASCVD risk.

A conservative estimate of adverse events includes excess cases of new-onset diabetes and rare cases of myopathy and hemorrhagic stroke. The rate of excess diabetes varies by statin intensity. For moderate-intensity statins, approximately 0.1 excess case of diabetes per 100 statin-treated individuals per year has been observed, and for high-intensity statins, approximately 0.3 excess case of diabetes per 100 statin-treated individuals per year has been observed (52,81). The long-term adverse effects of statin-associated cases of diabetes over a 10-year period are unclear and are unlikely to be equivalent to an MI, stroke, or ASCVD death. Myopathy (~0.01 excess case per 100) and hemorrhagic stroke (~0.01 excess case per 100) make minimal contributions to excess risk from statin therapy (13).

Although a similar level of evidence of a reduction in ASCVD events from moderate- and high-intensity statin therapy is present for those with a 5% to <7.5% estimated 10-year ASCVD risk, the potential for adverse effects may outweigh the potential for ASCVD risk-reduction benefit when high-intensity statin therapy is used in this risk group. However, for moderate-intensity statin therapy, the ASCVD risk reduction clearly exceeds the potential for adverse effects.

Before initiating statin therapy for the primary prevention of ASCVD in adults with ≥7.5% or 5% to <7.5% estimated 10-year ASCVD risk, it is reasonable for clinicians and patients to engage in a discussion of the proposed therapy. This discussion should include the potential for ASCVD benefit, the potential for adverse effects and drug–drug interactions, and consideration of patient preferences for treatment.

No primary-prevention RCT data were available for individuals 21 to 39 years of age, and few data were available for individuals >75 years of age. Additionally, in individuals 40 to 75 years of age with <5% estimated 10-year ASCVD risk, the net benefit from statin therapy over a 10-year period may be small. Therefore, in adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group or for whom a risk-based treatment decision is uncertain after quantitative risk assessment, clinician knowledge, experience, and skill ("the art of medicine") and patient preferences all contribute to the decision to initiate statin therapy (82). Before initiation of statin therapy, the clinician-patient discussion should include consideration of the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions. Additional factors may also be considered to inform treatment decision making in selected individuals. Factors that can contribute to assessment of ASCVD risk include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein ≥2 mg/L, coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ankle-brachial index <0.9; or elevated lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

For an individual <40 years of age, the 10-year horizon might not be optimal for predicting lifetime risk of ASCVD (see 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk) (11). Future RCTs will be needed to determine the optimal age at which to initiate statin therapy to reduce ASCVD risk, as well as to determine the optimum duration of statin therapy.

4.7. Risk Assessment in Primary Prevention

To estimate more closely the total burden of ASCVD, this guideline recommends a comprehensive assessment of the estimated 10-year risk for an ASCVD event that includes both CHD and stroke. This is in contrast to the use of an estimated 10-year risk for hard CHD (defined as nonfatal MI and CHD death) (83).

This guideline recommends using the new Pooled Cohort Risk Assessment Equations developed by the Risk Assessment Work Group to estimate the 10-year ASCVD risk (defined as first-occurrence nonfatal and fatal MI and nonfatal and fatal stroke) for the identification of candidates for statin therapy (see http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx for risk calculator). These equations should be used to predict stroke as well as CHD events in non-Hispanic, Caucasian, and African-American women and men 40 to 79 years of age with or without diabetes who have LDL-C levels 70 to 189 mg/dL and are not receiving statin therapy. A more complete discussion of risk assessment is provided in the Full Panel Report Supplement.

This guideline does not require specific risk factor counting for risk assessment or the use of RCT risk factor inclusion criteria to determine statin eligibility. Rather, a global ASCVD risk assessment to guide initiation of statin therapy was chosen for several important reasons (see rationale in Table 7 and further discussion in Section 7.3 of the Full Panel Report Supplement): 1) The Cholesterol Treatment Trialists individual-level meta-analyses were used to evaluate the effect of statins in various important patient subgroups, including risk factor cutpoints used for RCT eligibility. The Expert Panel found that statin therapy reduces ASCVD events regardless of risk factor characteristics in both primary and secondary prevention. Therefore, the rationale for using fixed cutpoints to determine whether statin therapy should be used is refuted by a consideration of the total body of evidence. 2) Use of absolute ASCVD risk facilitates a quantitative assessment of the potential for an ASCVD risk-reduction benefit as compared with the potential for adverse effects. 3) Use of an RCT eligibility criteria–based approach results in failure to identify a substantial proportion of higher-risk individuals who could benefit from statin therapy and over-identification of very-low-risk individuals who might not experience a net benefit from statin therapy over a 10-year period.

4.8. Heart Failure and Hemodialysis

No recommendation was made with regard to the initiation or continuation of statin therapy in 2 specific groups: 1) individuals with New York Heart Association class II–IV heart failure, and 2) individuals undergoing maintenance hemodialysis. In the 4 RCTs reviewed that specifically addressed statin treatment in these groups, there were individuals with and without heart disease (84–87). Although statin therapy did not reduce ASCVD events in 2 RCTs for each condition (84–87), there was insufficient information on which to base recommendations for or against statin treatment. Future research may identify subgroups of patients with these conditions that may benefit from statin therapy. In individuals with these conditions, the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions, along with other cautions and contraindications to statin therapy and choice of statin dose, must also be considered by the treating clinician.

5. Safety: Recommendations

See safety recommendations for statins (Table 8) and nonstatin drugs (Table 9).

RCT data were also used to examine the safety of lipid medications. From the statin RCTs and meta-analyses, patient characteristics and monitoring strategies were identified that should enhance the safe use of high- and moderate-intensity statin therapy. Patient characteristics that may influence statin safety include but are not limited to: multiple or serious comorbidities, including impaired renal or hepatic function; a history of previous statin intolerance or muscle disorders; concomitant use of drugs affecting statin metabolism; a history of hemorrhagic stroke; and age >75 years. Asian ancestry may also influence the initial choice of statin intensity.

This guideline recommends against routine measurement of creatine kinase in individuals receiving statin therapy. This measurement should be reserved for those with muscle symptoms. However, measurement of a baseline creatine kinase may be useful in those at increased risk of adverse muscle events. Such individuals include those with a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the likelihood of myopathy.

Expert recommendations are also provided for managing muscle symptoms while a patient is on statin therapy. These useful management suggestions were derived from other clinical trial data and clinical experience to enhance the safety and tolerability of statin therapy. Consistent with the protocols of the RCTs, patients should be asked at each visit, both before and after initiation of statin therapy, about muscle symptoms such as muscle weakness or fatigue, aching, pain, tenderness, cramps, or stiffness. The recommended approach for management of muscle symptoms is described in Table 8, Recommendation 8.

This guideline recommends that baseline measurement of transaminase (alanine transaminase; ALT) levels should be performed before initiation of statin therapy. This approach was taken in the RCTs reviewed for this report. There is no recommendation to monitor transaminase (ALT) levels because ALT monitoring was performed in the RCTs, and there was no significant difference between placebo groups and statin treatment groups in the rates of ALT elevations. In addition, the U.S. Food and Drug Administration has indicated that if the baseline hepatic transaminases are normal, further hepatic monitoring is not needed. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting

Table 8. Statin Safety Recommendations

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Safety				
1. To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD* risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present. Characteristics predisposing individuals to statin adverse effects include but are not limited to: • Multiple or serious comorbidities, including impaired renal or hepatic function. • History of previous statin intolerance or muscle disorders. • Unexplained ALT elevations ≥3 times ULN. • Patient characteristics or concomitant use of drugs affecting statin metabolism. • Age >75 years. Additional characteristics that could modify the decision to use higher statin intensities might include but are not limited to: • History of hemorrhagic stroke. • Asian ancestry.	A (Strong)	46–55	I	B
2a. CK should not be routinely measured in individuals receiving statin therapy.	A (Strong)	45,49–51,54,55	III: No Benefit	A
2b. Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events because of a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk of myopathy.	E (Expert Opinion)	—	IIa	C (88)
2c. During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.	E (Expert Opinion)	—	IIa	C (88)
3a. Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiation of statin therapy.	B (Moderate)	46,52,53	I†	B
3b. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, or yellowing of the skin or sclera).	E (Expert Opinion)	—	IIa	C (89)
4. Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are <40 mg/dL.	C (Weak)	45	IIb	C
5. It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.	B (Moderate)	6,54	III: Harm	A (67,90)
6. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines (91). Those who develop diabetes during statin therapy should be encouraged to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.	B (Moderate)	44	I‡	B
7. For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals who are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer's prescribing information may be useful before initiation of any cholesterol-lowering drug.	E (Expert Opinion)	—	IIa	C (16,64–70, 89,92–94)

Continued on the next page

hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, or yellowing of the skin or sclera).

Decreasing the statin dose may be considered when 2 consecutive values of LDL-C are <40 mg/dL. This recommendation was based on the approach taken in 2 RCTs. However, no data were identified that suggest an excess of adverse events occurred when LDL-C levels were below this level.

Statins modestly increase the excess risk of type 2 diabetes in individuals with risk factors for diabetes. The potential for an ASCVD risk-reduction benefit outweighs the excess risk of diabetes in all but the lowest-risk individuals (Section 4.5). All individuals receiving statins should be counseled on healthy-lifestyle habits. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines (91). Those who develop diabetes

Table 8. Continued

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
8. It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: • To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiation of statin therapy. • If unexplained *severe* muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK and creatinine and performing urinalysis for myoglobinuria. • If *mild to moderate* muscle symptoms develop during statin therapy: – Discontinue the statin until the symptoms can be evaluated. – Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). – If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. – If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. – Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. – If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above. – If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.	E (Expert Opinion)	—	IIa	B (15,88,96–98)
9. For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy.	E (Expert Opinion)	—	IIb	C (38,89,99,100)

*Based on the presence of clinical ASCVD, diabetes, LDL-C ≥190 mg/dL, or level of estimated 10-year ASCVD risk.
†Individuals with elevated ALT levels (usually >1.5 or 2 times ULN) were excluded from RCT participation. Unexplained ALT ≥3 times ULN is a contraindication to statin therapy as listed in manufacturer's prescribing information.
‡Statin use is associated with a very modest excess risk of new-onset diabetes in RCTs and meta-analyses of RCTs (i.e., ~0.1 excess cases per 100 individuals treated for 1 year with moderate-intensity statin therapy and ~0.3 excess cases per 100 individuals treated for 1 year with high-intensity statin therapy. The increased risk of new-onset diabetes appears to be confined to those with risk factors for diabetes. These individuals are also at higher risk of ASCVD because of these risk factors. Therefore, if a statin-treated individual develops diabetes as detected by current diabetes screening guidelines, he or she should be counseled to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce the risk of ASCVD events.
ACC indicates American College of Cardiology; AHA, American Heart Association; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CK, creatine kinase; COR, Class of Recommendation; NHLBI, National Heart, Lung, and Blood Institute; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; RCTs, randomized controlled trials; ULN, upper limit of normal; and —, not applicable.

during statin therapy should be encouraged to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.

Statins are listed as pregnancy category X and should not be used in women of childbearing potential unless these women are using effective contraception and are not nursing.

For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals who are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer's prescribing information might be useful before initiation of any cholesterol-lowering drug, because RCTs considered defined populations and many patients in everyday practice would not qualify for clinical trials. Thus, clinicians should also consult other sources of safety data, such as pharmacists, drug information centers, and manufacturers' prescribing information on a regular basis for up-to-date guidance about lipid medications and medication interactions.

Statins used in combination with other cholesterol-lowering drug therapies might require more intensive monitoring. The safety of nonstatin agents was reviewed, and that information is included in Table 9 and the Full Panel Report Supplement. Warnings about the use of

Table 9. Nonstatin Safety Recommendations

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Safety of Niacin				
1. Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiation of niacin, and again during up-titration to a maintenance dose and every 6 months thereafter.	B (Moderate)	77	I	B
2. Niacin should not be used if:				
• Hepatic transaminase elevations are higher than 2 to 3 times ULN.	A (Strong)	79	III: Harm	B
• Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout, or unexplained abdominal pain or gastrointestinal symptoms occur.	B (Moderate)	78,79	III: Harm	B
• New-onset atrial fibrillation or weight loss occurs.	C (Weak)	80	III: Harm	B
3. In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiation of niacin therapy.	E (Expert)	—	I	B (9,101–104)
4. To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: • Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. • Take niacin with food or premedicate with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. • If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over 4 to 8 weeks, with the dose of extended-release niacin increasing not more than weekly. • If immediate-release niacin is chosen, start at a dose of 100 mg 3 times daily and up-titrate to 3 g/day, divided into 2 or 3 doses.	E (Expert)	—	IIa	C (9,101–104)
Safety of BAS				
1. BAS should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. (A fasting lipid panel should be obtained before BAS is initiated, 3 months after initiation, and every 6 to 12 months thereafter.)	C (Weak)	60	III: Harm	B
2. It is reasonable to use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in 4 to 6 weeks after initiation. Discontinue the BAS if triglycerides exceed 400 mg/dL.	E (Expert)	—	IIa	C (105)
Safety of Cholesterol-Absorption Inhibitors				
1. It is reasonable to obtain baseline hepatic transaminases before initiation of ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent ALT elevations ≥3 times ULN occur.	C (Weak)	61–64	IIa	B
Safety of Fibrates				
1. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.	B (Moderate)	46	III: Harm	B
2. Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are ≥500 mg/dL are judged to outweigh the potential risk for adverse effects.	E (Expert)	—	IIb	C (14)
3. Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.	B (Moderate)	66,67	I	B
• Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m^2, is present.			III: Harm	B
• If eGFR is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day.*				
• If, during follow-up, the eGFR decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued.				
Safety of Omega-3 Fatty Acids				
1. If EPA and/or DHA are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.	C (Weak)	70	IIa	B

*Consult the manufacturer's prescribing information as there are several forms of fenofibrate available.

ACC indicates American College of Cardiology; AHA, American Heart Association; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrants; COR, Class of Recommendation; DHA, docosahexanoic acid; EPA, eicosapentaenoic acid; eGFR, estimated glomerular filtration rate; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; ULN, upper limit of normal; and —, not applicable.

Table 10. Recommendations for Monitoring, Optimizing, and Addressing Insufficient Response to Statin Therapy

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Monitoring Statin Therapy				
1. Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4–12 weeks after initiation or dose adjustment, and every 3–12 months thereafter. Other safety measurements should be measured as clinically indicated.	A (Strong)	45	I	A
Optimizing Statin Therapy				
1. The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended but not tolerated.	B (Moderate)	25,26,27,45	I*	B
Insufficient Response to Statin Therapy				
1. In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: • Reinforce medication adherence. • Reinforce adherence to intensive lifestyle changes. • Exclude secondary causes of hyperlipidemia.	A (Strong)	45	I	A
2. It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: • High-intensity statin therapy† generally results in an average LDL-C reduction of ≥50% from the untreated baseline. • Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30% to <50% from the untreated baseline. • LDL-C levels and percents reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.	E (Expert Opinion)	—	IIa	B (46–48,78, 106,107)
3. In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Higher-risk individuals include: • Individuals with *clinical* ASCVD‡ <75 years of age. • Individuals with baseline LDL-C ≥190 mg/dL. • Individuals 40–75 years of age with diabetes. Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs.	E (Expert Opinion)	—	IIb	C (9,14,108–110)
4. In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.	E (Expert Opinion)	—	IIa	B (88,101,111–116)

*Several RCTs found that low-intensity and low-moderate–intensity statin therapy reduced ASCVD events. In addition, the Cholesterol Treatment Trialists meta-analyses found that each 39-mg/dL reduction in LDL-C reduces ASCVD risk by 22%. Therefore, the Panel considered that submaximal statin therapy should be used to reduce ASCVD risk in those unable to tolerate moderate- or high-intensity statin therapy.

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C level <100 mg/dL was observed in most individuals receiving high-intensity statin therapy.

‡*Clinical* ASCVD includes acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.

ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; COR, Class of Recommendation; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; RCTs, randomized controlled trials; and —, not applicable.

cholesterol-lowering agents in pregnancy and lactation also apply to nonstatins, and the manufacturer's prescribing information should be consulted.

6. Managing Statin Therapy: Recommendations

See Table 10 for a summary of recommendations for monitoring, optimizing, and addressing insufficient response to statin therapy.

6.1. Monitoring Statin Therapy

A high level of RCT evidence supports the use of an initial fasting lipid panel (total cholesterol, triglycerides, HDL-C, and calculated LDL-C), followed by a second lipid panel 4 to 12 weeks after initiation of statin therapy, to determine a patient's adherence. Thereafter, assessments should be performed every 3 to 12 months as clinically indicated. Adherence to both medication and lifestyle regimens are required for ASCVD risk reduction. After statin therapy has been initiated, some

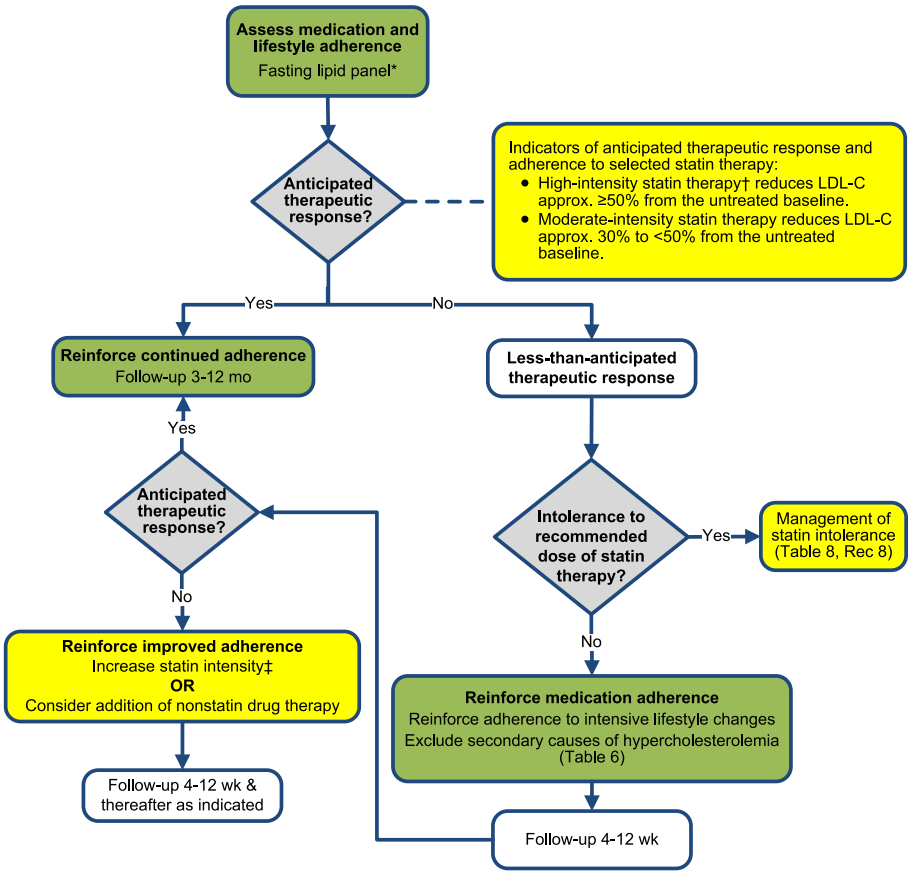

Figure 5. Statin Therapy: Monitoring Therapeutic Response and Adherence

Colors correspond to the Classes of Recommendation in Table 1.
*Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C level ≥220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.
†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.
‡See Section 6.3.1.
HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized clinical trials.

individuals experience unacceptable adverse effects when taking the recommended intensity of statin therapy. Once the severity and association of adverse effects with statin therapy has been established, and once factors potentially contributing to statin intolerance are resolved, the patient should be given lower doses of the same statin or an alternative appropriate statin, until a statin and dose that have no adverse effects have been identified (Table 8, Recommendation 8).

See Figure 5 for a flow diagram on monitoring statin response for the initiation of nonstatin therapy.

6.2. Optimizing Statin Therapy

Although high-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy, lower-intensity statin therapy has also been shown to reduce ASCVD events, although to a lesser degree. Therefore, individuals who merit guideline-recommended statin therapy should be treated with the maximum-appropriate intensity of a statin that does not cause adverse effects.

6.3. Insufficient Response to Statin Therapy

6.3.1. Testing

The evidence is less clear with regard to the most appropriate tests for determining whether an anticipated therapeutic response to statin therapy has occurred on the maximally tolerated dose. RCT evidence to support the use of specific LDL-C or non–HDL-C targets was not identified. The focus is on the intensity of the statin therapy, but as an aid to monitoring response to therapy and adherence, it is reasonable to use the following as indicators of anticipated therapeutic response to statin therapy:

- High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline.
- Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30% to <50% from the untreated baseline.
- LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.

In those already on a statin, in whom the baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.

However, there are many limitations of using LDL-C <100 mg/dL as a fixed target. If a moderate- or low-intensity statin results in an LDL-C level <100 mg/dL in a patient with ASCVD, the evidence suggests that a high-intensity statin, if tolerated, provides a greater reduction in ASCVD events. Conversely, in those with LDL-C levels slightly >100 mg/dL on a high-intensity statin, some options such as niacin might require down-titration of the statin intensity in an effort to improve safety. This would result in a suboptimal intensity of evidence-based statin therapy. Additional limitations to using LDL-C treatment targets are discussed in the Full Panel Report Supplement.

No evidence was found that titration or combination-drug therapy to achieve specific LDL-C or non–HDL-C levels or percent reductions improved ASCVD outcomes. Therefore, this guideline does not recommend their use as performance measures.

The percent LDL-C reduction may not only indicate adherence, but also may reflect biological variability in the response to statin therapy. This acknowledges that some individuals may have less than an average response. Attention to adherence of statin and lifestyle therapy and evaluation and treatment of secondary causes (Table 6) that might elevate LDL-C, may address less-than-anticipated responses to a specific statin dosage. Whether the dose of statin therapy should be increased on the basis of a less-than-anticipated average response should be left to clinical judgment.

6.3.2. Nonstatins Added to Statins or in Statin-Intolerant Individuals

Adherence to lifestyle changes and to statin therapy should be reemphasized before the addition of a nonstatin drug is considered (Figure 5). RCTs evaluating the ASCVD event reductions from nonstatins used as monotherapy were reviewed, as were RCTs evaluating the additional reduction in ASCVD events from nonstatin therapy added to statin therapy. The Expert Panel could find no data supporting the routine use of nonstatin drugs combined with statin therapy to further reduce ASCVD events. In addition, no RCTs that assessed ASCVD outcomes in statin-intolerant patients were found.

Clinicians treating high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant, may consider the addition of a nonstatin cholesterol-lowering therapy. High-risk individuals include those with ASCVD, those with LDL-C ≥190 mg/dL, and those with diabetes 40–75 years of age. In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug–drug interactions, and consider patient preferences.

7. Selected Clinical and Population Subgroups

7.1. Sex and Racial and Ethnic Subgroups

Because the RCT evidence shows that the absolute benefit of statin treatment is proportional to baseline ASCVD risk, treatment decisions for women and racial and ethnic subgroups should be based on the level of ASCVD risk. This conclusion is a departure from previous approaches that focused on LDL-C levels to guide treatment decisions. Statin treatment based on estimated 10-year ASCVD risk avoids the overtreatment of lower-risk groups, such as younger, non-Hispanic white women who, despite moderate elevations in LDL-C, are typically not at significantly increased risk for ASCVD in the next 10 years in the absence of substantial risk factor burden. However, ignoring the increased ASCVD risk in African American women and men might result in the undertreatment of some individuals who are at significantly higher ASCVD risk at the same LDL-C level. Thus, this guideline recommends statin therapy for individuals in whom it is most likely to provide ASCVD risk reduction on the basis of the estimated 10-year risk of ASCVD.

7.2. Individuals >75 Years of Age

Fewer people >75 years of age were enrolled in the statin RCTs reviewed. RCT evidence does support the continuation of statins beyond 75 years of age in persons who are already taking and tolerating these drugs. A larger amount of data supports the use of moderate-intensity statin therapy for secondary prevention in individuals with clinical ASCVD who are >75 years of age. However, the limited information available did not clearly support initiation of high-intensity statin therapy for secondary prevention in individuals >75 years of age.

Few data were available to indicate an ASCVD event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical ASCVD. Therefore, initiation of statins for primary prevention of ASCVD in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care. The Pooled Cohort Equations can also provide information on expected 10-year ASCVD risk for those 76 to 79 years of age that may inform the treatment decision. These factors may influence decisions about cholesterol-lowering drug therapy, especially in the primary-prevention setting. Accordingly, a discussion of the potential ASCVD risk-reduction benefits, risk of adverse effects, drug–drug interactions, and consideration of patient preferences should precede the initiation of statin therapy for primary prevention in older individuals.

8. Limitations

The evidence-based recommendations in this guideline focus on patient groups who are well represented in RCTs and/or are highly likely to have high-risk genetic conditions, so the recommendations are designed to inform rather than replace clinical judgment. However, there are other patient groups for which a robust evidence base is lacking but that may nevertheless include some persons for whom statin treatment should be considered (after taking patient preferences into account) on the basis of the potential for ASCVD benefits to exceed the risk of adverse events and drug–drug interactions. Clinician judgment is especially important for several patient groups for which the RCT evidence is insufficient for guiding clinical recommendations. These patient groups include younger adults (<40 years of age) who have a low estimated 10-year ASCVD risk but a high lifetime ASCVD risk based on single strong factors or multiple risk factors. Other groups include those with serious comorbidities and increased ASCVD risk (e.g., individuals with HIV or rheumatologic or inflammatory diseases, or who have undergone a solid organ transplantation). This guideline encourages clinicians to use clinical judgment in these situations, weighing potential benefits, adverse effects, drug–drug interactions, and consider patient preferences.

Previous guidelines have taken less rigorous approaches to identifying the evidence to support their recommendations. In contrast, to minimize various sources of bias, the present recommendations are based on data available from RCTs and systematic reviews and meta-analyses of RCTs that were graded as fair to good quality by an independent contractor and were reviewed by the Expert Panel, with the assistance of an independent methodologist. To avoid biases, evidence from post-hoc analyses of included RCTs, from poor-quality RCTs, and from observational studies was not considered. This approach resulted in a comprehensive set of evidence-based clinical recommendations for the treatment of blood cholesterol to reduce ASCVD risk.

9. Evidence Gaps and Future Research Needs

After a systematic review of the literature, several research priorities are suggested that address existing evidence gaps and offer the greatest potential to inform and influence clinical practice and reduce ASCVD morbidity and mortality. High-priority research areas are:

1. Outcomes of RCTs to evaluate statins for the primary prevention of ASCVD in adults >75 years of age.
2. Outcomes of RCTs to evaluate alternative treatment strategies for ASCVD risk reduction. These RCTs may compare titration to specific cholesterol or apolipoprotein goals versus fixed-dose statin therapy in high-risk patients.
3. RCTs to determine whether submaximal statin doses, combined with nonstatin therapies, reduce ASCVD risk in statin-intolerant patients.
4. Evaluation of the incidence, pathophysiology, clinical course, and clinical outcomes of new-onset diabetes associated with statin therapy.
5. Outcomes of RCTs of new lipid-modifying agents to determine the incremental ASCVD event-reduction benefits when added to evidence-based statin therapy.

Additional research recommendations are included in the Full Panel Report Supplement.

10. Conclusions

These recommendations arose from careful consideration of an extensive body of higher-quality evidence derived from RCTs and systematic reviews and meta-analyses of RCTs. Rather than LDL-C or non–HDL-C targets, this guideline used the intensity of statin therapy as the goal of treatment. Through a rigorous process, 4 groups of individuals were identified for whom an extensive body of RCT evidence demonstrated a reduction in ASCVD events with a good margin of safety from moderate- or high-intensity statin therapy:

Four Statin Benefit Groups:

1. Individuals with clinical ASCVD
2. Individuals with primary elevations of LDL-C ≥190 mg/dL
3. Individuals 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL without clinical ASCVD
4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age and have LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%. This requires a clinician-patient discussion.

Individuals in the last group can be identified by using the Pooled Cohort Equations for ASCVD risk prediction developed by the Risk Assessment Work Group. Lifestyle counseling should occur at the initial and follow-up visits as the foundation for statin therapy and may improve the overall risk factor profile.

Most importantly, our focus is on those individuals most likely to benefit from evidence-based statin therapy to reduce ASCVD risk. Implementation of these ASCVD risk-reduction guidelines will help to substantially address the large burden of fatal and nonfatal ASCVD in the United States. We realize that these guidelines represent a change from previous guidelines, but clinicians have become accustomed to change when that change is consistent with the current evidence. Continued accumulation of quality trial data will inform future cholesterol treatment guidelines.

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Key Words: ACC/AHA Practice Guideline ■ biomarkers, pharmacological ■ cardiovascular disease ■ cholesterol ■ diabetes mellitus ■ drug therapy ■ hydroxymethylglutaryl-CoA reductase inhibitors/statins ■ hypercholesterolemia ■ lipids ■ patient compliance ■ primary prevention ■ risk assessment ■ risk reduction behavior ■ secondary prevention.

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol in Adults to Reduce Atherosclerotic Cardiovascular Risk

Panel Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
Neil J. Stone *Chair*	Northwestern Memorial Hospital—Bonow Professor of Medicine, Feinberg School of Medicine, Northwestern University	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None
Jennifer G. Robinson *Co-Chair*	University of Iowa—Professor of Epidemiology and Medicine; Prevention Intervention Center—Director	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** • Aegerion • Amarin* • Amgen* • AstraZeneca* • Esperion • Genentech/ Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/ Regeneron *	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** • Amarin* • Amgen* • AstraZeneca* • Genentech/ Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/ Regeneron*	**2013:** None
Alice H. Lichtenstein *Co-Chair*	Tufts University, USDA Human Nutrition Research Center on Aging—Gershoff Professor of Nutrition Science and Policy; Professor of Public Health and Family Medicine	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None
C. Noel Bairey Merz	Cedars-Sinai Medical Center—Women's Guild Endowed Chair in Women's Health Barbara Streisand Women's Heart Center—Director; Preventive Cardiac Center—Professor of Medicine	**2008–2012:** • Abbott Vascular • Bayer • Bristol-Myers Squibb • Gilead • Novartis • Pfizer • Posen	**2008–2012:** None	**2008–2012:** • ATS Medical • Boston Scientific • Eli Lilly • Johnson & Johnson • Medtronic • Teva Pharmaceuticals	**2008–2012:** • RWISE • Ranexa Microvascular • Ranexa Angina	**2008–2012:** None
		2013: • Amgen* • Gilead • Bristol-MyersSquibb (DSMB)	**2013:** None	**2013:** None	**2013:** • RWISE	**2013:** None
Conrad Blum	Columbia University Medical Center, Columbia University College of Physicians and Surgeons—Professor of Medicine	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None	**2008–2012:** None **2013:** None

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Appendix 1. Continued

Panel Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
Robert H. Eckel	University of Colorado, Denver School of Medicine—Professor of Medicine; Professor of Physiology and Biophysics; and Charles A. Boettcher II Chair in Atherosclerosis	**2008–2012:** • Foodminds • Merck • Pfizer • Abbott	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None
		2013: • Amylin • Eli Lilly • Esperion • Foodminds • Johnson & Johnson • Novo Nordisk • Vivus	**2013:** None	**2013:** None	**2013:** • GlaxoSmithKline* • Sanofi-aventis/ Regeneron	**2013:** None
Anne Carol Goldberg	Washington University School of Medicine—Associate Professor of Medicine	**2008–2012:** • Abbott • Roche • ISIS/Genzyme • Sanofi-aventis • Unilever • Merck	**2008–2012:** None	**2008–2012:** None	**2008–2012:** • Abbott* • Aegerion* • Amarin* • Amgen* • Genentech/Roche* • GlaxoSmithKline* • ISIS/Genzyme* • Merck* • Novartis • Reliant* • Sanofi-aventis/Regeneron* • Sanofi-aventis*	**2008–2012:** None
		2013: • Merck	**2013:** None	**2013:** None	**2013:** • Abbott* • Amarin* • Amgen* • Genentech/Roche* • GlaxoSmithKline* • ISIS/Genzyme* • Merck* • Sanofi-aventis/Regeneron*	**2013:** None
David Gordon, *Ex-Officio*	NHLBI—Special Assistant for Clinical Studies, Division of Cardiovascular Diseases	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Daniel Levy, *Ex-Officio*	NHLBI—Director of the Center for Population Studies	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Donald M. Lloyd-Jones	Northwestern University Feinberg School of Medicine—Senior Associate Dean; Chair and Professor of Preventive Medicine; Professor of Medicine (Cardiology)	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Patrick McBride	University of Wisconsin School of Medicine and Public Health—Professor of Medicine and Family Medicine	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None

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Appendix 1. Continued

Panel Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
J. Sanford Schwartz	University of Pennsylvania School of Medicine—Leon Hess Professor of Internal Medicine, Health Management and Economics	**2008–2012:** • Abbott • Allergan • Amgen • Daiichi-Sankyo • Genentech • Johnson & Johnson • Merck • Pfizer • Shire Pharmaceuticals	**2008–2012:** None	**2008–2012:** None	**2008–2012:** • Pfizer	**2008–2012:** None
		2013: • Abbott • Allergan • Amgen • Daiichi-Sankyo • Genentech • Johnson & Johnson • Merck • Pfizer • Shire Pharmaceuticals	**2013:** None	**2013:** None	**2013:** • Pfizer	**2013:** None
Susan T. Shero *Ex-Officio*	NHLBI—Public Health Advisor	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Sidney C. Smith, Jr	University of North Carolina—Professor of Medicine; Center for Cardiovascular Science and Medicine—Director	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Karol Watson	University of California, Los Angeles School of Medicine—Co-Director	**2008–2012:** • Abbott • AstraZeneca • Genzyme • GlaxoSmithKline • Kos • Medtronic • Merck • Novartis • Pfizer	**2008–2012:** None	**2008–2012:** None	**2008–2012:** • Merck	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** • Merck	**2013:** None
Peter W.F. Wilson	Atlanta VA Medical Center and Emory University School of Medicine—Professor of Medicine	**2008–2012:** • Merck • XZK	**2008–2012:** None	**2008–2012:** None	**2008–2012:** • Merck • Liposcience	**2008–2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** • Merck	**2013:** None

This table reflects the relevant healthcare-related relationships of authors with industry and other entities provided by the panels during the document development process (2008–2012). Both compensated and uncompensated relationships are reported. These relationships were reviewed and updated in conjunction with all meetings and conference calls of the Expert Panel during the document development process. Authors with relevant relationships during the document development process recused themselves from voting on recommendations relevant to their relationships. In the spirit of full transparency, the ACC and AHA asked Expert Panel members to provide updates and approve the final version of this table, which includes current relevant relationships (2013). To review the NHLBI and ACC/AHA's current comprehensive policies for managing relationships with industry and other entities, please refer to http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm and http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx. *Per ACC/AHA policy:* A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

*Significant relationship.

ACC indicates American College of Cardiology; AHA, American Heart Association; NHLBI, National Heart, Lung, and Blood Institute; and USDA, U.S. Department of Agriculture.

Appendix 2. Expert Reviewers Relationships With Industry and Other Entities—2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol in Adults to Reduce Atherosclerotic Cardiovascular Risk

Reviewer	Employment	Representation	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
Roger Blumenthal	Johns Hopkins Hospital Ciccarone Preventive Cardiology Center—Professor of Medicine	ACC/AHA	None	None	None	None	None
William Virgil Brown	Emory University School of Medicine	NLA	• Abbott • Amgen • Anthera • Bristol-Myers Squibb • Catabasis • Cerenis • GlaxoSmithKline • Genzyme • LipoScience • Merck • Pfizer • Regeneron	None	None	None	None
Linda Hemphill	Massachusetts General Hospital—Director, LDL Apheresis Program	NLA	• Regeneron	None	None	None	None
Matthew Ito	Oregon Health & Science University, Department of Pharmacy Practice—Professor	NLA	• Aegeron • Kowa	None	None	None	None
Terry Jacobson	Emory University	NLA	• Abbott • Merck	None	None	• Amarin • HealthCore	None
Andrew Kates	Washington University School of Medicine in St. Louis—Cardiovascular Fellowship Program Director	ACC/AHA	None	None	None	None	None
James M. McKenney	Virginia Commonwealth University—Professor Emeritus	NLA	None	None	None	None	None
E. Magnus Ohman	Duke Clinical Research Institute—Professor of Medicine; Program for Advanced Coronary Disease—Director	ACC/AHA Task Force on Practice Guidelines	None	None	None	None	None
Carl E. Orringer	Case Western Reserve University School of Medicine—Associate Professor of Medicine	NLA	None	None	None	None	None
Robert S. Rosenson	Mount Sinai Hospital—Director, Preventive Cardiology; Professor of Medicine, Cardiology	NLA	• Amgen • LipoScience • Novartis • Pfizer • Sanofi-aventis/ Regeneron	None	• LipoScience	None	None
John Rumsfeld	Denver VA Medical Center, University of Colorado—National Director of Cardiology, U.S. Veterans Health Administration	ACC/AHA	None	None	None	None	None
Robert A. Wild	University of Oklahoma, College of Medicine, Department of Obstetrics and Gynecology—Professor	NLA	• Atherotec	None	None	None	None

This table represents the relationships of reviewers with industry and other entities that were self-disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. To review the NHLBI and ACC/AHA's current comprehensive policies for managing relationships with industry and other entities, please refer to http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm and http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx.
ACC indicates American College of Cardiology; AHA, American Heart Association; NLA, National Lipid Association; and VA, Veterans Affairs.

Appendix 3. Abbreviations

ALT = alanine transaminase
ASCVD = atherosclerotic cardiovascular disease
CHD = coronary heart disease
COR = Class of Recommendation
CQ = critical question
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
LOE = Level of Evidence
MI = myocardial infarction
NHLBI = National Heart, Lung, and Blood Institute
RCT = randomized controlled trial
RWI = relationships with industry and other entities

Appendix 4. Evidence Statements

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
1	Data are not available regarding treatment or titration to a specific LDL-C goal in adults with CHD/CVD. The Expert Panel found insufficient evidence to support setting LDL-C goals in CHD/CVD patients.	I	Secondary Prevention	Conclusion after reviewing 19 RCTs in CQ1 Evidence Table: 4D (87), A–Z (117), ACCORD (14), ALLIANCE (118), ASPEN (119), AURORA (84), CARE (73), CORONA (85), GREACE (120), HATS (121), HPS (16), IDEAL (47), LIPID (74), LIPS (122), MIRACL (93), MUSHASHI-AMI (123), PROVE-IT (48), SPARCL (78,107), TNT (46)
2	The Expert Panel did not identify any trials in adults with CHD/CVD reporting mean or median on-treatment non–HDL-C levels in adults with CHD/CVD.		Secondary Prevention	N/A
3	LDL-C goals <130 mg/dL or <100 mg/dL in patients without CHD/CVD. Randomized trial data are not available regarding dose titration to achieve a specific LDL-C goal.	I	Primary Prevention	Conclusion after reviewing 6 RCTs included in CQ2: AFCAPS (17), ASPEN (119), AURORA (84), CARDS (75), JUPITER (49), MEGA (18)
4	There was insufficient evidence in women without CHD/CVD to evaluate the reduction in CVD risk with achieved LDL-C levels <130 mg/dL or <100 mg/dL.	I	Primary Prevention	N/A
5	The Expert Panel did not identify any trials in adults without CHD/CVD reporting on-treatment non–HDL-C levels in adults with CHD/CVD.		Primary Prevention	N/A
6	In adults with CHD/CVD, fixed high-intensity statin treatment (atorvastatin 40–80 mg) that achieved a mean LDL-C 67–79 mg/dL reduced the RR for CHD/CVD events more than fixed lower-dose statin treatment that achieved a mean LDL-C 97–102 mg/dL. In these trials, the mean LDL-C levels achieved differed by 23–30 mg/dL, or 22%–32%, between the 2 groups. Simvastatin 80 mg did not decrease CVD events compared with simvastatin 20–40 mg. See Table 4 for definitions of high, moderate, and low intensity for statins. Higher intensity = atorvastatin 40–80 mg Moderate intensity = atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg	H	Secondary Prevention	Benefit: TNT (46), IDEAL (47), PROVE-IT (48) Lower LDL-C reductions, no benefit: A–Z (117), ACCORD (14) No difference in LDL-C between groups: (SEARCH (124) not included in CQ1)
7	In adults with CHD/CVD who do not have Class II–IV heart failure, fixed high-intensity statin (atorvastatin 80 mg) or statin-niacin treatment that achieved a mean LDL-C 72–79 mg/dL reduced the RR for CHD/CVD events compared with placebo with a mean LDL-C 112–135 mg/dL. In these trials, the mean LDL-C levels were reduced by 45–57 mg/dL or by 45% (HATS [121]) to 53% (SPARCL [107]).	H	Secondary Prevention	SPARCL (107) HATS (121) MIRACL (93) CORONA (85)–no benefit

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
8	In adults with CHD/CVD and diabetes, fixed high-intensity statin treatment (atorvastatin 80 mg) that achieved a mean LDL-C of 57–77 mg/dL reduced the RR for CHD/CVD events more than fixed lower-intensity statin treatment that achieved a mean LDL-C of 81–99 mg/dL. In these trials, the mean LDL-C levels achieved differed by 22–24 mg/dL, or 22%–30%, between the 2 groups.	M to H	Secondary Prevention (diabetes subgroup included)	TNT (46,94), PROVE-IT (48,125) No diabetes subgroup publications found for MIRACL (93) or IDEAL (47)
9	In adults ≥65 years of age with CHD/CVD, fixed high-intensity statin treatment (atorvastatin 80 mg) that achieved a mean LDL-C of 72 mg/dL reduced CHD/CVD events more than fixed lower-intensity statin treatment that achieved a mean LDL-C of 97 mg/dL. In this trial, the mean LDL-C levels achieved differed by 25 mg/dL, or 26%, between the 2 groups. In adults ≥65 years of age with a history of stroke or TIA, higher fixed-dose statin treatment that achieved a mean LDL-C of 72 mg/dL reduced CHD events more than placebo, with a mean LDL-C of 129 mg/dL. In this trial, the mean LDL-C level was reduced by 61 mg/dL, or 46%, from baseline in those ≥65 years of age.	L	Secondary Prevention (age subgroups included)	TNT (46,126), SPARCL (107,127) No publications by age included for: PROVE-IT (48) IDEAL (47) HATS (121)
10	In adults with CHD/CVD and CKD (excluding hemodialysis), fixed high-intensity statin treatment (atorvastatin 80 mg) that achieved a mean LDL-C of 79 mg/dL reduced CHD/CVD events more than fixed lower-dose statin treatment that achieved a mean LDL-C of 99 mg/dL. In this trial, the mean LDL-C levels achieved differed by 20 mg/dL, or 20% between the 2 groups.	L	Secondary Prevention (CKD subgroup included)	TNT (46,128) TNT (46,129) No publications included for CKD: PROVE-IT (48) IDEAL (47)
11	In adults with CHD or acute coronary syndromes, more intensive-dose statin therapy reduced LDL-C to a greater degree (by 20 mg/dL or an additional 20%) than less intensive-dose statin therapy or placebo and produced a greater reduction in CVD events. Each 1-mmol/L (38.7-mg/dL) reduction in LDL-C reduced the RR for CVD events by approximately 28%. See Table 4 for definitions of high-, moderate-, and low-intensity statin therapy. More intensive statin therapy = atorvastatin 80 mg, simvastatin 80 mg. Less intensive statin therapy = atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg.	H	Secondary Prevention	CTT 2010 (20)—data from 5 trials TNT (46) IDEAL (47) PROVE-IT (48) A–Z (117) SEARCH (124) (not included in CQ1)
12	In trials of more intensive statin therapy (atorvastatin 80 mg, simvastatin 80 mg) compared with less intensive statin therapy (atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg), women with CHD or acute coronary syndromes experienced a similar (approximately 25%) magnitude of relative CVD reduction as men (approximately 29%). Women also experienced a similar magnitude of absolute risk reduction as men.	H	Secondary Prevention (women included)	CTT 2010 (20)—5 trials TNT (46) IDEAL (47) PROVE-IT (48) A–Z (117) SEARCH (124) (not included in CQ1)
13	In adults with and without CVD, in trials comparing more intensive to less intensive statin therapy or statin therapy with placebo/control, the relative CVD risk reduction was similar for those <65 years, 65 to ≤75, or >75 years of age. There is less information to estimate the magnitude of benefit in those under age 45 or over age 75 years, because fewer participants in these age groups were enrolled in clinical trials. More intensive statin therapy did not appear to reduce CVD risk, compared with less intensive statin therapy, in those with ASCVD and age >75 years. Statin therapy, compared with control (most RCTs evaluated moderate-intensity statin therapy), had a similar magnitude of RR reduction in those >75 as in those ≤75 years of age with and without ASCVD. Statin therapy vs. control trials = atorvastatin (A) 10–20 mg, fluvastatin (F) 80 mg, lovastatin (L) 40–80 mg, pravastatin (P) 40 mg, rosuvastatin (R) 10–20 mg, simvastatin (S) 40 mg. See Table 4 for the Expert Panel's definitions for high-, moderate-, and low-intensity statin therapy. The Panel uses *moderate intensity* to refer to statin drugs and doses that lower LDL-C by 30% to approximately 50%. This dose refers to atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, rosuvastatin 10 mg, and simvastatin 40 mg.	H	Primary Prevention, Secondary Prevention	CTT 2010 (20)—26 trials Included: More vs. less statin TNT (46) IDEAL (47) PROVE-IT (48) A–Z (117) SEARCH (124) Statin vs. control (statin/dose, percent LDL-C reduction) 4S (47) S20–40, –36% WOSCOPS (72) P40, –22% CARE (130) P40, –29% AFCAPS/TexCAPS (17) L20-40, –24% LIPID (74) P40, –27% GISSI-P (86) P20, –9% LIPS (122) F40 BID, –27% HPS (16) S40, –38% PROSPER (38) P40, –27% ALLHAT-LLT (131) P40, –14% ASCOT-LLA (132) A10, –31% ALERT (133) F40, –20% CARDS (75) A10, –38% ALLIANCE (118)—NA 4D (87)—A20, –27% ASPEN (119) A10, –34% MEGA (18) P10–20, –17% JUPITER (49) R20, –40% GISSI-HF (86) R10, –30% AURORA (84) R10, –38%

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
14	In adults with CHD (including acute coronary syndromes, or a history of MI, stable or unstable angina, coronary revascularization), statin therapy reduced the RR for CVD events by approximately 21% per 1-mmol/L (38.7-mg/dL) LDL-C reduction. This relationship was similar for more intensive compared with less intensive statin therapy and for statin therapy compared with placebo/control.	H	Secondary Prevention	CTT 2010 (20)—26 trials—see above
15	In adults with CVD other than CHD (including stroke, TIA presumed to be of atherosclerotic origin, or peripheral arterial disease or revascularization), statin therapy reduced the RR for CVD events by approximately 19% per 1-mmol/L (38.7-mg/dL) LDL-C reduction. This relationship was similar for more intensive compared with less intensive statin therapy and for statin therapy compared with placebo/control.	H	Secondary Prevention	CTT 2010 (20)—26 trials
16	In adults with diabetes and CHD or other CVD, moderate-dose statin therapy reduced CVD events by approximately 20% per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Secondary Prevention (diabetes subgroup included)	CTT 2008 (134)—14 trials
17	In adults with and without CVD, statin therapy reduced CVD events in both men and women.	H	Primary Prevention, Secondary Prevention	CTT 2010 (20)—26 trials
18	In adults with and without CVD, in trials comparing more* intensive with less intensive statin therapy, or statin therapy with placebo/control, there were no clinically important differences in the CVD risk reduction between the subgroups listed below: • Treated hypertension or all others • Systolic blood pressure <140, ≥140 to <160, and ≥160 mm Hg • Diastolic blood pressure <80, ≥80 to <90, and ≥90 mm Hg • Body mass index <25, ≥25 to <30, and ≥30 kg/m^2 • Current smoking and nonsmokers • GFR <60, 60 to <90, ≥90 mL/min per 1.73 m^2) • Post-MI • Total cholesterol ≤5.2 (201 mg/dL), >5.2 to 6.5, >6.5 (251 mg/dL) mmol/L • Triglycerides ≤1.4 (124 mg/dL), >1.4 to 2.0, >2.0 (177 mg/dL) mmol/L • HDL-C ≤1.0 (39 mg/dL), >1.0 to ≤1.3, >1.3 (50 mg/dL) mmol/L	H	Primary Prevention, Secondary Prevention	CTT 2010 (20)—26 trials
19	In more vs. less statin and statin vs. control trials combined, each 1-mmol/L (38.7-mg/dL) reduction in LDL-C resulted in approximately 22% reductions in CVD risk across baseline LDL-C levels [<2 mmol/L (77 mg/dL), ≥2 to <2.5 mmol/L (97 mg/dL), ≥2.5 to <3.0 mmol/L (116 mg/dL), ≥3.0 to <3.5 mmol/L (135 mg/dL), and ≥3.5 mmol/L, either untreated or on statin therapy]. In the statin vs. placebo/control trials, those with LDL-C <2 mmol/L may have experienced less benefit than those with higher LDL-C level.	M		CTT 2010 (20)—26 trials
20	In adults, statins reduce the RR for CVD, CHD, and fatal CHD similarly in those with or without hypertension. This benefit applies across all levels of baseline systolic and diastolic blood pressure and in those with treated hypertension.	H	Primary Prevention, Secondary Prevention	CTT 2010 (20), Messerli AJC 2008 (135)
21	In adults with and without CVD who received more intensive compared with less intensive statin therapy, or statin therapy compared with placebo/control, the RR for first stroke was reduced by approximately 16% per 1-mmol/L (38.7-mg/dL) LDL-C reduction, primarily because of an approximately 21% reduction in the RR for ischemic stroke.	M to H	Primary Prevention, Secondary Prevention	CTT 2010 (20)—26 trials
22	In adults with and without CHD/CVD who received more intensive compared with less intensive statin therapy, or statin therapy compared with placebo/control: • The RR for major coronary events was reduced by approximately 24% per 1-mmol/L (38.7-mg/dL) LDL-C reduction. • The RR for nonfatal myocardial infarction was reduced by approximately 27% per 1-mmol/L LDL-C reduction. • Total mortality was reduced by approximately 10% per 1-mmol/L (38.7-mg/dL) LDL-C reduction, primarily because of a 16% reduction in the risk for cardiac death. • The risk for CVD mortality was reduced by approximately 14% per 1-mmol/L (38-mg/dL) LDL-C reduction, primarily because of a 16% reduction in the risk for cardiac death.	H	Primary Prevention, Secondary Prevention	CTT 2010 (20)—26 trials

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
23	In adults with CHD or acute coronary syndromes who received more intensive compared with less intensive statin therapy, the RR for coronary revascularization was reduced by approximately 34% per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Secondary Prevention	CTT 2010 (20)—5 trials
24	In adults with and without CVD who received statin therapy compared with placebo/control, the RR for coronary revascularization was reduced by approximately 24% per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Primary Prevention, Secondary Prevention	CTT 2010 (20)—21 trials
25	In adults with and without CVD who received statin therapy, a larger absolute reduction in LDL-C (mmol/L or mg/dL) was associated with a greater reduction in the risk for CVD.	M	Primary Prevention, Secondary Prevention	CTT2010 (20), Kizer 2010 (136)
26	In adults with and without CVD who received statin therapy, there was no variation in the relative reduction of CVD risk among the trials after adjustment for LDL-C reduction. Thus, LDL-C reduction appeared to account for the reduction in CVD risk.	M	Primary Prevention, Secondary Prevention	CTT 2010 (20)
27	Consistent 23%–28% relative reductions in CVD risk per 39-mg/dL (1-mmol/L) reduction in LDL-C were observed after 1 year to beyond 5 years of statin treatment.	H	Secondary Prevention, Primary Prevention	CTT 2008 (134), 2005 (50) CTT 2010 (96)
28	Statins reduce the RR for CVD similarly in primary- and secondary-prevention populations.	H	Primary Prevention; Secondary Prevention	CTT 2010 (20) CTT 2010 Web appendix (50)
29	In adults with diabetes (some of whom had CHD), statin therapy reduced the RR for CVD events by approximately 20% per 1-mmol/L (38.7-mg/dL) LDL-C reduction. This 1-mmol (20%) risk-reduction relationship was similar for more intensive compared with less intensive statin therapy and for statin therapy compared with placebo/control.	H	Secondary Prevention (includes diabetes subgroup) Primary Prevention in Individuals With Diabetes	CTT 2010 (20) CTT 2008 (134)
30	Adults with type 2, type 1, and no diabetes had similar RRRs in CVD per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Primary Prevention in Individuals With Diabetes	CTT 2010 (20)
31	In adults with diabetes without CVD, moderate-dose statin therapy, compared with placebo/control, reduced the RR for CVD events by approximately 27% per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Primary Prevention in Individuals With Diabetes	CTT 2008 (134)—14 trials
32	In adults with diabetes, statin therapy reduced the RR for CVD by a similar magnitude for subgroups of diabetic men and women, <65 and ≥65 years of age; treated hypertension; body mass index <25, >25 to <30, and ≥30; systolic blood pressure <160 and ≥160 mm Hg; diastolic blood pressure <90 and ≥90 mm Hg; current smokers and nonsmokers; estimated GFR <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2; and predicted annual risk for CVD <4.5%, >4.5% to <8.0%, and ≥8.0%. Whereas RRRs are similar across these subgroups, absolute risk reductions may differ for various subgroups.	H	Primary Prevention in Individuals With Diabetes	CTT 2008 (134)—14 trials
33	In adults 40 to 75 years of age with diabetes and ≥1 risk factor, fixed moderate-dose statin therapy that achieved a mean LDL-C of 72 mg/dL reduced the RR for CVD by 37% (in this trial, LDL-C was reduced by 46 mg/dL or 39%).	M	Primary Prevention in Individuals With Diabetes	CARDS (75)
34	In men and postmenopausal women 40 to 73 years of age without CHD/CVD, the majority of whom did not have diabetes and had baseline LDL-C levels <190 mg/dL, fixed low- to moderate-dose statin therapy that achieved a mean LDL-C of 115–127 mg/dL reduced the RR for CVD by 24%–25%, compared with placebo, with mean LDL-C levels of 153–156 mg/dL. (In these trials, LDL-C was reduced by 29–35 mg/dL and 19%–25% from baseline with a low- to moderate-dose statin.)	H	Primary Prevention	AFCAPS (17); MEGA (18)
35	In men ≥50 years and women ≥60 years of age without CHD/CVD with LDL <130 mg/dL and hs-CRP ≥2 mg/L, fixed intensive-dose statin that achieved a mean LDL-C of 53 mg/dL reduced the RR for CVD events by 44% compared with placebo, which had a mean LDL-C 110 mg/dL. In this trial, LDL-C was reduced by 53 mg/dL, or 49%.	M	Primary Prevention	JUPITER (49)
36	In adults without CVD (some of whom had diabetes) who received more intensive or less intensive statin therapy, or statin therapy compared with placebo/control, the RR for CVD events was reduced by approximately 25% per 1-mmol/L LDL-C reduction. This was similar to the CVD RRR observed in those with CHD or CVD.	H	Primary Prevention	CTT 2010 (20)
37	Statin therapy reduces CHD and stroke events in adults ≥40 years of age without CHD/CVD, and with a wide range of baseline LDL-C levels.	H	Primary Prevention	CTT 2010 (20) JUPITER (49) AFCAPS (17) MEGA (18)

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ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
38	Statin therapy, with a range of LDL-C lowering, reduces all-cause mortality, compared with placebo, in primary-prevention clinical trials of adults who were in general ≥40 years of age and had at least 1 risk factor, and with a wide range of baseline LDL-C levels.	M	Primary Prevention	CTT 2010 (20)
39	There is insufficient evidence to determine the benefit of statins in primary prevention on all-cause mortality separately for women and men or with advancing age.	I	Primary Prevention	CTT 2010 (20)
40	In MEGA (18), AFCAPS (17), JUPITER (49), and CARDS (75), the 10-year NNTs to prevent 1 hard CVD event were 82, 56, 30, and 15, respectively. These reflect RRRs of 24%, 26%, 44%, and 37%, respectively, and placebo event rates for major CVD calculated at 10 years of 5.1%, 6.9%, 7.6%, and 18%, respectively.	M	Primary Prevention	CTT 2010 (20) appendix individual trials—projected calculation
41	In adults without CVD (some of whom had diabetes) overall, who received statin therapy compared with placebo/control, the RR for CVD events was reduced by approximately 25% per 1-mmol/L LDL-C reduction. This was similar to the CVD RRR observed in those with CHD or CVD.	H	Primary Prevention, Primary Prevention in Individuals With Diabetes	CTT 2010 (20)
42	Statin therapy, with a range of LDL-C lowering, reduces all-cause mortality by about 10%, compared with placebo, in primary-prevention clinical trials of adults who were ≥40 years of age and in general who had at least 1 risk factor, and with a wide range of baseline LDL-C levels.	M	Primary Prevention, efficacy	Cochrane (15), Ray (137), Brugts (138), Bukkapatnam (139), JUPITER (49) MEGA—women (140)
43	In adults with and without CVD, intensive- and moderate-dose statins do not increase the risk for death from noncardiovascular causes, regardless of baseline LDL-C. Statins do not increase (or decrease) the risk for incident cancer overall or cancer of any type, or the risk for cancer death.	H	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010 (20), Mills 2008 (97), Cochrane (15), Bonovas (141)
44	In adults with or without CVD, statin therapy is associated with an excess risk for incident diabetes. • Statin therapy was associated with 1 excess case of incident diabetes per 1,000 individuals treated for 1 year, compared with placebo/control, with little heterogeneity among 13 trials (including JUPITER [49]). Risk for diabetes was highest in older persons (NNH=1,002 per year). • Statin therapy resulted in 5.4 fewer major CVD events per 1-mmol/L LDL-C reduction per 1,000 individuals treated for 1 year compared with placebo (NNT to benefit, 185 per year). • High-intensity statin therapy was associated with 2 excess cases of incident diabetes per 1,000 individuals treated for 1 year, compared with moderate-intensity statins (NNH=498 per year). High-intensity statin therapy resulted in 6.5 fewer major CVD events per 1,000 individuals treated for 1 year, compared with moderate-intensity statin therapy (NNT=155 per year). Rosuvastatin 20 mg was associated with 3 excess cases of incident diabetes per 1,000 individuals treated for 1 year, compared with placebo (NNH=332 per year). • Rosuvastatin 20 mg resulted in 5.9 fewer major CVD events per 1,000 individuals treated for 1 year, compared with placebo (NNT=169 per year).	M	Primary Prevention, Secondary Prevention, Safety of Statins	Sattar 2010 (81) Preiss (142), PROVE-IT (48), A–Z (117), TNT (46), IDEAL (47), SEARCH (124), JUPITER (49)

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ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
45	In trials of high-intensity compared with moderate-intensity statins (clinical CVD), moderate-intensity statin compared with placebo (diabetes—primary prevention), high-intensity statin compared with placebo (secondary and primary prevention), or statin-niacin versus placebo, participants were: • Seen at visits that occurred at 4–13 weeks after randomization, and every 3–6 months thereafter. • Counseled on diet (IDEAL [47], AFCAPS [17], MEGA [18], PROVE-IT [48], SPARCL [107]) and lifestyle (JUPITER [49]) at baseline and regularly thereafter or when LDL-C increased (JUPITER [49], CARDS [75]). • Assessed for adherence to study medication at every visit. • Assessed for adverse effects by history and laboratory measurements at every visit or every other visit. • Able to reduce the statin dose for adverse events so that atorvastatin 80 mg could be reduced to 40 mg (IDEAL [47], PROVE-IT [48]) or pravastatin 40 mg could be reduced to 20 mg (PROVE-IT [48]) or simvastatin reduced by 10 mg/d (HATS [121]). • Able to reduce the statin dose if LDL-C decreased to $<$39 mg/dL (1.0 mmol/L) (per investigator discretion in IDEAL [47]) or reduce the statin dose if total cholesterol was $<$100 mg/dL on 2 successive visits (AFCAPS [17]) or reduce by 10 mg simvastatin per day if LDL-C was $<$40 mg/d (HATS [121]), although they continued on study drug no matter how low the cholesterol in CARDS (75). • Allowed to have their statin doses uptitrated or switched to more potent statin to further reduce • LDL-C (IDEAL [47], CARDS [75], AFCAPS [17], MEGA [18], PROVE-IT [48]—pravastatin to 80 mg) if LDL-C exceeded 125 mg/dL. • Given counseling on diet and/or glycemic control when LDL-C or triglyceride levels increased (CARDS [75]). • Had study medication discontinued for CK $\geq$10 $\times$ ULN with muscle aches or weakness, or persistent ALT $\geq$3 $\times$ ULN on 2 consecutive tests (JUPITER [49], CARDS [75]); the dose of atorvastatin or pravastatin could be halved for abnormal LFTs, CK elevations, or myalgias (PROVE-IT [48]).	H	Statin Adherence	Reflects review of TNT (46), IDEAL (47), PROVE-IT (48), CARDS (75), JUPITER (49), SPARCL (107), MEGA (18), AFCAPS (17) baseline and main papers; these were statin trials that demonstrated significant CVD risk reduction (and were the basis of recommendations arising from CQ1 and CQ2) HATS (121)
46	Most RCTs of moderate-intensity statin therapy and all RCTs of high-intensity statin therapy excluded subjects with serious comorbidities and other conditions or concomitant drug therapy predisposing to adverse events from statin therapy (see Table 9).	H	Primary Prevention, Secondary Prevention, Safety of Statins, Safety of Nonstatins	RCTs included in CQ1, 2, and 3: A–Z (117), ACCORD (14), AIM-HIGH (9), ASPEN (119), CARE (130), CDP (101), FIELD (115), GREACE (120), HATS (121), HHS (111), HPS (16), IDEAL (47), JUPITER (49), LIPID (74), LIPS (122), LRC (113), MIRACL (93), MUSHASHI-AMI (123), PROVE-IT (48), SEAS (108), SHARP (109), SPARCL (107), TNT (46)
47	In adults with and without CVD who received more intensive compared with less intensive statin therapy, or statin therapy compared with placebo/control, overall the RR for first hemorrhagic stroke was not increased. Hemorrhagic stroke comprised 11% of total strokes in the more intensive/statin group, compared with 8% in the less intensive/control groups.	M	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010 (20)
48	In adults with and without CVD, statin-treated individuals in clinical trials are not more likely to discontinue treatment than placebo-treated individuals.	H	Primary Prevention, Secondary Prevention, Safety of Statins	Cochrane—14 trials (15), CTT 2010 (20)
49	In adults with and without CVD in clinical trials, low- to moderate-dose statins do not increase the risk for myalgias or muscle pain.	H	Primary Prevention, Secondary Prevention, Safety of Statins	Cochrane—14 trials (15), CTT 2010 (20)
50	In adults selected for participation in clinical trials of statin therapy, rhabdomyolysis occurred rarely ($<$0.06% over a mean 4.8- to 5.1-year treatment period).	H	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010 (20)
51	In adults with CHD, the rate of creatine kinase elevation $\geq$3 times ULN occurs infrequently and at a similar rate in those treated with intensive- or moderate-dose statin therapy.	H	Primary Prevention, Secondary Prevention, Safety of Statins	Dale (98), CTT 2010 (20)
52	In adults with CHD, although uncommon ($<$1.5% over 5 years), intensive statin therapy increases the risk for elevated hepatic transaminase (ALT and/or AST) levels $\geq$2–3 times ULN more than moderate-dose statin therapy. No cases of hepatic failure were reported.	H	Primary Prevention, Safety of Statins	Dale (98), Cochrane (15), CTT 2010 (20), TNT (46), IDEAL (47), PROVE-IT (48), JUPITER (49)
53	Low- to moderate-dose statin therapy has similar rates of elevated hepatic transaminase levels as placebo/no statin treatment. In general, clinical trials tend to underestimate those likely to have side effects, often related to selection procedures.	H	Primary Prevention, Safety of Statins	CTT 2010 (20)

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ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
54	With the exception of simvastatin 80 mg, intensive- and moderate-dose statins did not increase the risk for rhabdomyolysis.	L	Safety of Statins	CTT 2010 (20), Cochrane (15), Mills (97)
55	In adults with CHD, CK elevation ≥3 times ULN occurs infrequently and at a similar rate in those treated with intensive- or moderate-dose statin therapy (0.02% [moderate-dose statin] to 0.1% [higher-dose statin]) over a 1- to 5-year treatment period (RR 2.63, 95% CI 0.88–7.85).	H	Secondary Prevention, Safety	Dale 2007 (98)
56	The Expert Panel did not find evidence that statins had an adverse effect on cognitive changes or risk of dementia.	I	Safety of Statins	Reviewed RCTs in CQ1, CQ2; assessment of cognitive function only reported in HPS (16)

57	In men with CHD who are 30 to 64 years of age, immediate-release niacin (with an approximately 2-g dose):
	• Decreased total cholesterol by 10% and triglycerides by 27%.
	• Markedly increased the risk for adverse skin events (including flushing, pruritus, acanthosis nigricans, and other types of skin rash).
	• Increased the risk for other adverse events:
	  • Atrial fibrillation
	  • Gastrointestinal events (including nausea, stomach pain, decreased appetite, and unexplained weight loss)
	  • Gout
	  • Elevated levels of uric acid, serum glutamic oxaloacetic transaminase, alkaline phosphatase, and glucose
	• Lipids, LFTs, uric acid, and glucose were monitored during up-titration and every 4–12 months thereafter.
		L	Secondary Prevention, Safety, Monotherapy, Safety, Efficacy	CDP (101,143)

58	In a trial in 67 adults with CHD and low HDL-C, slow-release niacin (at a mean 2.4-g dose) plus low-dose simvastatin resulted in the following: • Low levels of LDL-C and raised levels of HDL-C. • Although not powered to detect a reduction in CVD events, the rate of major clinical events was 90% lower than that in the placebo group. • Slow-release niacin did not cause flushing in this trial. • The simvastatin-niacin group had increased ALT, CK, uric acid, and homocysteine. • Antioxidant vitamins diminished the beneficial effect of niacin on HDL-C. • Lipids, LFTs, uric acid, and glucose were monitored during up-titration and every 2–4 months thereafter.	L	Secondary Prevention, Combination Treatment	HATS Investigators (121)
59	In adults 45 years of age and older with established CVD and low HDL-C (<40 mg/dL in men or <50 mg/dL in women), elevated triglycerides (150–400 mg/dL), and LDL-C <180 mg/dL off statin, in whom the dose of simvastatin was adjusted, or ezetimibe was added, to maintain LDL-C in a range of 40–80 mg/dL, extended-release niacin 1,500–2,000 mg/day plus simvastatin (9.5% also on ezetimibe 10 mg) compared with placebo (with 50 mg immediate-release niacin) plus simvastatin (21.5% also on ezetimibe 10 mg: • Improved the lipid profile without a further decrease in CVD events. Specifically, it lowered LDL-C levels an additional 6%, increased HDL-C by an additional 14%, reduced triglycerides by an additional 23%, lowered apolipoprotein B by an additional 10%, and reduced lipoprotein(a) by an additional 19%. • There were similar rates of CVD events in subgroups by age, sex, or diabetes, metabolic syndrome, or previous myocardial infarction status, as well as similar rates of adverse events, including liver function abnormalities, muscle symptoms, and rhabdomyolysis. • Lipids, LFTs, uric acid, and glucose were monitored during up-titration and every 3–12 months thereafter.	M	Secondary Prevention, Combination Treatment	AIM-HIGH Investigators (9)
60	In men 35–59 years of age without CHD, hypertension, diabetes, or obesity and with LDL-C ≥175 mg/dL and triglycerides <300 mg/dL, cholestyramine: • Reduced LDL-C by 13%, with minimal changes in triglycerides or HDL-C levels. • Reduced the RR for CHD events by 19%. • Increased the risk for adverse gastrointestinal effects, including constipation, heartburn, abdominal pain, belching, bloating, gas, nausea. • Adherence was only modest.	L	Primary Prevention, Safety, Efficacy	LRC (113)
61	Insufficient data to evaluate the efficacy and safety of ezetimibe monotherapy.	I	Efficacy, Safety, Nonstatin	

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
62	Insufficient data to evaluate the additional efficacy and safety of ezetimibe in combination with a statin compared with a statin alone.	I	Safety, Efficacy, Combination Treatment	
63	In adults 45–85 years of age with mild to moderate aortic stenosis and without CVD or diabetes, simvastatin 40 mg coadministered with ezetimibe 10 mg, compared with placebo: • Decreased LDL-C by an average of 50%. • Reduced the RR for CVD events by 22% over 4.35 years of treatment. • Increased the risk for elevated hepatic transaminases.	L	Safety, Efficacy, Combination Treatment	SEAS (108)
64	In adults ≥40 years of age with CKD, of whom 33% were receiving dialysis (peritoneal or hemodialysis), ezetimibe 10 mg coadministered with simvastatin 20 mg, compared with placebo: • Lowered LDL-C by 37 mg/dL (33%) in those who were not receiving dialysis and by 23% in those who were receiving dialysis. • Reduced the risk for CVD events by 17% overall and 21% in those without CVD. • Reduced the risk for CVD events by 22% in those who were not receiving dialysis. • Did not reduce CVD events in those with CVD or in those receiving hemodialysis. • Modestly increased the risk for muscle symptoms requiring discontinuation of treatment (1.1% vs. 0.6% with p=0.02). • Did not increase the risk for elevated hepatic transaminases, cancer, hemorrhagic stroke, or noncardiovascular mortality.	L	Safety, Efficacy, Combination Treatment, CKD	SHARP (109)
65	Ezetimibe coadministered with simvastatin does not appear to increase the risk for cancer compared with placebo.	L	Safety, Combination Treatment	SHARP (109)
66	In adults 50–75 years of age with diabetes—with total cholesterol <250 mg/dL, and total cholesterol/HDL ratio ≥4.0 or triglycerides <450 mg/dL—fenofibrate, compared with placebo: • Modestly reduced LDL-C, minimally increased HDL-C, and substantially reduced triglycerides. • In those without clinical CVD, reduced the risk for CHD/CVD events. • In those with clinical CVD, did not reduce the risk for CHD/CVD events. • Was no different than placebo for myositis or rhabdomyolysis, CK or ALT elevations, renal disease requiring hemodialysis, or cancer. • Was associated with higher rates of pancreatitis and pulmonary embolism, and increased creatinine levels on average by 0.113–0.136 mg/dL (10–12 mmol/L).	L	Safety, Efficacy, Nonstatin Treatment	FIELD (115)
67	In adults 40–79 years of age with diabetes, CVD, and/or CVD risk factors, with LDL-C 60–180 mg/dL, HDL-C <55 mg/dL in women and black individuals, HDL-C <50 mg/dL for all others, and triglycerides <750 mg/dL on no medication or <400 mg/dL on medication: • Fenofibrate added to simvastatin did not additionally reduce LDL-C, minimally increased HDL-C (1 mg/dL or 2%), and moderately reduced triglycerides (23 mg/dL or 14%), compared with simvastatin therapy, which had on-treatment mean LDL-C of 80 mg/dL, HDL-C of 40.5 mg/dL, and triglycerides of 170 mg/dL. • In the trial overall, and in those without and with clinical CVD, fenofibrate-simvastatin did not reduce the risk for CVD events compared with simvastatin alone. • Those with triglycerides ≥204 mg/dL and HDL-C ≤40 mg/dL may have experienced a reduction in CVD events from fenofibrate-simvastatin, compared with simvastatin alone. • Fenofibrate-simvastatin had similar rates as simvastatin alone for myopathy, myositis, or rhabdomyolysis; CK or ALT elevations, renal disease requiring hemodialysis; cancer death; or pulmonary embolism/thrombosis. • Fenofibrate-simvastatin was more likely to increase ALT >5 times ULN and to increase creatinine level. • CVD event rates were higher in women with well-controlled diabetes who received fenofibrate-simvastatin compared with simvastatin alone.	M	Safety, Efficacy, Nonstatin Treatment	ACCORD (14)
68	In men 40–55 years of age without CHD or CHF and non–HDL-C ≥200 mg/dL, gemfibrozil: • Reduced LDL-C by 10% and triglycerides by 43%, and increased HDL-C by 10%. • Reduced the RR for CHD by 37%, compared with placebo. • Increased skin cancer, increased gastrointestinal surgery, and increased severe upper gastrointestinal symptoms, especially in first year. There was no difference in diarrhea, constipation, nausea, or vomiting. Total mortality was not reported.	M	Safety, Efficacy, Nonstatin Treatment	Helsinki Heart Study (111)

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
69	In men with CHD who were <74 years of age with HDL-C ≤40 mg/dL and LDL-C ≤140 mg/dL, and triglycerides ≤300 mg/dL, gemfibrozil, compared with placebo: • Did not reduce LDL-C, but did reduce triglycerides by 31% and increase HDL-C by 6%. • Reduced the RR for CVD by 24%.	M	Efficacy, Nonstatin Treatment	VA-HIT (114)
70	In Japanese men who were 40–75 years of age and postmenopausal women ≤75 years of age with and without CHD and LDL-C ≥170 mg/dL, EPA 1,800 mg added to statin therapy: • Did not reduce LDL-C and modestly reduced triglycerides (5%), compared with statin therapy alone. • Reduced the risk for CHD events (including revascularization and unstable angina) by 19%, compared with statin therapy alone. • Caused a similar magnitude of risk reduction in primary- and secondary-prevention populations, but the study was insufficiently powered to evaluate these populations separately. • Increased the risk for gastrointestinal disturbance, skin abnormalities, hemorrhage, and abnormal serum glutamic oxaloacetic transaminase.	M	Efficacy, Safety, Combination Treatment	JELIS (110)
71	In individuals with NYHA Classes II–IV systolic or ischemic heart failure, initiation of a statin did not change the absolute or RR for CVD compared with placebo.	M	Efficacy, Selected Population Subgroups	CORONA (85) from CQ1
72	In individuals receiving maintenance hemodialysis, initiation of a statin did not change the relative or absolute risk for CVD compared with placebo.	M	Efficacy, Selected Population Subgroups	4D (87) and AURORA (84) CQ1 & CQ2, SHARP (109)—HD subgroup
73	In men and women of mean age 58 to 68 years with aortic stenosis, treatment with statin or statin plus ezetimibe for a mean of 2.1–4.4 years resulted in a reduction in LDL-C of 50%–55% (67–73 mg/dL) from a baseline LDL-C of 123–140 mg/dL and did not alter the progression of aortic stenosis as assessed by change in valve area, peak aortic valve jet velocity, peak or mean aortic valve gradient, or need for aortic valve surgery.	H	Aortic Stenosis, Combination Treatment	Parolari (144)
74	Women who were pregnant or nursing were excluded from statin, fenofibrate, niacin-statin, and ezetimibe-statin RCTs. Only men were enrolled in RCTs of niacin, BAS, and gemfibrozil.	H	Primary Prevention, Secondary Prevention	All RCTs CQ1, CQ2, and CQ3
75	Only individuals with primary hypercholesterolemia were included in RCTs.	H	Primary Prevention, Secondary Prevention	AFCAPS (17) JUPITER (49) JELIS (110) HATS (121) FIELD (115) ACCORD (14) MEGA (18)
76	In the 3 exclusively primary-prevention RCTs, low-, moderate-, and high-intensity statin therapy reduced the risk for ASCVD when LDL-C levels were approximately 70–130 mg/dL, 130–190 mg/dL, and 160–200 mg/dL.	H	Primary Prevention	JUPITER (49) MEGA (18) AFCAPS (17)
77	Lipids, liver function, uric acid, and glucose tests were obtained at baseline, during up-titration, and every 2–12 months thereafter.	H	Secondary Prevention	CDP (101) (fair) 4–12 months; HATS (121) (good) 2–4 months; AIM-HIGH (9) (good) 3–12 months
78	Immediate- and extended-release niacin increase cutaneous adverse effects.	M	Secondary Prevention	CDP (101), AIM-HIGH (9) (not HATS [121]—Slo-Niacin)
79	When used as monotherapy or with a statin, niacin increases: • Hepatic function tests. • Hyperglycemia. • Gastrointestinal adverse effects. • Gout or increased uric acid.	H M M M	Secondary Prevention, Safety	(CDP [101], HATS [121], AIM-HIGH [9]) (CDP [101], AIM-HIGH [9]—niacin dose reduced or discontinued) (CDP [101], AIM-HIGH [9]—niacin dose reduced or discontinued) Gout (CDP [101]) Increased uric acid (HATS [121])
80	Niacin increases the incidence of atrial fibrillation and weight loss.	L	Secondary Prevention, Safety	CDP (101) (atrial fibrillation not reported in AIM-HIGH [9] or HATS [121])

ALT indicates alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrant; BID, twice daily; CHD, coronary heart disease; CHF, congestive heart failure; CK, creatine kinase; CKD, chronic kidney disease; CVD, cardiovascular disease; EPA, eicosapentaenoic acid; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LFT, liver function test; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; NYHA, New York Heart Association; RCT, randomized controlled trial; RR, relative risk; RRR, relative risk reduction; TIA, transient ischemic attack; and ULN, upper limit of normal.

Appendix 5. Expanded Discussion of What's New in the Guideline

Focus on ASCVD Risk Reduction: 4 Statin Benefit Groups

- The 2013 guideline focuses on **treatment of blood cholesterol to reduce ASCVD risk.** Each Expert Panel was limited in the number of CQs it could choose. When the CQs from the Risk Assessment and Lifestyle Work Groups were combined with the 3 Cholesterol Panel CQs, there were 8 CQs in total that were systematically reviewed. All 3 CQs of the Cholesterol Panel evaluated evidence from RCTs with ASCVD outcomes. CQ1 and CQ2 evaluated the evidence for LDL-C and non–HDL-C goals in secondary and primary prevention. CQ3 was a comprehensive evaluation of the reduction in ASCVD events and safety for each of the cholesterol-lowering drugs available in the United States.
- The systematic review of evidence from the highest-quality RCTs with ASCVD outcomes identified strong evidence to indicate who should get which therapy at what intensity.
- The statin RCTs provided the most extensive evidence for the greatest magnitude of ASCVD event reduction, with the best margin of safety.
- ***Four statin benefit groups*** were identified, in which the potential for an ASCVD risk-reduction benefit clearly exceeds the potential for adverse effects in:
  1. Individuals with clinical ASCVD
  2. Individuals with primary elevations of LDL-C ≥190 mg/dL
  3. Individuals 40–75 years of age with diabetes but without clinical ASCVD and LDL-C 70–189 mg/dL
  4. Individuals 40–75 years of age without diabetes or clinical ASCVD with LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher. This requires a clinician-patient discussion.
- Because few trials have been performed with nonstatin cholesterol-lowering drugs in the statin era, and those that have been performed were unable to demonstrate significant additional ASCVD event reductions in the RCT populations studied, there was less evidence to support the use of nonstatin drugs for ASCVD prevention.
- It is difficult to determine how observational data could override the conclusions from the extensive body of evidence from the statin RCTs and the paucity of evidence from nonstatin RCTs. Inherent biases of observational data are well understood and include biases in the decisions on whom to treat and who is adherent to therapy, as well as multiple measurement biases, including verification of statin use, type and dose of statin used, consistency of use over time, and outcome ascertainment. All of these problems are addressed in intent-to-treat analyses of RCTs, which is why the FDA requires well-designed RCTs to determine drug efficacy for ASCVD event reduction and common adverse effects.
- Other approaches to treatment of blood cholesterol have been advocated, including:
  - **A. Treat to target**—This strategy has been the most widely used in the past 15 years, but there are 3 problems with this approach. First, current clinical trial data do not indicate what the target should be. Second, we do not know the magnitude of additional ASCVD risk reduction that would be achieved with one target lower than another. Third, this strategy does not take into account potential adverse effects from statin monotherapy or from multidrug therapy that might be needed to achieve a specific goal. Thus, in the absence of these data, this approach is less useful than it appears (Section 3). It is possible that future clinical trials may provide information warranting reconsideration of this strategy.
  - **B. Lowest is best**—This approach was not taken because it does not consider the potential adverse effects of multidrug therapy with an unknown magnitude of ASCVD event reduction. Ongoing RCTs of new LDL-C–lowering drugs in the setting of maximal statin therapy may address this question.
  - **C. Treat level of ASCVD risk**—A modified version of this approach was taken, which considers both the ASCVD risk-reduction benefits and the adverse effects of statin treatment on the basis of an extensive body of RCT evidence to determine the 4 statin benefit groups. By focusing treatment on the 4 statin benefit groups, the approach is practical and simpler to implement than the past strategies. There are also important exceptions for routine initiation of statin treatment for individuals requiring hemodialysis or with NYHA class II to IV heart failure.
  - **D. Lifetime risk**—Treatment strategies based on lifetime ASCVD risk are problematic because of the lack of data on the long-term follow-up of RCTs >15 years, the safety and ASCVD event reduction when statins are used for periods >10 years, and treatment of individuals <40 years of age.

A New Perspective on LDL-C and/or Non–HDL-C Goals

- The difficulty of giving up the treat-to-goal paradigm was deliberated extensively over a 3-year period. Many clinicians use targets such as LDL-C <70 mg/dL and LDL-C <100 mg/dL for secondary and primary ASCVD prevention (non–HDL-C targets are 30 mg/dL higher). However, the RCT evidence clearly shows that ASCVD events are reduced by using the maximum-tolerated statin intensity in those groups shown to benefit. After a comprehensive review, no RCTs were identified that titrated drug therapy to specific LDL-C or non–HDL-C goals to improve ASCVD outcomes. However, one RCT was identified that showed no additional ASCVD event reduction from the addition of nonstatin therapy to further treat non–HDL-C levels once an LDL-C goal was reached. In AIM-HIGH (9), the additional reduction in non–HDL-C levels [as well as additional reductions in Apo B, Lp(a), and triglycerides in addition to HDL-C increases] with niacin therapy ***DID NOT*** further reduce ASCVD risk in individuals treated to LDL-C levels of 40–80 mg/dL.
- Use of LDL-C targets may result in under treatment with evidence-based statin therapy or overtreatment with nonstatin drugs that have not been shown to reduce ASCVD events in RCTs (even though the drug may additionally lower LDL-C and/or non–HDL-C). Implications of treating to an LDL-C goal may mean that a suboptimal intensity of statin is used because the goal has been achieved, or that adding a nonstatin therapy to achieve a specific target results in down-titration of the evidence-based intensity of statin for safety reasons. However, when RCT evidence is available that a nonstatin therapy further reduces ASCVD events when added to statin therapy, the nonstatin therapy may be considered.
- Some examples comparing a strategy based on the 4 statin benefit groups to a strategy using LDL-C/non–HDL-C targets:
  - **A. Secondary prevention**—Evidence supports high-intensity statin therapy for this group to maximally lower LDL-C. It does not support the use of an LDL-C target. For example, if a secondary-prevention patient achieves an LDL-C of 78 mg/dL on a dose of 80 mg of atorvastatin, he/she is receiving evidence-based therapy. *As of yet, there are no data to show that adding nonstatin drug(s) to high-intensity statin therapy will provide incremental ASCVD risk-reduction benefit with an acceptable margin of safety.* Indeed, AIM-HIGH (9) demonstrated the futility of adding niacin in individuals with low HDL-C and high triglycerides, and ACCORD (14) demonstrated the futility of adding fenofibrate in persons with diabetes. Although an ACCORD subgroup analysis of those with high triglycerides and low HDL-C levels suggested that fenofibrate may reduce ASCVD events in patients with diabetes, this is hypothesis generating and needs further testing in comparison to the evidence-based use of a high-intensity statin. In addition, not having a goal of <70 mg/dL for LDL-C means that the patient who is adhering to optimal lifestyle management and receiving a high-intensity statin avoids additional, non–evidence-based therapy just because his/her LDL-C is higher than an arbitrary cutpoint. Indeed, the LDL-C goal approach can make this patient unnecessarily feel like a failure.

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Appendix 5. Continued

B. **Familial hypercholesterolemia with LDL-C ≥190 mg/dL**—In many cases, individuals with familial hypercholesterolemia are unable to achieve an LDL-C goal <100 mg/dL. For example, an individual with familial hypercholesterolemia may achieve an LDL-C of only 120 mg/dL despite use of 3 cholesterol-lowering drugs. Although this patient may have fallen short of the 100-mg/dL goal, he/she has decreased his/her LDL-C by >50% (starting from an untreated LDL-C level of ~325–400 mg/dL). These patients are not treatment failures, as observational data has shown significant reductions in ASCVD events without achieving specific LDL-C targets. This is an area where observational data supports the recommended approach.

C. **Type 2 diabetes**—For those 40–75 years of age with risk factors, the potential benefits of LDL-C lowering with a high-intensity statin are substantial. Because those with diabetes often have lower LDL-C levels than those without diabetes, "goal"-directed therapy often encourages use of a lower statin dose than is supported by the RCTs, and nonstatin drugs may be added to address low HDL-C or high triglycerides, for which RCT evidence of an ASCVD event reduction is lacking. Giving a maximally tolerated statin intensity should receive primary emphasis because it most accurately reflects the data that statins reduce the relative risk of ASCVD events similarly in individuals with and without diabetes, and in primary and secondary prevention in those with diabetes, along with evidence that high-intensity statins reduce ASCVD events more than moderate-intensity statins.

D. **Estimated 10-year ASCVD risk ≥7.5%**—Data have shown that statins used for primary prevention have substantial ASCVD risk-reduction benefits across the range of LDL-C levels of 70–189 mg/dL. Moreover, the Cochrane meta-analysis (15), as well as a meta-analysis by the Cholesterol Treatment Trialists (13), confirms that primary prevention with statins reduces total mortality as well as nonfatal ASCVD events.

- RCTs are used to identify those who are unlikely to benefit from initiation of statin therapy despite being at high ASCVD risk, such as those with higher NYHA classes of heart failure or those on hemodialysis.

Global Risk Assessment for Primary Prevention

- Use of the new Pooled Cohort Equations is recommended to estimate 10-year ASCVD risk in both white and black men and women who do not have clinical ASCVD.
- By more accurately identifying higher-risk individuals for statin therapy, the guideline focuses statin therapy on those most likely to benefit.
- It also indicates, on the basis of RCT data, those high-risk groups that might not benefit. The Expert Panel emphasizes that the guideline is "patient centered" in primary prevention. It is recommended that the potential for an ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions, along with patient preferences, must be considered before statins are initiated for the primary prevention of ASCVD. Other factors such as LDL-C ≥160 mg/dL may also be considered. This gives clinicians and patients the opportunity for input into treatment decisions rather than a simplistic "one-treatment-fits-all" approach to drug therapy.
- These guidelines are not a replacement for clinical judgment; they are meant to guide and inform decision making.
- Some worry that a person 70 years of age without other risk factors will receive statin treatment on the basis of age alone. The estimated 10-year risk is still ≥7.5%, a risk threshold for which a reduction in ASCVD risk events has been demonstrated in RCTs. Most ASCVD events occur after age 70 years, giving individuals ≥70 years of age the greatest potential for absolute risk reduction.
- Some have proposed using selected inclusion criteria from RCTs to determine the threshold for statin initiation. However, the Cholesterol Treatment Trialists individual-level meta-analysis showed that statin therapy reduces ASCVD events regardless of categorical risk factors in both primary and secondary prevention. Therefore, the rationale for using fixed cutpoints to determine whether statin therapy should be initiated is refuted by a consideration of the total body of evidence from RCTs.
- In addition, a trial-based strategy identifies those at increased ASCVD risk less accurately than does a strategy based on an assessment of global ASCVD risk. This selective use of inclusion criteria excludes well-established risk factors, such as smoking and advancing age (the strongest risk factor because it represents cumulative risk factor exposure).
- The poor discrimination of RCT inclusion criteria for identifying those at increased 10-year ASCVD risk is shown by a calculation performed by the Risk Assessment Work Group using nationally representative data from NHANES. Use of the RCT inclusion criteria (from RCTs that found a reduction in ASCVD events to guide initiation of statin therapy) would result in the treatment of 16% of individuals with <2.5% estimated 10-year ASCVD risk and 45% of those with 2.5% to <5% estimated 10-year ASCVD risk (many would say inappropriately), whereas 38% of those with ≥7.5% 10-year ASCVD risk would not have been identified as candidates for statin therapy.

Safety

- RCTs are used to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk and to determine statin adverse effects to facilitate understanding of the net benefit from statin therapy.
- Safety issues that are uncommon or unlikely to be seen in the populations studied in RCTs require more than analyses of single RCTs. This limitation was overcome, in part, by considering high-quality systematic reviews and meta-analyses of statin RCTs.
- Expert guidance is provided on management of statin-associated adverse effects, including muscle symptoms.
- This guideline emphasizes the importance of using additional sources of information on safety, including FDA reports, manufacturers' prescribing information, and pharmacists, to aid in the safe use of cholesterol-lowering drug therapy.

Role of Biomarkers and Noninvasive Tests

- There is a concern about other factors that may indicate elevated ASCVD risk but were not included in the Pooled Cohort Equations for predicting 10-year ASCVD risk.
- The Risk Assessment Work Group has performed an updated systematic review of nontraditional risk factors, such as CAC, and has included recommendations to consider their use to the extent that the evidence allows.
- In selected individuals who are not in 1 of the 4 statin benefit groups, and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision making.
- These factors include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein ≥2 mg/L; CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity; ankle-brachial index <0.9; and elevated lifetime risk of ASCVD. Additional factors may be identified in the future.

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Appendix 5. Continued

Future Updates to the Blood Cholesterol Guideline

- This guideline focuses on treatments proven to reduce ASCVD events. It is not and was never intended to be a comprehensive approach to lipid management.
- Using RCT evidence assessed for quality provides a strong foundation for treatment of blood cholesterol to reduce ASCVD risk that can be used now. There are many clinical questions for which there is an absence of RCT data available to develop high-quality, evidence-based recommendations. For these questions, expert opinion may be helpful to clinicians and could be developed in the next iteration of the guideline.
- CQs for future guidelines could examine:
  1. the treatment of hypertriglyceridemia;
  2. the use of non–HDL-C in treatment decision making;
  3. whether on-treatment markers such as Apo B, Lp(a), or LDL particles are useful for guiding treatment decisions;
  4. the best approaches to using noninvasive imaging for refining risk estimates to guide treatment decisions;
  5. how lifetime ASCVD risk should be used to inform treatment decisions and the optimal age for initiating statin therapy to reduce lifetime risk of ASCVD;
  6. subgroups of individuals with heart failure or undergoing hemodialysis who might benefit from statin therapy;
  7. long-term effects of statin-associated new-onset diabetes and management;
  8. efficacy and safety of statins in patient groups excluded from RCTs to date (e.g., those who are HIV positive or have received a solid organ transplant); and
  9. role of pharmacogenetic testing.

*For additional information, see http://www.mesa-nhlbi.org/CACReference.aspx.

AIM-HIGH indicates Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; Apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CQ, critical question; FDA, U.S. Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NHANES, National Health and Nutrition Examination Survey; and RCTs, randomized controlled trials.

APPENDIX B. GUIDANCE FOR ELEVATED LIVER BIOCHEMISTRY VALUES

For subjects who progress to cirrhosis and decompensation while participating in the study, elevation in liver biochemistry and development of other laboratory and clinical abnormalities may be expected. Clinical adverse events (AEs) should be reported and recorded as described in Section 12.1.5 and appropriate action should be taken regarding investigational product use and study participation as described in Section 8.4.

However, if these abnormalities are not consistent with the pattern of change attributable to disease progression (as assessed by the Investigator) and no other cause is readily apparent (eg, acute biliary obstruction caused by gallstones in the common bile duct), further actions are appropriate as outlined below. The Sponsor should be contacted to discuss the case further.

Per guidance from the FDA (FDA 2009), subjects with normal ALT/AST and bilirubin at baseline, an increase in ALT/AST to >3× ULN or total bilirubin >2× ULN should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. In conjunction with this, a physical exam should be performed and AE information should be collected. If symptoms persist or repeat testing shows ALT/AST >3× ULN or total bilirubin >2× ULN, subjects should be closely monitored. In subjects with abnormal ALT/AST or bilirubin at baseline, fold increase should be assessed against baseline levels instead of ULN as follows: 3× baseline ALT/AST, or total bilirubin >2× baseline (and >2 mg/dL). In subjects with abnormal values at baseline who develop a nadir value during the study, the reference points noted above should be changed from baseline to the nadir value for subsequent assessments.

In subjects who are far from their study site, it may be difficult for the subjects to return to the site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to the Investigator immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows persistent abnormality as described above, it is appropriate to initiate close observation (defined below) to determine whether the abnormalities are improving or worsening.

If close observation is not possible, investigational product should be interrupted until further investigation can be performed.

Close observation may include:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the investigational product has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and other biliary tract disease.

- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).

Discontinuation of treatment should be considered if the following abnormality or group of abnormalities occur (in subjects with baseline values within the normal range):

- ALT or AST >8× ULN
- ALT or AST >5× ULN for more than 2 weeks
- ALT or AST >3× ULN **and** total bilirubin >2× ULN **or** INR >1.5)
- ALT or AST >3× ULN with the appearance of new onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

In subjects with abnormal baseline values, the reference point should be changed from ULN to baseline. In subjects with abnormal values at baseline who develop a nadir value during the study, the reference points noted above should be changed from ULN or baseline to the nadir value for subsequent assessments. Baseline is defined as the average of all on-study, predose values (including Screening Visit and Day 1). A nadir value is defined as the average of at least 2 consecutive post-baseline assessments, including the lowest value, regardless of when it occurs (ie, on or off treatment). Repeat and unscheduled visits will be included in the determination of the nadir value. A new nadir value may develop over the course of the study if liver biochemistries improve over time.

APPENDIX C. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

CONTENTS

Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.					
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a lymph node.					
Spleen disorder	Incidental findings (e.g., Howell-Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the spleen.					
Thrombotic thrombocytopenic purpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Cardiac disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death
Definition: A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction.					
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in aortic valve function or structure.					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the pumping function of the heart.					
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.					
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.					
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles.					
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart.					
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation.					
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by pathological irregularities in the cardiac conduction system.					
Constrictive pericarditis	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by a thickened and fibrotic pericardial sac; these fibrotic changes impede normal myocardial function by restricting myocardial muscle action.					
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.					

Cardiac disorders					
	Grade				
Adverse Event	1	2	3	4	5
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in mitral valve function or structure.					
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.					
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart.					
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).					

Cardiac disorders					
	Grade				
Adverse Event	1	2	3	4	5
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in pulmonary valve function or structure.					
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility.					
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
Definition: A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall.					
Sick sinus syndrome	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.					
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.					
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in tricuspid valve function or structure.					
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia that originates in the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles.					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His.					
Wolff-Parkinson-White syndrome	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with procedure	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of an accessory conductive pathway between the atria and the ventricles that causes premature ventricular activation.					
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Congenital, familial and genetic disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Congenital, familial and genetic disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Ear and labyrinth disorders					
	Grade				
Adverse Event	1	2	3	4	5
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the ear.					
External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation, swelling and redness to the outer ear and ear canal.					
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the external ear region.					
Hearing impaired	Adults enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: subjective change in hearing in the absence of documented hearing loss. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 8 kHz in at least one ear.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz and above in at least one ear.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in Monitoring Program: hearing loss with hearing aid or intervention indicated; limiting self care ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	Adults: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); non-servicable hearing. Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.					
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear.					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, and vision problems.					
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Endocrine disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.					
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-
Definition: A disorder characterized by unusually late sexual maturity.					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age.					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).					
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.					
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of parathyroid hormone by the parathyroid glands.					
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.					
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-
Definition: A disorder characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.					
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal male.					
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Eye disorders					
	Grade				
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.					
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; topical intervention indicated (e.g., antibiotics); limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
Corneal ulcer	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Limiting self care ADL; declining vision (worse than 20/40 but better than 20/200)	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber.					
Dry eye	Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder characterized by dryness of the cornea and conjunctiva.					
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by incomplete paralysis of an extraocular muscle.					
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the eye.					
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by impaired eyelid function.					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light.					
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens.					
Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficits; multiple topical or oral agents indicated; limiting instrumental ADL	EIOP causing marked visual field deficits (e.g., involving both superior and inferior visual fields); operative intervention indicated; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow.					
Keratitis	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Decline in vision (worse than 20/40 but better than 20/200); limiting self care ADL	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the cornea of the eye.					
Night blindness	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an inability to see clearly in dim light.					

Eye disorders					
	Grade				
Adverse Event	1	2	3	4	5
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve).					
Papilledema	Asymptomatic; no visual field defects	Symptomatic decline in vision; visual field defect present sparing the central 20 degrees	Marked visual field defect (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by swelling around the optic disc.					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of light.					
Retinal detachment	Asymptomatic	Exudative and visual acuity 20/40 or better	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium.					
Retinal tear	-	Laser therapy or pneumopexy indicated	Vitroretinal surgical repair indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters.					
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects vision.					
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder involving the retina.					
Scleral disorder	Asymptomatic; clinical or diagnostic observations only	Symptomatic, limiting instrumental ADL; moderate decrease in visual acuity (20/40 or better)	Symptomatic, limiting self care ADL; marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by involvement of the sclera of the eye.					
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye.					
Vitreous hemorrhage	Asymptomatic or mild symptoms; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; vitrectomy indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by blood extravasation into the vitreous humor.					
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct.					
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characterized by swelling of the abdomen.					
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region.					
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the opening in the anal canal to the perianal skin.					
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the anal region.					
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the anus.					
Anal necrosis	-	-	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the anal region.					
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the anal region.					
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non-emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the anal canal.					
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal.					
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity.					
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen.					
Cecal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cecum.					
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
Definition: A disorder characterized by inflammation of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site.					
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the colon.					
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.					
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall.					
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the colon.					
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the colon.					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.					
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-
Definition: A disorder characterized by the decay of a tooth, in which it becomes softened, discolored and/or porous.					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Duodenal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site.					
Duodenal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the duodenum.					
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization or elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of stomach contents through the duodenum.					
Duodenal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the duodenal wall.					
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the duodenum.					
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing.					
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines.					
Enterovesical fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; noninvasive intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine.					
Esophageal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site.					
Esophageal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the esophageal wall.					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the esophagus.					
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus.					
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the esophagus.					
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the esophageal wall.					
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from esophageal varices.					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site.					
Gastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the gastric wall.					
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastric wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Gastric perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall.					
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the stomach.					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach.					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.					
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site.					
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gastrointestinal region.					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss; refractory to medical intervention; unable to maintain nutrition orally	-	-
Definition: A disorder characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine.					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region.					
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the hemorrhoids.					
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characterized by the presence of dilated veins in the rectum and surrounding area.					
Ileal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the ileum and another organ or anatomic site.					
Ileal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ileal wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Ileal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the ileum.					
Ileal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall.					
Ileal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the ileum.					
Ileal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the ileum.					
Ileus	-	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.					
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity.					
Jejunal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the jejunum and another organ or anatomic site.					
Jejunal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the jejunal wall.					
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the jejunum.					
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the jejunal wall.					
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the jejunum.					
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the jejunum.					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Lower gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the lower gastrointestinal tract (small intestine, large intestine, and anus).					
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked discomfort, bloating and diarrhea.					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the oral mucosal.					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the stomach.					
Oral cavity fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the oral cavity and another organ or anatomic site.					
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-
Definition: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth.					
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mouth.					
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.					
Pancreatic duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the pancreatic duct.					
Pancreatic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pancreas and another organ or anatomic site.					
Pancreatic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pancreas.					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pancreas.					
Pancreatitis	-	Enzyme elevation or radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by inflammation of the pancreas.					
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-
Definition: A disorder in the gingival tissue around the teeth.					
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the peritoneum.					
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the rectum.					
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the rectum and another organ or anatomic site.					
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the rectal wall and discharged from the anus.					
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the rectum.					
Rectal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the rectal wall.					
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the rectal region.					
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the rectal wall.					
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the rectum.					
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the retroperitoneal area.					
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the salivary duct.					
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a salivary gland and another organ or anatomic site.					
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the small intestine.					
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents.					
Small intestinal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the small intestine wall.					
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the small intestine.					
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the small intestine.					
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the stomach.					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development.					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint.					
Toothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the tooth.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the cecum.					
Upper gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach).					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

General disorders and administration site conditions					
	Grade				
Adverse Event	1	2	3	4	5
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Definition: A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.					
Death neonatal	-	-	-	-	Death
Definition: A disorder characterized by cessation of life occurring during the first 28 days of life.					
Death NOS	-	-	-	-	Death
Definition: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues.					
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities.					
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area.					
Facial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face.					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal.					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough.					
Gait disturbance	Mild change in gait (e.g., wide-based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Disabling; limiting self care ADL	-	-
Definition: A disorder characterized by walking difficulties.					
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below.					

General disorders and administration site conditions					
	Grade				
Adverse Event	1	2	3	4	5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Infusion site extravasation	-	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling.					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms.					
Neck edema	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck.					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by discomfort in the chest unrelated to a heart disorder.					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony.					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
General disorders and administration site conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Hepatobiliary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the bile duct.					
Biliary fistula	-	Symptomatic and intervention not indicated	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site.					
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones.					
Gallbladder fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Symptomatic or severely altered GI function; TPN indicated; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site.					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gallbladder.					
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder.					
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall.					
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase.					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver.					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma.					
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the liver region.					
Perforation bile duct	-	-	Radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.					

Hepatobiliary disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in blood pressure in the portal venous system.					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein.					
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Immune system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the abdominal cavity.					
Anorectal infection	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the anal area and the rectum.					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent.					
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity.					
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving an artery.					
Biliary tract infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the biliary tract.					
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bladder.					
Bone infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bones.					
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the breast.					
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bronchi.					
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process that arises secondary to catheter use.					
Cecal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the cecum.					
Cervicitis infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
Conjunctivitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the conjunctiva. Clinical manifestations include pink or red color in the eyes.					
Corneal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cornea.					
Cranial nerve infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a cranial nerve.					
Device related infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the use of a medical device.					
Duodenal infection	-	Moderate symptoms; medical intervention indicated (e.g., oral antibiotics)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the duodenum.					
Encephalitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain tissue.					
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain and spinal cord tissues.					
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endocardial layer of the heart.					
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye.					

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Enterocolitis infectious	-	Passage of >3 unformed stools per 24 hrs or duration of illness >48 hrs; moderate abdominal pain	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small and large intestines.					
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the esophagus.					
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death
Definition: A disorder characterized by an infectious process involving the eye.					
Gallbladder infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gallbladder.					
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gums.					
Hepatic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the liver.					
Hepatitis viral	Asymptomatic, treatment not indicated	-	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma.					
Infective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skeletal muscles.					
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a joint.					
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney.					

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammatory process involving the larynx.					
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the lips.					
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lungs.					
Lymph gland infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lymph nodes.					
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mediastinum.					
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord.					
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a mucosal surface.					
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the nail.					
Otitis externa	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.					
Otitis media	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the middle ear.					
Ovarian infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary.					

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pancreas.					
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail.					
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pelvic cavity.					
Penile infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the penis.					
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the orbit of the eye.					
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peripheral nerves.					
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peritoneum.					
Pharyngitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the throat.					
Phlebitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein.					
Pleural infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pleura.					
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the prostate gland.					
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus.					
Rhinitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	-	-	-
Definition: A disorder characterized by an infectious process involving the nasal mucosal.					
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the salivary gland.					
Scrotal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the scrotum.					
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock.					
Sinusitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses.					
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skin.					
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine.					
Soft tissue infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving soft tissues.					
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the spleen.					
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a stoma (surgically created opening on the surface of the body).					
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a tooth.					
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the trachea.					
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).					
Urethral infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urethra.					
Urinary tract infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra.					
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial tissues.					
Vaginal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vagina.					
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vulva.					
Wound infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the wound.					
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Ankle fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot.					
Aortic injury	-	-	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta.					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery.					
Biliary anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures).					
Bladder anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures).					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.					
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment.					
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.					
Esophageal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures).					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury.					
Fallopian tube anastomotic leak	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures).					
Fallopian tube perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A finding of rupture of the fallopian tube wall.					
Fracture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Gastric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of a necrotic process occurring in the gastrointestinal tract stoma.					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-surgical intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken.					
Injury to carotid artery	-	-	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery.					
Injury to inferior vena cava	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava.					
Injury to jugular vein	-	-	Symptomatic limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein.					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the superior vena cava.					
Intestinal stoma leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from an intestinal stoma (surgically created opening on the surface of the body).					
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of blockage of the normal flow of the contents of the intestinal stoma.					
Intestinal stoma site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of blood leakage from the intestinal stoma.					
Intraoperative arterial injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to an artery during a surgical procedure.					
Intraoperative breast injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A finding of damage to the breast parenchyma during a surgical procedure.					
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the heart during a surgical procedure.					
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection of injured organ/structure indicated; disabling (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the ear during a surgical procedure.					
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the endocrine gland during a surgical procedure.					
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the gastrointestinal system during a surgical procedure.					
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the head and neck during a surgical procedure.					
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure.					
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the hepatic parenchyma and/or biliary tract during a surgical procedure.					
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the musculoskeletal system during a surgical procedure.					
Intraoperative neurological injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the nervous system during a surgical procedure.					
Intraoperative ocular injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the eye during a surgical procedure.					
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the kidney during a surgical procedure.					
Intraoperative reproductive tract injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A finding of damage to the reproductive organs during a surgical procedure.					
Intraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the respiratory system during a surgical procedure.					
Intraoperative skin injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the skin during a surgical procedure.					
Intraoperative splenic injury	-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the spleen during a surgical procedure.					
Intraoperative urinary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the urinary system during a surgical procedure.					
Intraoperative venous injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to a vein during a surgical procedure.					
Kidney anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a kidney anastomosis (surgical connection of two separate anatomic structures).					
Large intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large intestine.					
Pancreatic anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures).					
Pharyngeal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures).					
Postoperative hemorrhage	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding occurring after a surgical procedure.					
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of a previously undocumented problem that occurs after a thoracic procedure.					
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A finding of protrusion of the intestinal stoma (surgically created opening on the surface of the body) above the abdominal surface.					
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of displacement of the urostomy.					
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent.					
Rectal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a rectal anastomosis (surgical connection of two separate anatomic structures).					
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective radiologic or operative intervention indicated	-	-
Definition: A finding of tumor-like collection of serum in the tissues.					
Small intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small bowel.					
Spermatic cord anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures).					
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Definition: A finding of traumatic injury to the spine in which the continuity of a vertebral bone is broken.					
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the gastrointestinal stoma (surgically created opening on the surface of the body).					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure.					
Tracheal hemorrhage	Minimal bleeding identified on clinical or diagnostic exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding from the trachea.					
Tracheal obstruction	Partial asymptomatic obstruction on examination (e.g., visual, radiologic or endoscopic)	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor; radiologic or endoscopic intervention indicated (e.g., stent, laser); limiting self care ADL	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of blockage of the lumen of the trachea.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of blood leakage from the tracheostomy site.					
Ureteric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures).					
Urethral anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a urethral anastomosis (surgical connection of two separate anatomic structures).					
Urostomy leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from a urostomy.					
Urostomy obstruction	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A finding of blockage of the urostomy.					
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding from the urostomy site.					
Urostomy stenosis	-	Symptomatic but no hydronephrosis, no sepsis or no renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the opening of a urostomy.					
Uterine anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a uterine anastomosis (surgical connection of two separate anatomic structures).					
Uterine perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the uterine wall.					
Vaginal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures).					
Vas deferens anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures).					
Vascular access complication	-	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated; disabling	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to a vein.					
Wound complication	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound; local care indicated	Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated	Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of development of a new problem at the site of an existing wound.					
Wound dehiscence	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia or symptomatic hernia without evidence of strangulation	Fascial disruption or dehiscence without evisceration; primary wound closure or revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation of the approximated margins of a surgical wound.					
Wrist fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of traumatic injury to the wrist joint in which the continuity of a wrist bone is broken.					
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Investigations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen.					
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.					
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen.					
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g. , >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide.					
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin I in a biological specimen.					
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin T in a biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen.					
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen.					
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.					

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.					
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a blood specimen.					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds.					
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.					
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen.					
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.					
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.					
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.					

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.					
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues.					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches.					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues.					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite.					
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inability to properly metabolize glucose.					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.					
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.					
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.					
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.					
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.					
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.					
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues.					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat.					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.					
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g. tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the abdominal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint.					
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving a joint.					
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the back region.					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the bones.					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the buttocks.					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the chest wall region.					
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-
Definition: A disorder characterized by non-neoplastic overgrowth of bone.					
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the deep connective tissues.					
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation on the lateral side of the body in the region below the ribs and above the hip.					
Generalized muscle weakness	Symptomatic; weakness perceived by patient but not evident on physical exam	Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL	Weakness limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites.					
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-
Definition: A disorder characterized by of stature that is smaller than normal as expected for age.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Head soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the head.					
Joint effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated; disabling	-	-
Definition: A disorder characterized by excessive fluid in a joint, usually as a result of joint inflammation.					
Joint range of motion decreased	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity	>25 - 50% decrease in ROM; limiting instrumental ADL	>50% decrease in ROM; limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a decrease in joint flexibility of any joint.					
Joint range of motion decreased cervical spine	Mild restriction of rotation or flexion between 60 - 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	-	-
Definition: A disorder characterized by a decrease in flexibility of a cervical spine joint.					
Joint range of motion decreased lumbar spine	Stiffness; difficulty bending to the floor to pick up a very light object but able to do athletic activity	Pain with range of motion (ROM) in lumbar spine; requires a reaching aid to pick up a very light object from the floor	<50% lumbar spine flexion; associated with symptoms of ankylosis or fused over multiple segments with no L-spine flexion (e.g., unable to reach to floor to pick up a very light object)	-	-
Definition: A disorder characterized by a decrease in flexibility of a lumbar spine joint.					
Kyphosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the thoracic portion of the spine.					
Lordosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the lumbar portion of the spine.					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the left side of the body.					
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the lower limb muscles.					
Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the right side of the body.					
Muscle weakness trunk	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles.					
Muscle weakness upper limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the upper limb muscles.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; disabling	-	-
Definition: A disorder characterized by of a malformation of the musculoskeletal system.					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group of muscles.					
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving the skeletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the neck area.					
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the neck.					
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the bone of the mandible.					
Osteoporosis	Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated	BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated; limiting instrumental ADL	Loss of height >=2 cm; hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the upper or lower extremities.					
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis.					
Scoliosis	<20 degrees; clinically undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a malformed, lateral curvature of the spine.					
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the lower extremity.					
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the superficial soft tissues.					
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-
Definition: A disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication.					
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	Severe length discrepancy >5 cm; limiting self care ADL; disabling; operative intervention indicated	-	-
Definition: A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities.					
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematapoietic cell production by the bone marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis.					
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the abducens nerve (sixth cranial nerve).					
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the accessory nerve (eleventh cranial nerve).					
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the acoustic nerve (eighth cranial nerve).					
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory.					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.					
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.					
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.					
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.					
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.					
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by a conspicuous change in cognitive function.					
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death
Definition: A disorder characterized by a decrease in ability to perceive and respond.					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.					
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.					
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.					
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-
Definition: A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.					
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the facial muscles.					
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the facial nerve (seventh cranial nerve).					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.					
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized by characterized by excessive sleepiness during the daytime.					

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the hypoglossal nerve (twelfth cranial nerve).					
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cranium.					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the trochlear nerve (fourth cranial nerve).					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.					
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Definition: A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function.					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements.					
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs.					
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the oculomotor nerve (third cranial nerve).					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the olfactory nerve (first cranial nerve).					

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation or degeneration of the peripheral motor nerves.					
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.					
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.					
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.					
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by paralysis of the recurrent laryngeal nerve.					
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.					
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Definition: A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses.					
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by characterized by excessive sleepiness and drowsiness.					
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death
Definition: A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.					
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event.					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					

Nervous system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.					
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).					
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the vagus nerve (tenth cranial nerve).					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.					
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Pregnancy, puerperium and perinatal conditions					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Fetal death	-	-	-	-	Fetal loss at any gestational age
Definition: A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.					
Fetal growth retardation	-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-
Definition: A disorder characterized by inhibition of fetal growth resulting in the inability of the fetus to achieve its potential weight.					
Premature delivery	Delivery of a liveborn infant at >34 to 37 weeks gestation	Delivery of a liveborn infant at >28 to 34 weeks gestation	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-
Definition: A disorder characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation.					
Unintended pregnancy	-	-	Unintended pregnancy	-	-
Definition: A disorder characterized by an unexpected pregnancy at the time of conception.					
Pregnancy, puerperium and perinatal conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Psychiatric disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm.					
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death
Definition: A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a lack of clear and orderly thought and behavior.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; hospitalization indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.					
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense.					
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by melancholic feelings of grief or unhappiness.					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-being which is disproportionate to events and stimuli.					
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by a false sensory perception in the absence of an external stimulus.					
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characterized by difficulty in falling asleep and/or remaining asleep.					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized by a decrease in sexual desire.					
Libido increased	Mild increase in sexual interest not adversely affecting relationship	Moderate increase in sexual interest adversely affecting relationship	Severe increase in sexual interest leading to dangerous behavior	-	-
Definition: A disorder characterized by an increase in sexual desire.					
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behavior and elevation of mood.					
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death

Psychiatric disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a conspicuous change in a person's behavior and thinking.					
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be still.					
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own life.					
Suicide attempt	-	-	Suicide attempt or gesture without intent to die which may not require hospitalization	Suicide attempt with intent to die which requires hospitalization	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own life.					
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; disabling; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death

Renal and urinary disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
Bladder perforation	-	Extraperitoneal perforation, indwelling catheter indicated	Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.					
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract.					
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin in the urine.					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.					
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death
Definition: A disorder characterized by the formation of crystals in the pelvis of the kidney.					
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

Renal and urinary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the kidney.					
Urinary fistula	-	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals.					
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by inability to control the flow of urine from the bladder.					
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate.					
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract.					
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized by a change in the color of the urine.					
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen.					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast.					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the breast region.					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses.					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus.					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation.					
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.					
Fallopian tube obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube.					
Fallopian tube stenosis	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A disorder characterized by a narrowing of the fallopian tube lumen.					
Female genital tract fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors.					
Genital edema	Mild swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals.					
Gynecomastia	Asymptomatic breast enlargement	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males.					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by the presence of blood in a fallopian tube.					
Irregular menstruation	Intermittent menses with skipped menses for no more than 1 to 3 months	Intermittent menses with skipped menses for more than 4 to 6 months	Persistent amenorrhea for more than 6 months	-	-
Definition: A disorder characterized by irregular cycle or duration of menses.					
Lactation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-
Definition: A disorder characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males.					
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormally heavy vaginal bleeding during menses.					
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-
Definition: A disorder characterized by a malformation of the nipple.					
Oligospermia	Sperm concentration >48 million/mL or motility >68%	Sperm concentration 13 - 48 million/mL or motility 32 - 68%	Sperm concentration <13 million/mL or motility <32%	-	-
Definition: A disorder characterized by a decrease in the number of spermatozoa in the semen.					
Ovarian hemorrhage	Minimal bleeding identified on imaging study or laproscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the ovary.					
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by tearing or disruption of the ovarian tissue.					
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle.					
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the strength of the muscles of the pelvic floor.					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pelvis.					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the penis.					
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the area between the genital organs and the anus.					
Premature menopause	-	-	Present	-	-
Definition: A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, night sweats, mood swings and a decrease in sex drive.					
Prostatic hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by bleeding from the prostate gland.					
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).					
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the prostate gland.					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the scrotal area.					
Spermatic cord hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the spermatic cord.					
Spermatic cord obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents of the spermatic cord.					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with urination or sexual activities; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with urination or sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the testis.					
Testicular hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the testis.					
Testicular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the testis.					
Uterine fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the uterus and another organ or anatomic site.					
Uterine hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the uterus.					
Uterine obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the uterine outlet.					
Uterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the uterus.					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years.					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the vagina and another organ or anatomic site.					
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the vagina.					
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge.					
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal.					
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the vagina.					
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the vaginal wall.					
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterized by a narrowing of the vaginal canal.					
Vaginismus	Mild discomfort or pain associated with vaginal spasm/tightening; no impact upon sexual function or physical examination	Moderate discomfort or pain associated with vaginal spasm/tightening; disruption in sexual function and physical examination	Severe discomfort or pain associated with vaginal spasm/tightening; unable to tolerate vaginal penetration or physical examination	-	-
Definition: A disorder characterized by involuntary spasms of the pelvic floor muscles, resulting in pathologic tightness of the vaginal wall during penetration such as during sexual intercourse.					
Reproductive system and breast disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching.					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing.					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by inhalation of solids or liquids into the lungs.					
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by the collapse of part or the entire lung.					
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between the bronchus and another organ or anatomic site.					
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates.					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the bronchial tube.					
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.					
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by milky pleural effusion (abnormal collection of fluid) resulting from accumulation of lymph fluid in the pleural cavity.					
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.					
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the nose.					
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.					
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder characterized by harsh and raspy voice arising from or spreading to the larynx.					
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal edema	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
Laryngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characterized by an abnormal communication between the larynx and another organ or anatomic site.					
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by bleeding from the larynx.					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the larynx.					
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the laryngeal airway.					
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pharynx.					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the pharynx.					
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by a necrotic process occurring in the pharynx.					
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the pharyngeal airway.					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pharyngolaryngeal region.					
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung.					
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing.					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing.					
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder characterized by accumulation of fluid in the lung tissues that causes a disturbance of the gas exchange that may lead to respiratory failure.					
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure.					
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site.					
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder.					
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide.					
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid.					
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characterized by involvement of the paranasal sinuses.					
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characterized by cessation of breathing for short periods during sleep.					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the involuntary expulsion of air from the nose.					
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characterized by of marked discomfort in the throat					
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a high pitched breathing sound due to laryngeal or upper airway obstruction.					
Tracheal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site.					
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the trachea.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-
Definition: A disorder characterized by a change in the sound and/or speed of the voice.					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.					
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location.					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.					
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale center).					
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area.					
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or tenderness; limiting instrumental ADL	Covering >30% BSA; associated with erythema or tenderness; limiting self-care ADL	-	-
Definition: A disorder characterized by shrinking of adipose tissue.					
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen)					
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Generalized involving sites other than palms, soles, or axillae; associated with electrolyte/hemodynamic imbalance	-	-
Definition: A disorder characterized by excessive perspiration.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating.					
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by loss of all or a portion of the nail.					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by vertical or horizontal ridges on the nails.					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the skin.					
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face.					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color.					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the skin covering the top and the back of the head.					
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition.					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by loss of skin pigment.					
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin.					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of the skin or mucous membranes.					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-
Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.					
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Social circumstances					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Menopause	Menopause occurring at age 46 - 53 years of age	Menopause occurring at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-
Definition: A disorder characterized by the permanent cessation of menses, usually defined by 12 consecutive months of amenorrhea in a woman over 45 years of age.					
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Surgical and medical procedures					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Surgical and medical procedures - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Vascular disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Capillary leak syndrome	-	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ failure.					
Flushing	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characterized by episodic reddening of the face.					
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel.					
Hot flashes	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied by sweating upon cooling.					
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Pediatric: Same as adult	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
Definition: A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mm Hg.					
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment.					
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity.					
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by excessive fluid collection in tissues that causes swelling.					
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characterized by a cystic lesion containing lymph.					
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (>=24 hrs) and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by impaired circulation to an extremity.					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein.					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities.					

Vascular disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi-modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characterized by obstruction of the blood flow in the superior vena cava. Signs and symptoms include swelling and cyanosis of the face, neck, and upper arms, cough, orthopnea and headache.					
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.					
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the wall of a vessel.					
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by a decrease in blood supply due to narrowing or blockage of a visceral (mesenteric) artery.					
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

NIH Publication No. 09-5410
Revised June 2010
Reprinted June 2010

APPENDIX D. STANDARDIZED DEFINITIONS FOR CARDIOVASCULAR ENDPOINT EVENTS

Event	Definitions
Cardiovascular (CV) Death:	
Death due to Acute MI	Death due to Acute MI refers to a death by any CV mechanism (eg, arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days[a] after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤30 days of the MI, it will be considered a death due to MI. Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (Clinical Data Interchange Standards Consortium [CDISC], Chapter 4) or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery [CABG]), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (ie, chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

Event	Definitions
Sudden Cardiac Death	Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths: a. Death witnessed and occurring without new or worsening symptoms b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI c. Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review) d. Death after unsuccessful resuscitation from cardiac arrest (eg, implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest) e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology f. Unwitnessed death in a subject seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-CV cause of death (information regarding the subject's clinical status preceding death should be provided, if available). Unless additional information suggests an alternate specific cause of death (eg, death due to Other CV Causes), if a subject is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion f above) should be recorded. For subjects who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (eg, a subject found dead in bed, but who had not been seen by family for several days).
Death due to HF	Death due to HF refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology (CDISC, Chapter 7). Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
Death due to Stroke	Death due to Stroke refers to death after a stroke (hemorrhagic, ischemic, or undetermined) that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (CDISC, Chapter 6).
Death due to CV Procedures	Death due to CV Procedures refers to death caused by the immediate complications of a cardiac procedure.
Death due to CV Hemorrhage	Death due to CV Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (CDISC, Chapter 6), non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or hemorrhage causing cardiac tamponade.
Death due to Other CV Causes	Death due to Other CV Causes refers to a CV death not included in the above categories but with a specific, known cause (eg, pulmonary embolism or peripheral arterial disease).

Event	Definitions
Non-CV Death:	
The following is a suggested list of non-CV causes of death: • Pulmonary • Renal • Gastrointestinal • Hepatobiliary • Pancreatic • Infection (includes sepsis) • Inflammatory (eg, Systemic Inflammatory Response Syndrome (SIRS) / immune (including autoimmune; may include anaphylaxis from environmental [eg, food] allergies) • Hemorrhage that is neither CV bleeding nor a stroke (see Chapter 1, Section 6, and Chapter 6) • Non-CV procedure or surgery • Trauma • Suicide • Non-prescription drug reaction or overdose • Prescription drug reaction or overdose (may include anaphylaxis) • Neurological (non-CV) • Malignancy • Other non-CV	Non-CV death is defined as any death with a specific cause that is not thought to be CV in nature, as listed in CDISC Chapter 1, or as listed for CV Death.

Event	Definitions
Undetermined Cause of Death:	
Undetermined Cause of Death (will be classified as a CV death)	Undetermined cause of death refers to a death not attributable to one of the above categories of CV death or is due to a non-CV cause. Inability to classify the cause of death may be due to lack of information (eg, the only available information is "subject died") or there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few subjects in well-run clinical trials.
Cardiovascular Events:	
Myocardial Infarction[b]	a) Clinical Presentation The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (eg, trauma, surgery, pacing, ablation, HF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process. b) Biomarker Elevations For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the ninety-ninth percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the ninety-ninth percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the ninety-ninth percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. In general, troponins are preferred. Creatine kinase-myocardial band (CK-MB) should be used if troponins are not available, and total creatine kinase (CK) may be used in the absence of CK-MB and troponin. For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL. Since it is not practical to stipulate the use of a single biomarker or assay, the locally available results are to be used as the basis for adjudication. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces inter-assay variability. Since the prognostic significance of different types of MIs (eg, periprocedural MI versus spontaneous MI) may be different, outcomes for these subsets of subjects may be evaluated separately.

Event	Definitions
	c) ECG Changes Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves. ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and left bundle branch block [LBBB]) include: • ST elevation: New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women • ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1. The above ECG criteria illustrate patterns consistent with myocardial ischemia. In subjects with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings. • Criteria for pathological Q-wave – Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3 – Q-wave ≥0.03 seconds and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)[c] • ECG changes associated with prior MI – Pathological Q-waves, as defined above – R-wave ≥0.04 seconds in V1-V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect • Criteria for prior MI: Any one of the following criteria meets the diagnosis for prior MI: – Pathological Q waves with or without symptoms in the absence of non-ischemic causes – Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause Pathological findings of a prior myocardial infarction

Event	Definitions
Hospitalization for Unstable Angina	Unstable angina requiring hospitalization is defined as: 1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥10 minutes in duration occurring • at rest, or • in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity. AND 2. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available). AND 3. At least one of the following: a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH) • Transient ST elevation (duration <20 minutes) New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women. • ST depression and T-wave changes • New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥0.3 mV in two contiguous leads with prominent R wave or R/S ratio >1. b. Definite evidence of inducible myocardial ischemia event as demonstrated by: • an early positive exercise stress test, defined as ST elevation or ≥2 mm ST depression prior to 5 mets OR • stress echocardiography (reversible wall motion abnormality) OR • myocardial scintigraphy (reversible perfusion defect), OR • magnetic resonance imaging (MRI; myocardial perfusion deficit under pharmacologic stress). • And believed to be responsible for the myocardial ischemic symptoms/signs. c. Angiographic evidence of new or worse ≥70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td></td><td>d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.
AND
Negative cardiac biomarkers and no evidence of acute MI</td></tr>
<tr><td>Transient Ischemic Attack (TIA)</td><td>TIA is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.</td></tr>
<tr><td>Stroke (Includes Ischemic Stroke, Hemorrhagic Stroke, Undetermined Stroke, or Stroke Disability)</td><td>Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.
A. Ischemic Stroke: Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.
Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.
B. Hemorrhagic Stroke: Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.
C. Undetermined Stroke: Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.
Stroke Disability: Disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. For example, the modified Rankin Scale may be used to address this requirement:
<table>
<tr><th>Scale</th><th>Disability</th></tr>
<tr><td>0</td><td>No symptoms at all</td></tr>
<tr><td>1</td><td>No significant disability despite symptoms; able to carry out all usual duties and activities</td></tr>
<tr><td>2</td><td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td></tr>
<tr><td>3</td><td>Moderate disability; requiring some help, but able to walk without assistance</td></tr>
<tr><td>4</td><td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td></tr>
<tr><td>5</td><td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td></tr>
<tr><td>6</td><td>Dead</td></tr>
</table>
</td></tr>
</table>

Event	Definitions
Heart Failure (A HF event includes hospitalization for HF and may include urgent outpatient visits)	A HF hospitalization is defined as an event that meets ALL of the following criteria: 1. The subject is admitted to the hospital with a primary diagnosis of HF 2. The subject's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable) 3. The subject exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following: • Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea) • Decreased exercise tolerance • Fatigue • Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol) 4. The subject has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including: a. Physical examination findings considered to be due to HF, including new or worsened: i.Peripheral edema ii.Increasing abdominal distention or ascites (in the absence of primary hepatic disease) iii.Pulmonary rales/crackles/crepitations iv.Increased jugular venous pressure and/or hepatojugular reflux v.S_3 gallop vi.Clinically significant or rapid weight gain thought to be related to fluid retention b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including: i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT pro-BNP) concentrations consistent with decompensation of HF (such as BNP > 500 pg/mL or NT-proBNP >2,000 pg/mL). In subjects with chronically elevated natriuretic peptides, a significant increase should be noted above baseline. ii.Radiological evidence of pulmonary congestion

Event	Definitions
	iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, ECG criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI]) OR iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m^2 Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events. 5. The subject receives initiation or intensification of treatment specifically for HF, including at least ONE of the following: a. Augmentation in oral diuretic therapy b. Intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator) c. Mechanical or surgical intervention, including: i. Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart) ii.Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis) An urgent HF visit is defined as an event that meets all of the following: 6. The subject has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization (i.e. urgent outpatient visit) 7. All signs and symptoms for HF hospitalization (ie, symptoms and physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met 8. The subject receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Event	Definitions
Interventional Cardiology: Clinical Definitions	
Clinically-Driven Target Lesion Revascularization:	Revascularization is clinically-driven if the target lesion diameter stenosis is >50% by quantitative coronary angiography (QCA) and the subject has clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following: a. A history of angina pectoris, presumably related to the target vessel b. Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel c. Abnormal results of any invasive functional diagnostic test [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)] **Comment:** Target lesion revascularization of a >70% diameter stenosis by QCA in the absence of the above signs or symptoms may be considered clinically-driven. **Comment:** In the absence of QCA data or if a ≤50% stenosis is present, TLR may be considered clinically-driven by the Adjudication Committee (AC) if severe ischemic signs and symptoms attributed to the target lesion are present.
Non-Target Lesion and Non-Target Lesion Revascularization:	A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
Non-Target Vessel and Non-Target Vessel Revascularization:	A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
Percutaneous Coronary Intervention (PCI) Status:	a. **Elective:** The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of MI or death. For stable inpatients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and **NOT** because the subject's clinical situation demands the procedure prior to discharge. b. **Urgent:** The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Subjects who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation. c. **Emergency:** The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a subject who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

Event	Definitions
	d. **Salvage:** The procedure is a last resort. The subject is in cardiogenic shock when the PCI begins (ie, the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) **OR** within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the subject has also received chest compressions or has been on unanticipated circulatory support (eg, intra-aortic balloon pump, extracorporeal membrane oxygenation, or cardiopulmonary support).
Percutaneous Coronary Intervention (PCI):	Placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, coronary flow reserve (CFR), or fractional flow reserve (FFR), insertion of a guide wire will **NOT** be considered PCI.
Procedural Success:	Achievement of <30 % residual diameter stenosis of the target lesion assessed by visual inspection or QCA and no in-hospital major adverse cardiac events (MACE, a composite of death, MI, or repeat coronary revascularization of the target lesion). Ideally, the assessment of the residual stenosis at the end of the procedure should be performed by an angiographic core laboratory. **Comment:** For some device interventions (eg, balloon angioplasty), achievement of <50% diameter stenosis by visual inspection or QCA is an acceptable definition for procedural success.
Target Lesion:	Any lesion treated or attempted to be treated during the PCI with the study device. The target lesion includes the arterial segment treated with the study device (stent, in most cases) plus 5 mm proximal and 5 mm distal to the treatment site.
Target Lesion Failure (TLF):	The composite of ischemia-driven revascularization of the target lesion, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TLF.
Target Lesion Revascularization (TLR):	Any repeat percutaneous intervention of the target lesion (including 5 mm proximal and 5 mm distal to the target lesion) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the AC for review upon request.
Target Vessel:	A major native coronary artery (eg, left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) or bypass graft containing the target lesion. A native coronary artery target vessel includes the arterial segments upstream and downstream to the target lesion plus major side branches.
Target Vessel Failure (TVF):	The composite of ischemia-driven revascularization of the target vessel, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TVF.

<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td>Target Vessel, Non-Target Lesion, and Target Vessel, Non-Target Lesion Revascularization:</td><td>Any lesion or revascularization of a lesion in the target vessel other than the target lesion, respectively.</td></tr>
<tr><td>Target Vessel Revascularization (TVR):</td><td>Any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review upon request.</td></tr>
<tr><td>Vascular Complications:</td><td>• Access site hematoma: Development of a new, localized collection of blood at a vascular access site sufficient to produce a palpable mass within 72 hours of a procedure.
• Arteriovenous fistula: Development of a new, unintended communication between an artery and a vein occurring at a vascular access site within 72 hours of a procedure.
• Peripheral ischemia: Development of new arterial insufficiency sufficient to produce clinical signs or symptoms of ischemia (pallor, pain, paresthesia) distal to a vascular access site within 72 hours of a procedure.
• Peripheral nerve injury: Development of new sensory or motor loss of peripheral nerve function from external nerve compression (e.g., as a result of positioning during a procedure), or internal compression or direct nerve damage from the procedure, occurring within 72 hours of a procedure.
• Pseudoaneurysm: Development of a new localized collection of blood with a persistent communication (neck) originating at a vascular access site and occurring within 72h of a procedure.
• Retroperitoneal hemorrhage: Development of new bleeding into the retroperitoneal space originating at a vascular access site and occurring within 72 hours of a procedure.</td></tr>
<tr><td colspan="2">Interventional Cardiology: Angiographic Definitions</td></tr>
<tr><td>Abrupt Closure:</td><td>New intra-procedural severely reduced flow (TIMI grade 0-1) within the target vessel that persists and requires intervention by stenting or other treatment, or results in MI or death. Abrupt closure requires an association with a vascular dissection, thrombus, or severe spasm at the treatment site or within the instrumented vessel.</td></tr>
<tr><td>Coronary Lesions Treated</td><td>
<table>
<tr><th>Coronary Artery Segments</th><th>Definitions</th></tr>
<tr><td>Right coronary artery ostium</td><td>Origin of the right coronary artery, including the first 3 mm of the artery</td></tr>
<tr><td>Proximal right coronary artery</td><td>Proximal portion of the right coronary artery, from the ostium of the right coronary artery to the origin of the first right ventricular branch (pRCA)</td></tr>
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Event	Definitions	
	Mid right coronary artery	Middle portion of the right coronary artery, from the origin of the first right ventricular branch to the acute margin (mRCA)
	Distal right coronary artery	Distal portion of the right coronary artery, from the acute margin to the origin of the posterior descending artery (dRCA)
	Right posterior descending artery	In right dominant and mixed circulations, the vessel that runs in the posterior interventricular groove and supplies septal perforator branches (PDA)
	Posterolateral segmental artery	In right dominant circulations, the distal continuation of the right coronary artery in the posterior atrioventricular groove after the origin of the right posterior descending artery (PLSA)
	First right posterolateral branch	In right dominant circulations, the first posterolateral branch originating from the right posterior atrioventricular artery (RPL1)
	Second right posterolateral branch	In right dominant circulations, the second posterolateral branch originating from the right posterior atrioventricular artery (RPL2)
	Third right posterolateral branch	In right dominant circulations, the third posterolateral branch originating from the right posterior atrioventricular artery (RPL3)
	Posterior descending septal perforator	Septal perforator vessel originating from the posterior descending artery
	Right ventricular branch	Branch arising from the right coronary artery to supply the right ventricular wall (RV)
	Left main coronary artery ostium	Origin of the left coronary artery, including the first 3 mm of the artery
	Left main coronary artery body	Body of the left main coronary artery, from the ostium to the bifurcation (LM)
	Left main coronary artery bifucation	Distal end of the left main, including the terminal 3 mm through the bifurcation of the left main into the left anterior descending and left circumflex arteries
	Left anterior descending artery ostium	Origin of the left anterior descending coronary artery, including the first 3 mm of the artery
	Proximal left anterior descending artery	Proximal portion of the left anterior descending coronary artery, from the ostium to the origin of the first septal (pLAD)
	Mid left anterior descending artery	Middle portion of the left anterior descending coronary artery, from the origin of the first septal artery to the origin of the third septal artery (mLAD)

Event	Definitions	
	Distal left anterior descending artery	Distal portion of the left anterior descending coronary artery, from the origin of the third septal artery to the terminus (dLAD)
	First diagonal branch	First of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D1)
	First diagonal lateral branch	Branch of the first diagonal branch
	Second diagonal branch	Second of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D2)
	Second diagonal lateral branch	Branch of the second diagonal branch
	Third diagonal branch	Third of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D3)
	Third diagonal lateral branch	Branch of the third diagonal branch
	Anterior descending septal perforator	Septal perforator vessel originating from the left anterior descending artery to supply the interventricular septum
	Left circumflex artery ostium	Origin of the left circumflex coronary artery, including the first 3 mm of the artery
	Proximal left circumflex artery	Proximal portion of the left circumflex coronary artery, from the ostium to the origin (or the nominal location of) the first marginal branch (pLCX)
	Mid left circumflex artery	Middle portion of the left circumflex coronary artery, from the origins of (or nominal locations of) the first marginal to the second marginal (mLCX)
	Distal left circumflex artery	Distal portion of the left circumflex coronary artery, from the origin of (or the nominal location of) the second marginal to the terminus (in right dominant systems), or to the origin of the 1st left posterolateral in all other dominance systems (dLCX)
	First obtuse marginal branch	First of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM1)
	First obtuse marginal lateral branch	Branch of the first marginal branch
	Second obtuse marginal branch	Second of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM2)

<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td></td><td>
<table>
<tr><td>Second obtuse marginal lateral branch</td><td>Branch of the second marginal branch</td></tr>
<tr><td>Third obtuse marginal branch</td><td>Third of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM3)</td></tr>
<tr><td>Third obtuse marginal lateral branch</td><td>Branch of the third marginal branch</td></tr>
<tr><td>Left atrioventricular artery</td><td>In left dominant and mixed circulations, the distal continuation of the left circumflex coronary artery in the posterior atrioventricular groove</td></tr>
<tr><td>Left posterior descending artery</td><td>In left dominant circulations, the vessel that arises from the distal continuation of the left atrioventricular artery, travels in the posterior interventricular groove, and supplies septal perforator branches (LPDA)</td></tr>
<tr><td>First left posterolateral branch</td><td>In left dominant and mixed circulations, the first posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL1)</td></tr>
<tr><td>Second left posterolateral branch</td><td>In left dominant and mixed circulations, the second posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL2)</td></tr>
<tr><td>Third left posterolateral branch</td><td>In left dominant and mixed circulations, the third posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL3)</td></tr>
<tr><td>Ramus intermedius branch</td><td>Branch vessel whose origin bisects the origins of the left anterior descending and circumflex arteries (RI)</td></tr>
<tr><td>Ramus intermedius lateral branch</td><td>Branch of the ramus intermedius branch</td></tr>
</table>
</td></tr>
<tr><td>Dissection:</td><td>Based on the National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System:
• Grade A: Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance
• Grade B: Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance
• Grade C: Extraluminal cap with persistence of contrast after dye clearance from the lumen
• Grade D: Spiral luminal filling defect with delayed but complete distal flow
• Grade E: New persistent filling defect with delayed antegrade flow
• Grade F: Non-A-E types with total coronary occlusion and no distal antegrade flow
Note: Grade E and F dissections may represent thrombus</td></tr>
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Event	Definitions
Late Loss:	Minimum lumen diameter (MLD) assessed at follow-up angiography minus the MLD assessed immediately after the index procedure. MLDs are measured by QCA.
Minimum Lumen Diameter (MLD):	The mean minimum lumen diameter (typically measured in-lesion, in-stent, and in-segment) derived from two orthogonal views by QCA.
No Reflow:	An acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion.
Percent Diameter Stenosis (% DS):	The value calculated as 100 x (1 – MLD/RVD) using the mean values determined by QCA from two orthogonal views (when possible).
Reference Vessel Diameter (RVD):	Defined as the average of normal segments within 10 mm proximal and 10 mm distal to the target lesion from two orthogonal views using QCA.
Restenosis:	Re-narrowing of the vessel following the treatment of a prior stenosis • **Binary restenosis:** A diameter stenosis of > 50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 5 mm proximal and 5 mm distal to the site. • **In-stent restenosis (ISR):** A previously stented lesion with a > 50% diameter stenosis.
Thrombus (Angiographic):	A discrete, mobile, intraluminal filling defect with defined borders with or without associated contrast staining.
TIMI (Thrombolysis in Myocardial Infarction) Flow Grades:	• **Grade 0 (no perfusion):** There is no antegrade flow beyond the point of occlusion. • **Grade 1 (penetration without perfusion):** The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence. • **Grade 2 (partial perfusion):** The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (eg, the opposite coronary artery or the coronary bed proximal to the obstruction). • **Grade 3 (complete perfusion):** Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery.
Vessels	• Left main coronary artery (LMCA) • Left anterior descending artery (LAD) with septal and diagonal branches

Event	Definitions
	• Left circumflex artery (LCX) with obtuse marginal branches • Ramus intermedius artery • Right coronary artery (RCA) and any of its branches • Posterior descending artery • Saphenous vein bypass graft(s) • Arterial bypass graft(s): Right internal mammary graft, left internal mammary graft, radial artery graft, and gastroepiploic artery graft.
Peripheral Vascular Intervention	
Peripheral Vascular Intervention (PVI):	Peripheral vascular intervention[d] is a catheter based or open surgical procedure designed to improve arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, percutaneous transluminal balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, treatment of dialysis conduits, placement of various devices, intravascular thrombolysis or other pharmacotherapies, and open surgical bypass or revision. In general, the intention to perform *percutaneous* peripheral vascular intervention is denoted by the insertion of a guide wire into a peripheral artery or vein. The target vessel(s) and the type of revascularization procedure (e.g., surgical bypass, thrombectomy, endarterectomy, percutaneous transluminal angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. For the sake of simplicity, this definition applies to the extracranial carotid artery and other non-cardiac arteries and veins and excludes the intracranial vessels and lymphatics.
Procedural Success:	In the case of percutaneous intervention for obstructive lesions, procedural success is defined as the achievement of a satisfactory final residual diameter stenosis by angiography at the end of the procedure (and without flow limiting dissection or hemodynamically significant translesional pressure gradient). The specific parameter for final percent residual stenosis is typically between <30% and <50%; selection of the appropriate percentage may vary depending upon the specific intervention applied, the vascular territory, and anticipated or desired therapeutic response. Procedural success also implies absence of in-hospital major adverse events (eg, death, stroke, myocardial infarction, acute onset of limb ischemia, need for urgent/emergent vascular surgery, and other procedure-specific major adverse events). The balloon inflation, stent placement, or other therapeutic intervention may be preceded by use of adjunctive devices (eg, percutaneous mechanical thrombectomy, directional or rotational atherectomy, laser, and chronic total occlusion crossing device), as predefined in the protocol.

Event	Definitions
Procedural Status: Non-Elective and Elective:	e. **Non-Elective:** Non-elective procedures include emergent and urgent procedures. A non elective procedure is a procedure that is performed without delay, because there is clinical consensus that the procedure should occur imminently. Non-elective procedures imply a degree of instability of the subject, urgency of the medical condition, or instability of the threatening lesion. – **Emergent:** A procedure that is performed immediately because of the acute nature of the medical condition (e.g., acute limb ischemia, acute aortic dissection), and the increased morbidity or mortality associated with a temporal delay in treatment. – **Urgent:** An urgent procedure is one that is not an emergency but is required to be performed on a timely basis (≤24 hrs) (e.g., a subject who has been stabilized following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive procedure should occur within the next 24 hours). f. **Elective:** An elective procedure is one that is scheduled and is performed on a subject with stable disease, or in whom there is no urgency and/or increased morbidity or mortality associated with a planned procedure.
Target Lesion:	A target lesion is any vascular segment treated or attempted to be treated during the trial procedure with the index device. The target lesion is the treated segment starting 10 mm proximal and ending 10 mm distal to the index device or therapy (stent, balloon, atherectomy catheter, or aortic stent-graft).
Target Vessel:	A target vessel is any vessel (eg, non-cardiac or non-intracranial) that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as the entire length of native vessel upstream and downstream from the target lesion, including side branches. For the arteries of the leg, the vasculature is divided into 3 vessel "levels:" aorto-iliac, femoral-popliteal, and tibial-crural.
Non-Target Lesion and Non-Target Lesion Revascularization:	A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
Non-Target Vessel and Non-Target Vessel Revascularization:	A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
Target Vessel, Non-Target Lesion and Target Vessel, Non-Target Lesion Revascularization:	Any lesion or revascularization of a lesion in the target vessel other than the target lesion, respectively.
Target Lesion Revascularization (TLR):	Target lesion revascularization is any repeat intervention of the target lesion (including 10 mm proximal and 10 mm distal to the index device, as target lesion is defined above) or surgical intervention/bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated). Angiograms (and core laboratory assessment thereof) and other source documentation should be made available to the CEC for review upon request.

Event	Definitions
Target Vessel Revascularization (TVR):	Target vessel revascularization is any repeat intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated). Angiograms (and core laboratory assessment thereof) and other source documentation should be made available to the CEC for review upon request.
Clinically-Driven Target Lesion Revascularization:	Clinically-driven target lesion revascularization is defined as target lesion revascularization performed due to target lesion diameter stenosis >50% **AND** either evidence of clinical or functional ischemia (eg, recurrent/progressive intermittent claudication, critical limb ischemia) **OR** recurrence of the clinical syndrome for which the initial procedure was performed. Clinically-driven target lesion revascularization occurs in the absence of protocol-directed surveillance ultrasound or angiography.
Vessel Patency:	Vessel patency at a given time point will be determined by the absence of clinically-driven target lesion revascularization and/or absence of recurrent target lesion diameter stenosis >50% by imaging (eg, invasive angiography or most commonly, duplex ultrasonography). If patency data are incorporated within the primary endpoint of a clinical trial, the angiographic images or duplex ultrasonographic images should be assessed by appropriate core laboratories and made available to the AC for review upon request.
Restenosis:	Re-narrowing of the artery following the treatment of a prior stenosis • **Binary restenosis:** A diameter stenosis of >50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 10 mm proximal and 10 mm distal to the site (or as otherwise defined by the protocol, as noted above). • **In-stent restenosis (ISR):** A previously stented lesion that has >50% diameter stenosis.

<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td colspan="2">Stent Thrombosis</td></tr>
<tr><td>Stent Thrombosis: Timing</td><td>Stent thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the cardiac catheterization laboratory.

Stent Thrombosis: Timing
<table>
<tr><td>Acute stent thrombosis[1]</td><td>0-24 hours post stent implantation</td></tr>
<tr><td>Subacute stent thrombosis[1]</td><td>>24 hours – 30 days post stent implantation</td></tr>
<tr><td>Late stent thrombosis[2]</td><td>>30 days – 1 year post stent implantation</td></tr>
<tr><td>Very late stent thrombosis[2]</td><td>>1 year post stent implantation</td></tr>
<tr><td colspan="2">[1] Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0-30 days) will be used herein.
[2] Includes “primary” as well as “secondary” late stent thrombosis; “secondary” late stent thrombosis is a stent thrombosi after a target lesion revascularization.</td></tr>
</table></td></tr>
<tr><td>Stent Thrombosis Categories</td><td>1. Definite Stent Thrombosis
Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:
a. Angiographic confirmation of stent thrombosis[e]
• The presence of a thrombus[f] that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
– Acute onset of ischemic symptoms at rest
– New ischemic ECG changes that suggest acute ischemia
– Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
– Nonocclusive thrombus: Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream
– Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).</td></tr>
</table>

Event	Definitions
	b. Pathological Confirmation of Stent Thrombosis: Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. 2. **Probable Stent Thrombosis:** Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases: a.Any unexplained death within the first 30 days[g] b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause 3. **Possible Stent Thrombosis:** Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

[a] The 30-day cut-off is arbitrary.
[b] 2012 Third Universal Definition of Myocardial Infarction.
[c] The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.
[d] Peripheral vascular disease includes veins, arteries, and lymphatics. However, for simplicity, this definition focuses on peripheral artery and venous interventions.
[e] The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
[f] Intracoronary thrombus.
[g] For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.
Source: "Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials," dated August 20, 2014, and available at the CDISC website (http://www.cdisc.org/system/files/all/standard/Draft%20Definitions%20for%20CDISC%20August%2020,%202014.pdf).
Note: CEC = Cardiovascular Events Committee, which is referred to in the body of the protocol as the CAC = Cardiovascular Adjudication Committee

Event	Mechanism/Classification	Definitions
Hospitalization for Unstable Angina	**General Considerations** 1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under item 3 above, would be insufficient to support classification as hospitalization for unstable angina. 2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for MI should not be adjudicated as unstable angina. 3. Planned hospitalization or rehospitalization for performance of an elective revascularization in subjects who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. • Hospitalization of a subject with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina. • Rehospitalization of a subject meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization,	Unstable angina requiring hospitalization is defined as: 1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥10 minutes in duration occurring • at rest, or • in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity. AND 2. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available). AND 3. At least one of the following: a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH) • Transient ST elevation (duration <20 minutes) New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25mV in men <40 years) or ≥0.15 mV in women.

Event	Mechanism/Classification	Definitions
Hospitalization for Unstable Angina (Continued)	does not constitute a second hospitalization for unstable angina. A subject who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina endpoint.	• ST depression and T-wave changes • New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥0.3 mV in two contiguous leads with prominent R wave or R/S ratio >1. b. Definite evidence of inducible myocardial ischemia event as demonstrated by: • an early positive exercise stress test, defined as ST elevation or ≥2 mm ST depression prior to 5 mets OR • stress echocardiography (reversible wall motion abnormality) OR • myocardial scintigraphy (reversible perfusion defect), OR • magnetic resonance imaging (MRI; myocardial perfusion deficit under pharmacologic stress). • And believed to be responsible for the myocardial ischemic symptoms/signs. c. Angiographic evidence of new or worse ≥70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs. d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

Event	Mechanism/Classification	Definitions
		AND 4. Negative cardiac biomarkers and no evidence of acute MI
Transient Ischemic Attack (TIA) and Stroke	TIA	TIA is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.
	Stroke Classification: A. Ischemic Stroke Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke. B. Hemorrhagic Stroke Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. C. Undetermined Stroke Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

<table>
<tr><th>Event</th><th>Mechanism/Classification</th><th>Definitions</th></tr>
<tr><td>Transient Ischemic Attack (TIA) and Stroke (Continued)</td><td>D. Stroke Disability
Disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. For example, the modified Rankin Scale may be used to address this requirement:
<table>
<tr><th>Scale</th><th>Disability</th></tr>
<tr><td>0</td><td>No symptoms at all</td></tr>
<tr><td>1</td><td>No significant disability despite symptoms; able to carry out all usual duties and activities</td></tr>
<tr><td>2</td><td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td></tr>
<tr><td>3</td><td>Moderate disability; requiring some help, but able to walk without assistance</td></tr>
<tr><td>4</td><td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td></tr>
<tr><td>5</td><td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td></tr>
<tr><td>6</td><td>Dead</td></tr>
</table></td><td></td></tr>
</table>

Event	Mechanism/Classification	Definitions
HF Event : A HF event includes hospitalization for HF and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.		A HF hospitalization is defined as an event that meets ALL of the following criteria: 1. The subject is admitted to the hospital with a primary diagnosis of HF 2. The subject's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable) 3. The subject exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following: • Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea) • Decreased exercise tolerance • Fatigue • Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol) 4. The subject has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including: a. Physical examination findings considered to be due to HF, including new or worsened: i.Peripheral edema

Event	Mechanism/Classification	Definitions
HF Event (Continued): A HF event includes hospitalization for HF and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.		ii.Increasing abdominal distention or ascites (in the absence of primary hepatic disease) iii.Pulmonary rales/crackles/crepitations iv.Increased jugular venous pressure and/or hepatojugular reflux v.S_3 gallop vi.Clinically significant or rapid weight gain thought to be related to fluid retention b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including: i.Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT pro-BNP) concentrations consistent with decompensation of HF (such as BNP >500 pg/mL or NT-proBNP >2,000 pg/mL). In subjects with chronically elevated natriuretic peptides, a significant increase should be noted above baseline. ii.Radiological evidence of pulmonary congestion iii.Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, ECG criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI]) OR iv.Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion

Event	Mechanism/Classification	Definitions
HF Event (Continued): A HF event includes hospitalization for HF and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.		pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m^2 Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events. 5. The subject receives initiation or intensification of treatment specifically for HF, including at least ONE of the following: a. Augmentation in oral diuretic therapy b. Intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator) c. Mechanical or surgical intervention, including: i.Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart) ii.Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis) An urgent HF visit is defined as an event that meets all of the following: 6. The subject has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization (i.e. urgent outpatient visit) 7. All signs and symptoms for HF hospitalization (ie, symptoms and physical examination findings/laboratory evidence of

Event	Mechanism/Classification	Definitions
		new or worsening HF, as indicated above) must be met 8. The subject receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

[a] ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non ST- 954 Elevation Myocardial Infarction: Executive Summary. A Report of the American College of 955 Cardiology/American Heart Association Task Force on Practice Guidelines (Writing 956 Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable 957 Angina/Non ST-Elevation Myocardial Infarction): Developed in Collaboration with the 958 American College of Emergency Physicians, the Society for Cardiovascular Angiography 959 and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American 960 Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic 961 Emergency Medicine, Circulation, 2007, 116:803-877.

[b] The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

Source: "Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials," dated August 20, 2014, and available at the CDISC website (http://www.cdisc.org/system/files/all/standard/Draft%20Definitions%20for%20CDISC%20August%2020,%202014.pdf)

APPENDIX E. ATORVASTATIN PRESCRIBING INFORMATION

ATORVASTATIN CALCIUM- atorvastatin calcium trihydrate tablet, film coated
Greenstone LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use atorvastatin calcium tablets safely and effectively. See full prescribing information for atorvastatin calcium tablets.

Atorvastatin Calcium Tablets for oral administration
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Atorvastatin calcium is an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use
Atorvastatin calcium tablets have not been studied in *Fredrickson* Types I and V dyslipidemias.

DOSAGE AND ADMINISTRATION

Dose range: 10 to 80 mg once daily (2.1).
Recommended start dose: 10 or 20 mg once daily (2.1).
Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

DOSAGE FORMS AND STRENGTHS

10, 20, 40, and 80 mg tablets (3).

CONTRAINDICATIONS

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).
Women who are pregnant or may become pregnant (4.3).
Nursing mothers (4.4).
Hypersensitivity to any component of this medication (4.2).

WARNINGS AND PRECAUTIONS

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole,

HIV protease inhibitors). Predisposing factors include advanced age (> 65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. Atorvastatin therapy should be discontinued if myopathy is diagnosed or suspected (5.1, 8.5).

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter (5.2).

A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the atorvastatin calcium tablets 80 mg group vs. placebo (5.5).

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin calcium tablets in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Greenstone LLC at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

- Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with atorvastatin calcium tablets (7).
- Digoxin: Patients should be monitored appropriately (7.8).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.9).
- Rifampin should be simultaneously co-administered with atorvastatin calcium tablets (7.7).

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously with diet.

1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels *(Fredrickson* Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

  a. LDL-C remains ≥ 190 mg/dL or

  b. LDL-C remains ≥ 160 mg/dL and:
  - there is a positive family history of premature cardiovascular disease or
  - two or more other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin calcium tablets have not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons *(Fredrickson* Types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

The recommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin calcium tablets should be individualized according to patient characteristics such as goal of therapy and response (see current *NCEP Guidelines*). After initiation and/or upon titration of atorvastatin calcium tablets, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10–17 years of age)

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy [see current *NCEP Pediatric Panel Guidelines*, *Clinical Pharmacology (12)*, and *Indications and Usage (1.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin calcium tablets in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin calcium tablets; thus, dosage adjustment in patients with renal dysfunction is not necessary [see *Warnings and Precautions, Skeletal Muscle (5.1), Clinical Pharmacology, Pharmacokinetics (12.3)*].

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with atorvastatin calcium tablets should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with atorvastatin calcium tablets should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin calcium tablets should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White, elliptical, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin calcium tablets may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of atorvastatin calcium tablets use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN CALCIUM TABLETS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, atorvastatin calcium tablets should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing mothers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require atorvastatin calcium tablets treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin calcium tablets and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase,

which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing atorvastatin calcium tablets. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see *Drug Interactions (7)*). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.6)*, *Drug Interactions (7)*, *Clinical Pharmacology (12.3)*].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

* Use with caution and with the lowest dose necessary (12.3)

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine [see *Drug Interactions (7.11)*].

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin calcium tablets in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin calcium tablets.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin calcium tablets and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin calcium tablets, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin calcium tablets.

Atorvastatin calcium tablets should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin calcium tablets [see *Contraindications (4.1)*].

5.3 Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin calcium tablets.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0–24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0–24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin calcium tablets 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a

stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin calcium tablets 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

Rhabdomyolysis and myopathy [see *Warnings and Precautions (5.1)*]

Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the atorvastatin calcium tablets placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin calcium tablets vs. 7311 placebo; age range 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium tablets and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin calcium tablets that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin calcium tablets in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin calcium tablets (n=8755), from seventeen placebo-controlled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patients treated with any dose of atorvastatin calcium tablets and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0

Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

* Adverse Reaction ≥ 2% in any dose greater than placebo

Other adverse reactions reported in placebo-controlled studies include:

Body as a whole: malaise, pyrexia; *Digestive system:* abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system*: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system*: nightmare; *Respiratory system:* epistaxis; *Skin and appendages*: urticaria; *Special senses*: vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40–80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin calcium tablets 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin calcium tablets was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)

In CARDS [see *Clinical Studies (14.1)*] involving 2,838 subjects (age range 39–77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with atorvastatin calcium tablets 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)

In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29–78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with atorvastatin calcium tablets 10 mg daily (n=5006) or atorvastatin calcium tablets 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 × ULN twice within 4–10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 × ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)

In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26–80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin calcium tablets 80 mg/day (n=4439) or simvastatin 20–40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4731 subjects (age range 21–92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin calcium tablets 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥ 3 × ULN twice

within 4–10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 × ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium tablets 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin calcium tablets vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin calcium tablets vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium tablets 80 mg/day group vs. 211 (8.9%) in the placebo group. The proportions of subjects who experienced cardiovascular death were numerically smaller in the atorvastatin calcium tablets 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin calcium tablets 80 mg group (5.0%) than in the placebo group (4.0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of atorvastatin calcium tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, myositis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, and pancreatitis.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see *Warnings and Precautions (5.1)*].

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6.3 Pediatric Patients (ages 10–17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium tablets 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4

Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin calcium tablets with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium tablets 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium tablets with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin calcium tablets should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin calcium tablets should not exceed 20 mg and should be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*]. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of atorvastatin calcium tablets should not exceed 40 mg and close clinical monitoring is recommended.

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium tablets 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

7.2 Grapefruit Juice

Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

7.3 Cyclosporine

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium tablets 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. The co-administration of atorvastatin calcium tablets with cyclosporine should be avoided [see *Warnings and Precautions, Skeletal Muscle (5.1)*].

7.4 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of atorvastatin calcium tablets with gemfibrozil should be avoided [see *Warnings and Precautions (5.1)*].

7.5 Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, atorvastatin calcium tablets should be administered with caution when

used concomitantly with other fibrates [see *Warnings and Precautions (5.1)*].

7.6 Niacin

The risk of skeletal muscle effects may be enhanced when atorvastatin calcium tablets are used in combination with niacin; a reduction in atorvastatin calcium tablets dosage should be considered in this setting [see *Warnings and Precautions (5.1)*].

7.7 Rifampin or other Inducers of Cytochrome P450 3A4

Concomitant administration of atorvastatin calcium tablets with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin calcium tablets with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin

When multiple doses of atorvastatin calcium tablets and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

7.9 Oral Contraceptives

Co-administration of atorvastatin calcium tablets and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol [see *Clinical Pharmacology (12.3)*]. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

7.10 Warfarin

Atorvastatin calcium tablets had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

7.11 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Atorvastatin calcium tablets are contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy. Lipid lowering drugs offer no benefit during pregnancy because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports

of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2) [see *Contraindications, Pregnancy (4.3)*].

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Statins may cause fetal harm when administered to a pregnant woman. Atorvastatin calcium tablets should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking atorvastatin, it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women requiring atorvastatin treatment should be advised not to nurse their infants [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness in patients 10–17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin calcium tablets had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10–17 years) (6.3)*; and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10–17 years of age) (2.2)*]. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin calcium tablets have not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients [see *Clinical Studies, Homozygous Familial Hypercholesterolemia (14.5)*].

8.5 Geriatric Use

Of the 39,828 patients who received atorvastatin calcium tablets in clinical studies, 15,813 (40%) were ≥65 years old

and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

Atorvastatin calcium tablets are contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Pharmacokinetics (12.3)*].

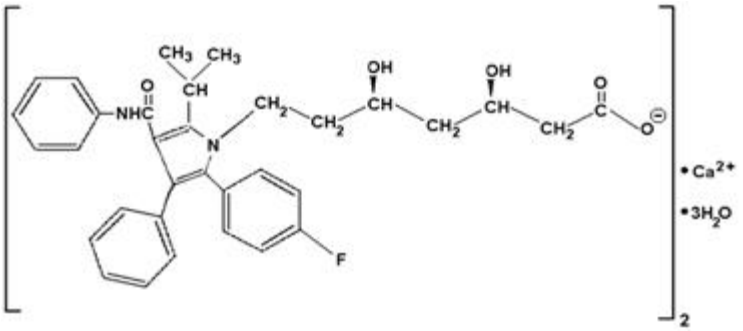
10 OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

11 DESCRIPTION

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that

converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

Atorvastatin calcium, as well as some of its metabolites, is pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response [see *Dosage and Administration (2)*].

12.3 Pharmacokinetics

Absorption: Atorvastatin calcium tablets are rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin calcium dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin calcium tablets are given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see *Dosage and Administration (2)*].

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk [see *Contraindications, Nursing Mothers (4.4)* and *Use in Specific Populations, Nursing Mothers (8.3)*].

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin calcium tablets is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary [see *Dosage and Administration, Dosage in Patients with Renal Impairment (2.5)*, *Warnings and Precautions, Skeletal Muscle (5.1)*].

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see *Contraindications (4.1)*].

TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin	
		Change in

	Dose (mg)	Change in AUC*	Cmax*
†Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑10.7 fold
†Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
†Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10.6 fold
†,‡Saquinavir 400 mg BID/ ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
†Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
†Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
†Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
†Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
†Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
†Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
†Grapefruit Juice, 240 mL QD §	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QID, 2 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%¶
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
†Rifampin 600 mg QD, 7 days (co-administered) #	40 mg SD	↑ 30%	↑ 2.7 fold
†Rifampin 600 mg QD, 5 days (doses separated) #	40 mg SD	↓ 80%	↓ 40%
†Gemfibrozil 600mg BID, 7 days	40mg SD	↑ 35%	↓ Less than 1%
†Fenofibrate 160mg QD, 7 days	40mg SD	↑ 3%	↑ 2%
Boceprevir 800 mg TID, 7 days	40 mg SD	↑2.30 fold	↑2.66 fold

* Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

† See Sections 5.1 and 7 for clinical significance.

‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

§ Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL – 1.2 liters per day).

¶ Single sample taken 8–16 h post dose.

Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		

	Drug/Dose (mg)	Change in AUC	Change in Cmax
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	* Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1mg - ethinyl estradiol 35µg	 ↑ 28% ↑ 19%	 ↑ 23% ↑ 30%
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	↓ 18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

* See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0–24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

14 CLINICAL STUDIES

14.1 Prevention of Cardiovascular Disease

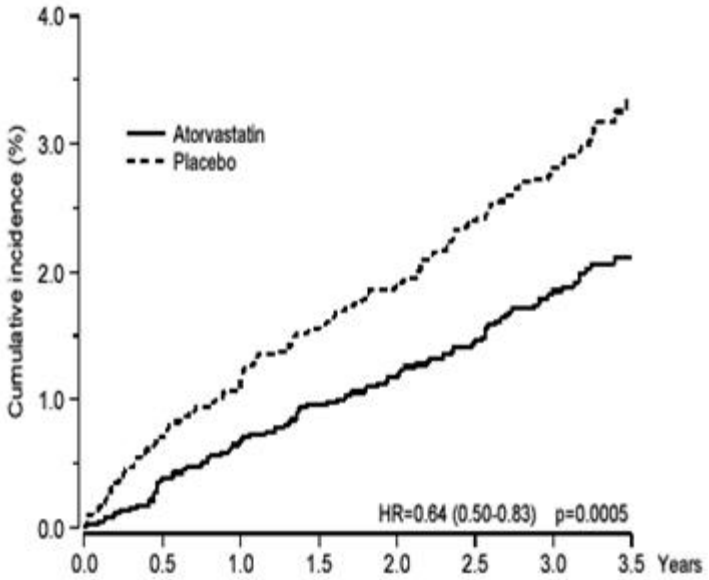
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and non-fatal

coronary heart disease was assessed in 10,305 hypertensive patients 40–80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients; <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin calcium tablets 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin calcium tablets on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin calcium tablets group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium tablets group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin calcium tablets vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin calcium tablets and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40–75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were

enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin calcium tablets 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

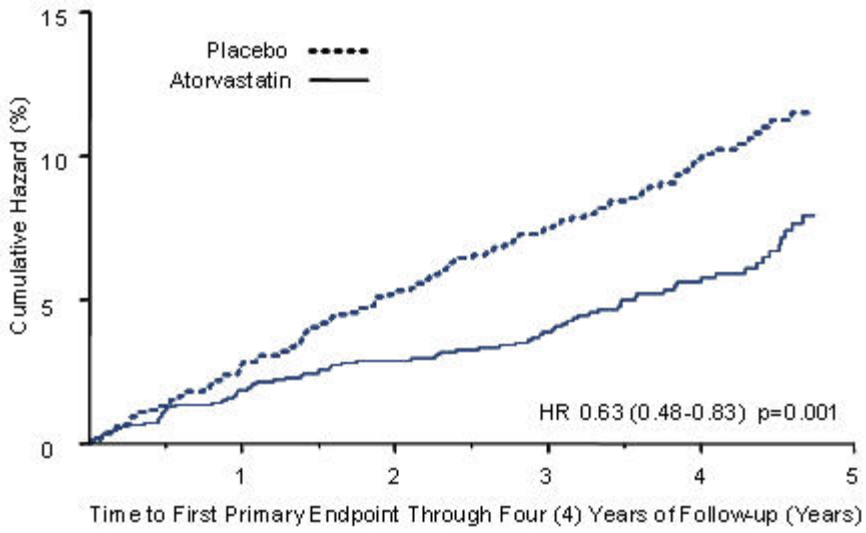
The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin calcium tablets group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 2). An effect of atorvastatin calcium tablets was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin significantly reduced the risk of stroke by 48% (21 events in the atorvastatin calcium tablets group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium tablets group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin calcium tablets group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

Figure 2: Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In the Treating to New Targets Study (TNT), the effect of atorvastatin calcium tablets 80 mg/day vs. atorvastatin calcium tablets 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin calcium tablets 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium tablets and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin calcium tablets and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin calcium tablets.

Treatment with atorvastatin calcium tablets 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69,

0.89), p=0.0002 (see Figure 3 and Table 5). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

Figure 3: Effect of Atorvastatin 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

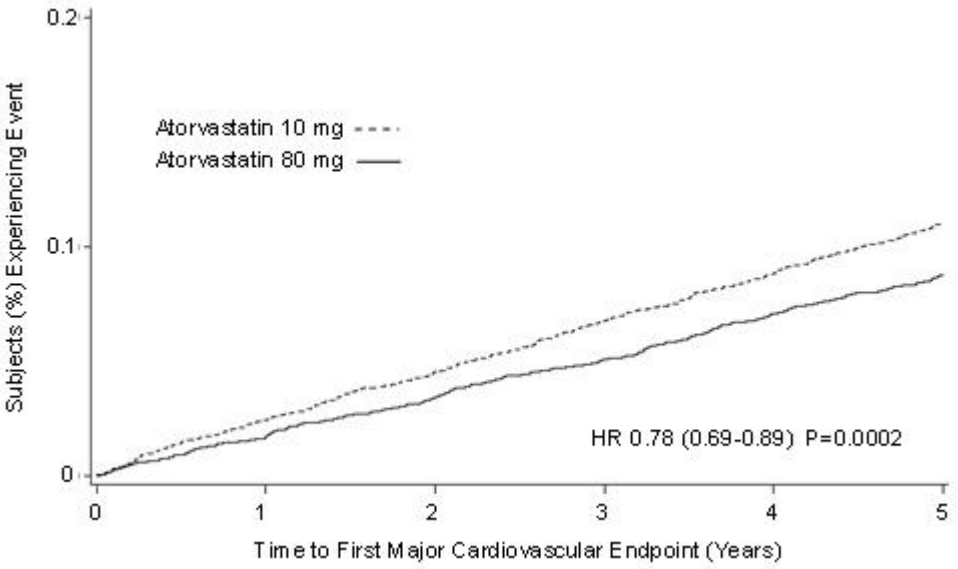


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR* (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS†					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure‡	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint‡	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV					

death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

* Atorvastatin 80 mg: atorvastatin 10 mg

† Secondary endpoints not included in primary endpoint

‡ Component of other secondary endpoints

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin calcium tablets 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 5). Of the predefined secondary endpoints, treatment with atorvastatin calcium tablets 80 mg/day significantly reduced the rate of coronary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 5). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the atorvastatin calcium tablets 80 mg group than in the atorvastatin calcium tablets 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin calcium tablets 80 mg group than in the atorvastatin calcium tablets 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin calcium tablets 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of atorvastatin calcium tablets and 105, 179, 142, 47, and 132 mg/dL during treatment with 20–40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin calcium tablets 80 mg/day group vs. 463 (10.4%) in the simvastatin 20–40 mg/day group, HR 0.89, 95% CI (0.78, 1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the atorvastatin calcium tablets 80 mg/day group vs. 374 (8.4%) in the simvastatin 20–40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin calcium tablets 80 mg group and the simvastatin 20–40 mg group.

14.2 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (*Fredrickson* Types IIa and IIb)

Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin calcium tablets are effective in a wide variety of patient populations with hyperlipidemia, with and without hypertriglyceridemia, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, atorvastatin calcium tablets given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 6.)

TABLE 6. Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)*

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

* Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25^{th} and 75^{th} percentile) percent changes from baseline in HDL-C for atorvastatin calcium tablets 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hyperlipidemia, atorvastatin was compared to other statins. After randomization, patients were treated for 16 weeks with either atorvastatin calcium tablets 10 mg per day or a fixed dose of the comparative agent (Table 7).

TABLE 7. Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27*	-36*	-28*	-17*	+7	-37*
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff†		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25‡	-35‡	-27‡	-17‡	+6	-36‡
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff†		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29§	-37§	-34§	-23§	+7	-39§
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff†		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

* Significantly different from lovastatin, ANCOVA, $p \leq 0.05$

† A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.

‡ Significantly different from pravastatin, ANCOVA, $p \leq 0.05$

§ Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 7 is

not known. Table 7 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

14.3 Hypertriglyceridemia (*Fredrickson* Type IV)

The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 8). For the atorvastatin calcium tablets-treated patients, median (min, max) baseline TG level was 565 (267–1502).

TABLE 8. Combined Patients With Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N=12)	atorvastatin 10 mg (N=37)	atorvastatin 20 mg (N=13)	atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

14.4 Dysbetalipoproteinemia (*Fredrickson* Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia *(Fredrickson* Type III) are shown in the table below (Table 9).

TABLE 9. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (Fredrickson Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	atorvastatin 10 mg	atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin calcium tablets. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10–17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to atorvastatin calcium tablets (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin calcium tablets for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the atorvastatin calcium tablets group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of atorvastatin calcium tablets (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium tablets-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 10).

TABLE 10. Lipid-altering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0–385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

15 REFERENCES

[1]National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, *Pediatrics.* 89(3):495–501. 1992.

16 HOW SUPPLIED/STORAGE AND HANDLING

10 mg tablets: coded "PD 155" on one side and "10" on the other.
NDC 59762-0155-1 bottles of 90
NDC 59762-0155-2 bottles of 1000

20 mg tablets: coded "PD 156" on one side and "20" on the other.
NDC 59762-0156-1 bottles of 90
NDC 59762-0156-2 bottles of 1000

40 mg tablets: coded "PD 157" on one side and "40" on the other.
NDC 59762-0157-1 bottles of 90

NDC 59762-0157-2 bottles of 500

80 mg tablets: coded "PD 158" on one side and "80" on the other.
NDC 59762-0158-1 bottles of 90
NDC 59762-0158-2 bottles of 500

Storage

Store at controlled room temperature 20 – 25°C (68 – 77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Patients taking atorvastatin calcium tablets should be advised that cholesterol is a chronic condition and they should adhere to their medication along with their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program as appropriate, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with atorvastatin /see *Warnings and Precautions (5.1)*/. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking atorvastatin calcium tablets.

17.1 Muscle Pain

All patients starting therapy with atorvastatin calcium tablets should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing atorvastatin calcium tablets. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

It is recommended that liver enzyme tests be performed before the initiation of atorvastatin calcium tablets and if signs or symptoms of liver injury occur. All patients treated with atorvastatin calcium tablets should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. .

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using atorvastatin calcium tablets. Discuss future pregnancy plans with your patients, and discuss when to stop atorvastatin calcium tablets if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking atorvastatin calcium tablets and call their healthcare professional.

17.4 Breast-feeding

Women who are breastfeeding should be advised to not use atorvastatin calcium tablets. Patients who have a lipid disorder and are breast-feeding, should be advised to discuss the options with their healthcare professional.

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PATIENT INFORMATION

Atorvastatin Calcium Tablets

Read the Patient Information that comes with atorvastatin calcium tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

If you have any questions about atorvastatin calcium tablets, ask your doctor or pharmacist.

What Are Atorvastatin Calcium Tablets?

Atorvastatin calcium is a prescription medicine that lowers cholesterol in your blood. It lowers the LDL-C ("bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. Atorvastatin calcium tablets are for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

Atorvastatin calcium tablets can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:

- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

Atorvastatin calcium tablets can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

- eye problems, kidney problems, smoking, or high blood pressure.

Atorvastatin calcium tablets start to work in about 2 weeks.

What is Cholesterol?

Cholesterol and triglycerides are fats that are made in your body. They are also found in foods. You need some cholesterol for good health, but too much is not good for you. Cholesterol and triglycerides can clog your blood vessels. It is especially important to lower your cholesterol if you have heart disease, smoke, have diabetes or high blood pressure, are older, or if heart disease starts early in your family.

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take atorvastatin calcium tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium tablets may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast feeding**.** Atorvastatin calcium tablets can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

Atorvastatin calcium tablets have not been studied in children under 10 years of age.

Before You Start Atorvastatin Calcium Tablets

Tell your doctor if you:

- have muscle aches or weakness

drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with atorvastatin calcium tablets. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:
- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist.

How Should I Take Atorvastatin Calcium Tablets?
- Take atorvastatin calcium tablets exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium tablets without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium tablets. Your dose of atorvastatin calcium tablets may be changed based on these blood test results.
- Take atorvastatin calcium tablets each day at any time of day at about the same time each day. Atorvastatin calcium tablets can be taken with or without food.
  Don't break atorvastatin calcium tablets before taking.
- Your doctor should start you on a low-fat diet before giving you atorvastatin calcium tablets. Stay on this low-fat diet when you take atorvastatin calcium tablets.
- If you miss a dose of atorvastatin calcium tablets, take it as soon as you remember. Do not take atorvastatin calcium tablets if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of atorvastatin calcium tablets at the same time.
- If you take too much atorvastatin calcium tablets or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking Atorvastatin Calcium Tablets?
- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking atorvastatin calcium tablets right away and call your doctor.

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or atorvastatin calcium tablets are stopped.

These serious side effects include:
- **Muscle problems.** Atorvastatin calcium tablets can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with atorvastatin calcium tablets.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium tablets, and if you have symptoms of liver problems while you take atorvastatin calcium tablets. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite

- upper belly pain
- dark amber colored urine
- yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual. This may be an early sign of a rare muscle problem.
- muscle problems that do not go away even after your doctor has advised you to stop taking atorvastatin calcium tablets. Your doctor may do further tests to diagnose the cause of your muscle problems.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium tablets: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with atorvastatin calcium tablets: tiredness, tendon problems, memory loss, and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of atorvastatin calcium tablets. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets?

- Store atorvastatin calcium tablets at room temperature, 68 to 77°F (20 to 25°C).
- Do not keep medicine that is out of date or that you no longer need.
- **Keep atorvastatin calcium tablets and all medicines out of the reach of children.** Be sure that if you throw medicine away, it is out of the reach of children.

General Information about Atorvastatin Calcium Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium tablets for a condition for which it was not prescribed. Do not give atorvastatin calcium tablets to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about atorvastatin calcium tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium tablets that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

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APPENDIX F. 747-209 PROTOCOL VERSION 2 SUMMARY OF CHANGES

Background

Protocol 747-209 has been prepared as a Phase 2 trial to evaluate the effect of OCA on LDL metabolism in subjects with biopsy-confirmed NASH and to assess the ability of atorvastatin to modulate this effect.

Protocol 747-209 Version 2 (dated 22 October 2015) incorporates suggestions made by the FDA regarding the 747-303 protocol that are also relevant to this study.

Rationale

Protocol 747-209 Version 2 has been prepared to:

1. Clarify stopping rules for subjects presenting with a CTCAE of ≥Grade 3, per FDA's comments on the 747-303 protocol.
2. Clarify that subjects discontinued due to significant drug-induced liver injury will be followed until the AE has resolved, stabilized, or is not of clinical concern.
3. Clarify atorvastatin safety profile.
4. Include a description for the cardiovascular events adjudication committee, and add Appendix D to define major cardiovascular events.

In addition, Protocol 747-209 Version 2 also:

1. Clarifies contraception requirements.
2. Adds additional exploratory objectives: markers of cardiovascular safety
3. Clarifies exclusion criteria related to chronic liver diseases at Screening.
4. Removes the requirement that a study site must have prior experience treating patients with NASH to participate in this study.
5. Clarifies PD assessments; markers of inflammation, fibrosis, and apoptosis; and PK assessments in the Schedule of Study Procedures tables, and in the text.
6. Clarifies timepoints for PK blood sample collection.
7. Corrects the title of Appendix A to reflect ACA/AHA guidance for the use of statins.

Summary of Changes

The following revisions were made to the protocol in Protocol Version 2.

Note: (1) Revised text in Version 2 is indicated in bold font, and the text deleted from the Original protocol is crossed out in the table below. (2) Minor/editorial changes, including additional abbreviations defined are not listed individually in the summary table below.

Section	Original Text (Original protocol)	Revised Text (Version 2)
Global changes (throughout document)		*CK-18-M65 added in addition to CK-18-M30 assessment as a marker for hepatic apoptosis and fibrosis under Exploratory Endpoints*
		Data and Safety Monitoring Committee (DSMC) changed to Data Monitoring Committee (DMC)
Study Personnel Contact Information (Cover Page)	~~Emergency Contact Information~~ Medical Monitor ~~– 24-hour Emergency Reporting~~ Contact: Roya Hooshmand-Rad, MD PhD, Executive Director, Clinical Research Intercept Pharmaceuticals, Inc. (Intercept) ~~Telephone: +1 844 250 6396~~ Email: rhooshmand-rad@interceptpharma.com ~~SAE Fax: + 1 800 497 8521~~ ~~SAE Email: sae@interceptpharma.com~~ ~~Or if Not Available:~~	Medical Monitor **Investigators are encouraged to call the NASH medical monitor hotline at +1 844 250 6396 or send an email to the NASH medical monitor at NASH209@interceptpharma.com with safety questions as these lines of contact are monitored 24 hours a day.** **Primary Medical Monitor** Contact: Roya Hooshmand-Rad, MD PhD Executive Director, Clinical Research Intercept Pharmaceuticals, Inc. (Intercept Email: rhooshmand-rad@interceptpharma.com

Section	Original Text (Original protocol)	Revised Text (Version 2)
	Contact: Barbara Scholz, MD, Medical Director, Drug Safety Intercept Telephone: ~~+1 844 250 6396~~ Email: barbara.scholz@interceptpharma.com	**Secondary** Contact: Barbara Scholz, MD, Medical Director, Drug Safety Intercept Telephone: **+1 858 353 1350 (Pacific time zone)** Email: barbara.scholz@interceptpharma.com
Synopsis (Exploratory Objectives)	Liver biochemistry and markers of liver function: Albumin, ALP, ALT, AST, , direct bilirubin, GGT, INR, total bilirubin	Liver biochemistry and markers of liver function: Albumin, ALP **(isoenzymes)**, ALT, AST, , direct bilirubin, GGT, INR, total bilirubin *NOTE:* **ALP (isoenzyme)** *was also added to the list of laboratory assessments in Section 11.1 (Table 4) and Section 12.2.6 (Table 9).*
Synopsis (Exploratory Objectives) *And* Section 6.3 (Exploratory Objectives)		**Cardiovascular risk scores (eg, Framingham Risk Score [FRS] and Reynolds score)**
Synopsis (Methodology) *And* Section 7.1 Overall Study Design (Double-Blind Phase)		**Subjects who discontinue investigational product or atorvastatin during the double-blind phase are still expected to attend scheduled study visits and are to be followed through the Week 16 Visit.** **Subjects who discontinue atorvastatin during the double-blind phase are eligible to continue OCA during the double-blind phase and enroll into the LTSE at the discretion of the Investigator, provided they continue to meet exclusion criteria #4 (LDL <200 mg/dL).**

Section	Original Text (Original protocol)	Revised Text (Version 2)
Synopsis (Study Design Diagram) *And* Section 7.1.1 Study Design, Figure 1		*Footnote Added:* **Δ = Telephone safety contact at Week 6, Week 10, and Week 14**
Synopsis (Key Inclusion Criteria) *And* Section 8.2 Subject Inclusion Criteria	6. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during ~~both the double-blind and LTSE phases of~~ the study and ~~4 weeks~~ following the last dose of investigational product o~~r at study termination (whichever is greater)~~. Effective methods of contraception are considered to be those listed ~~as follows:~~ •Double-barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~; or~~ •Intrauterine device~~; or~~ •Vasectomy (partner)~~; or~~ •Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)~~; or~~ •Abstinence~~, if in line with the preferred and usual lifestyle of the subject~~	6. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and **until 30 days** following the last dose of investigational product. Effective methods of contraception are considered to be those listed **below.** •Double-barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide •Intrauterine device •Vasectomy (partner) •Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection) •Abstinence **(defined as refraining from heterosexual intercourse)**
Synopsis (Key Exclusion Criteria) *And* Section 8.3 Subject Exclusion Criteria	3.LDL cholesterol ~~>190~~ mg/dL and already on statin therapy at Screening Visit 1.	3.LDL cholesterol **≥190** mg/dL and already on statin therapy at Screening Visit 1.
	10. Evidence of other forms of chronic liver disease including but not limited to: •~~Concomitant hepatitis B or C virus infection~~ •	10. Evidence of other forms of chronic liver disease including but not limited to: **•Positive test result at Screening for hepatitis B surface antigen or hepatitis C antibody (and positive hepatitis C virus [HCV] ribonucleic acid [RNA])**

Section	Original Text (Original protocol)	Revised Text (Version 2)
	11. ~~Presence of clinically significant hepatic decompensation, including:~~ •History of liver transplant, current placement on a liver transplant list, or current Model for End-Stage Liver Disease (MELD) score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (eg, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria. ~~•History (within the past 12 months) or presence of:~~ ~~oVariceal bleed~~ ~~oUncontrolled ascites~~ ~~oHepatic encephalopathy~~ ~~oSpontaneous bacterial peritonitis~~ ~~oHepatorenal or hepatopulmonary syndromes~~	11. History of liver transplant, current placement on a liver transplant list, or current Model for End-Stage Liver Disease (MELD) score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (eg, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.
		12. Presence of hepatic decompensation, including: **- Gastroesophageal varices** **- Ascites** - Hepatic encephalopathy - Spontaneous bacterial peritonitis - Hepatorenal or hepatopulmonary syndromes
	14. Creatine phosphokinase >5x ULN at ~~any~~ Screening visit.	14. Creatine phosphokinase >5x ULN at Screening Visit **2**.
	19a. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting)	19a. **Peripheral or** Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting)
		Note: Exclusion criteria numbered 12 through 27 in the Original Protocol updated to numbers 13 through 28 in Version 2 as a result of new exclusion criteria number 12 above.

<table>
<tr><th>Section</th><th>Original Text (Original protocol)</th><th>Revised Text (Version 2)</th></tr>
<tr><td>Synopsis (Statistical Methods)</td><td>Secondary Endpoints<table><tr><td>Safety and tolerability</td><td>TEAEs, physical exams, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)</td></tr></table></td><td>Secondary Endpoints<table><tr><td>Safety and tolerability</td><td>TEAEs (including cardiovascular events), physical exams, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)</td></tr></table></td></tr>
<tr><td>Synopsis (Statistical Methods)
<u>And</u>
Section 11.1 Efficacy Assessments (Table 4)</td><td>Exploratory Endpoints<table><tr><td>Liver biochemistry and markers of liver function</td><td>Albumin, ALP, ALT, AST, ~~creatinine,~~ GGT, total bilirubin, ~~conjugated (~~direct~~)~~ bilirubin, INR</td></tr><tr><td>Marker for hepatic apoptosis and fibrosis</td><td>CK-18-M30</td></tr></table></td><td>Exploratory Endpoints<table><tr><td>Liver biochemistry and markers of liver function</td><td>Albumin, ALP, ALT, AST, direct bilirubin, GGT, INR, total bilirubin</td></tr><tr><td>Marker for hepatic apoptosis and fibrosis</td><td>CK-18-M30 and CK-18-M65</td></tr><tr><td>Cardiovascular risk scores</td><td>FRS and Reynolds scores</td></tr></table></td></tr>
<tr><td>Synopsis (Sample Size Justification)
<u>And</u>
Section 13.2 Determination of Sample Size</td><td>It is the intent of this study to characterize the components of LDL metabolism (cholesterol concentration, particle size, particle concentration) 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 ~~U/L~~ increase from baseline with a standard deviation of ~~20~~ in LDL in the OCA 25 mg group, a sample size of 20 subjects per group will provide greater than ~~99.9%~~ power to demonstrate the statistically significant difference of LDL increase from baseline with a 2-sided type I error of 0.05</td><td>It is the intent of this study to characterize the components of LDL metabolism (cholesterol concentration, particle size, particle concentration) 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, 22 mg/dL increase from baseline with a standard deviation of 24 in LDL in the OCA 25 mg group without atorvastatin therapy after 16 weeks of treatment based on data from FLINT, a sample size of 20 subjects per group will provide greater than 97.3% power to demonstrate the statistically significant difference of LDL increase from baseline with a 2-sided type I error of 0.05.</td></tr>
<tr><td>Section 5.6.4.1 Rationale for</td><td>At risk subjects include subjects with existing cardiovascular disease (including but not limited to stable or unstable angina, previous myocardial infarction or</td><td>At risk subjects include subjects with existing cardiovascular disease (including but not limited to stable or unstable angina, previous myocardial infarction or stroke or a previous</td></tr>
</table>

Section	Original Text (Original protocol)	Revised Text (Version 2)
statin withdrawal (Paragraph 5)	stroke or a previous coronary revascularization procedure), significant dyslipidemia (as defined by LDL ~~>190~~ mg/dL) despite the use of statin therapy, unstable hypertension, and familial hypercholesterolemia.	**peripheral or** coronary revascularization procedure), significant dyslipidemia (as defined by LDL **≥190** mg/dL) despite the use of statin therapy, unstable hypertension, and familial hypercholesterolemia
Section 5.8. Summary of Known Potential Risks with Atorvastatin	*(Section 5.8 added to Version 2)*	**Muscle complaints are the most frequent adverse reports among patients treated with statins, with the most severe side effects including myopathy and rhabdomyolysis. The Statin Muscle Safety Task Force (Rosenson 2014) has provided a classification of the spectrum of statin-associated muscle AEs that may be seen in clinical practice and can be used in characterizing reports of muscle-related events.** **a. Myalgia – unexplained muscle discomfort often described as "flu-like" symptoms** – **Muscle aches** – **Muscle soreness** – **Muscle stiffness** – **Muscle tenderness** – **Muscle cramps with or shortly after exercise (not nocturnal cramping)** **b. Myopathy – muscle weakness (not attributed to pain and not necessarily associated with elevated CPK)** **c. Myositis – muscle inflammation** **d. Myonecrosis – muscle enzyme elevations or hyperCPKemia** – **Mild >3x baseline or ULN** – **Moderate ≥10x baseline or ULN** – **Severe ≥50x baseline or ULN**

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		e. Clinical Rhabdomyolysis - Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine ≥0.5 mg/dL **There is no evidence that these muscle-related AEs are a continuum beginning with myalgia and progressing to more severe manifestations of myopathy; rather events occur independent of each other. Myalgia events, with frequencies ranging from 1% to 5% in clinical trials to 11% to 29% in observational cohorts, typically occur within 1 month of statin initiation and resolve within 2 weeks of statin cessation (Rosenson 2014). Retrospective analyses have suggested that patients who discontinue statins due to intolerance are able to tolerate statins long-term following re-challenge (Zhang 2013, Mampuya 2013).** **Historically, statins have been associated with biochemical abnormalities of liver function, but available data suggest that increases in liver transaminases associated with statins are asymptomatic and generally reversible (Desai 2014). In the absence of liver disease, US guidelines (Stone 2013) recommend that baseline transaminase levels should be checked before initiating statin therapy and subsequent testing should only be done in the presence of symptoms suggestive of hepatic disease. As this study is being conducted in subjects with confirmed NASH, liver enzymes will be frequently monitored and Section 8.4.1.2, Section 8.4.1.3, and Appendix B provide detailed guidance for handling elevated liver biochemistry values.** **Statins modestly increase the risk of type 2 diabetes mellitus in individuals with risk factors for diabetes. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines (American Diabetes Association 2013).**

Section	Original Text (Original protocol)	Revised Text (Version 2)
		Confusion and memory loss have been reported with statins, but medical evidence supporting a causal effect is weak or nonexistent (Simic 2015). However, any reports of cognitive events should be appropriately evaluated, particularly in individuals whose symptoms persist despite statin discontinuation. **In this study, any AEs (including signs and symptoms described above) regardless of relationship to investigational product or study medication, must be documented appropriately (See Section 12)**
7.1 Overall Study Design (Table 1)		*Added* **Week 6 (Contact), Week 10 (Contact), and Week 14 (Contact)** *with associated* **X** *in AEs, Prior and Concomitant Medications, and Collect bottles/Investigational Product Accountability/Compliance; Collect Bottles/Atorvastatin Accountability/Compliance (for Week 10 and Week 14).*
		Added procedure "Hepatitis B Virus and Hepatitis C Virus Tests" at Screening Visit 1.
		Transient Elastography timepoint added: ET/EOS. *(Also, added this procedure to Section 9.7.15)*
		The list of assessments replaced with 3 broad subcategories: PD Assessments; Markers of Inflammation, Fibrosis, or Apoptosis; and Vitamin D.
		Added footnote l to Serum Chemistry
	~~Urine Based β-hCG~~ Pregnancy Test[q]	Pregnancy Test[q]
		Added hepatitis B and hepatitis C tests at Screening Visit 1
	[d] Heart rate, blood pressure, temperature, and respiratory rate	[d] **Sitting** heart rate, blood pressure, temperature, and respiratory rate

<table>
<tr><th>Section</th><th>Original Text (Original protocol)</th><th>Revised Text (Version 2)</th></tr>
<tr><td></td><td>[n] Serum samples will be collected for lipoprotein analyses…</td><td>[n] Serum and plasma samples will be collected for lipoprotein analyses…</td></tr>
<tr><td></td><td>[q] Serum pregnancy test will be administered if urine-based β-hCG pregnancy test is positive.</td><td>[q] Serum pregnancy test will be administered if urine-based β-hCG pregnancy test is positive. Screening pregnancy tests will be serum-based tests.</td></tr>
<tr><td></td><td>[r] <s>Blood sample for future exploratory analysis, including</s> markers of cardiovascular risk (adiponectin, plasminogen activator inhibitor-[(PAI-1], and B-type natriuretic peptide [BNP]).</td><td>[r] Includes markers of cardiovascular risk (adiponectin, plasminogen activator inhibitor-[(PAI-1], and B-type natriuretic peptide [BNP]).</td></tr>
<tr><td></td><td>[s] At selected investigational sites, subjects will have the option to provide blood samples for measurement of OCA PK.</td><td>[s] At selected investigational sites, subjects will have the option to provide blood samples for measurement of OCA PK. PK samples will be collected within 30 minutes prior to dosing and again 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.</td></tr>
<tr><td rowspan="4">7.1
Overall Study Design
(Table 2)</td><td rowspan="2">Header row updated as follows<table><tr><td>Month 3</td><td>Month 6</td><td>Month 9</td></tr></table></td><td><table><tr><td>Month 3,
Month 15</td><td>Month 6,
Month 18</td><td>Month 9,
Month 21</td></tr></table></td></tr>
<tr><td>The list of assessments replaced with 3 broad subcategories: PD Assessments; Markers of Inflammation, Fibrosis, or Apoptosis; and Vitamin D.</td></tr>
<tr><td></td><td>Additional timepoints added as follows:
AUDIT alcohol measures: EOS/ET
(Also, added this procedure to Section 9.7.20.)</td></tr>
<tr><td></td><td>Timepoints removed as follows:
Reverse Cholesterol Transport analysis: Month 3, Month 9, Month 15, and Month 21.</td></tr>
</table>

Section	Original Text (Original protocol)	Revised Text (Version 2)
	[d] Heart rate, blood pressure, temperature, and respiratory rate.	[d] **Sitting** heart rate, blood pressure, temperature, and respiratory rate.
		[i] **NOTE: Any time atorvastatin is up-titrated or re-initiated, a telephone safety contact must be conducted to assess AEs, concomitant medications, and atorvastatin compliance.**
		All subsequent footnotes have been adjusted by one
7.4.2 Atorvastatin Dose Adjustments		*Added:* **If at any time during the double-blind or LTSE phases, serum chemistry results indicate LDLc <40 mg/dL, the subject should be brought back to the site within 1 to 2 weeks after the first result is obtained for an unscheduled (repeat) laboratory assessment. If LDLc <40 mg/dL is obtained on 2 consecutive visits, the subject may discontinue or reduce the dose of atorvastatin.** **Subjects may also interrupt or discontinue atorvastatin due to tolerability issues including muscle-related symptoms (Section 5.8) and abnormal liver biochemistry. Any muscle-related complaints should be assessed per the ACC/AHA Guidelines (Appendix A) and statin dose adjusted accordingly:** • **To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline prior to initiation of statin therapy.** • **If mild to moderate muscle symptoms develop during statin therapy:**

Section	Original Text (Original protocol)	Revised Text (Version 2)
		○ **Discontinue the statin until symptoms can be evaluated.** ○ **Evaluate the patient for other conditions that might increase the risk for muscle symptoms.** ○ **If muscle symptoms resolve, and if no contraindication exists, re-challenge the subject with the same or a reduced dose of atorvastatin to establish a causal relationship between the muscle symptoms and statin therapy.** ○ **Once a low dose statin is tolerated, the dose may be gradually increased as tolerated and clinically indicated.** ○ **If after 2 months without statin treatment, muscle symptoms or elevated CPK levels do not completely resolve, consider other causes of muscle symptoms.** ○ **If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.** • **If unexplained severe muscle symptoms or fatigue develop during statin therapy, discontinue the statin and address the possibility of rhabdomyolysis by evaluating CPK and**

Section	Original Text (Original protocol)	Revised Text (Version 2)
		creatinine, and performing urinalysis for myoglobinuria. **Elevations in liver biochemistry should be monitored per protocol subject withdrawal criteria (Section 8.4 and Appendix B).** **Subjects who discontinue atorvastatin may continue on investigational product through the double-blind and LTSE phases, as deemed appropriate by the Investigator and Medical Monitor, and provided they continue to meet exclusion criteria #4 (LDL <200 mg/dL).**
8.1 Subject Population	Approximately 80 subjects with biopsy-confirmed NASH without evidence of hepatic decompensation who meet eligibility criteria will be enrolled at approximately 30 investigational sites in the US ~~with experience in treating patients with NASH~~.	Approximately 80 subjects with biopsy-confirmed NASH without evidence of hepatic decompensation who meet eligibility criteria will be enrolled at approximately 30 investigational sites in the US.
8.4 Subject Withdrawal Criteria	*Subsections were rearranged as follows:* 8.4.1 Reasons for Mandatory Discontinuation of Investigational Product ~~8.4.1.1~~ Pregnancy ~~8.4.1.2~~ Severe Drug-Induced Liver Injury ~~8.4.1.3 Clinical Laboratory Values~~	8.4.1 Reasons for Mandatory Discontinuation of Investigational Product **or Atorvastatin** **8.4.1.1 Adverse Events ≥Grade 3 in Severity and Possibly, Probably, or Definitely Related to Investigational Product** **8.4.1.2** Pregnancy **8.4.1.3** Severe Drug-Induced Liver Injury **8.4.1.4 Myonecrosis** **8.4.2 Reasons for Mandatory Interruption of Investigational Product** **8.4.2.1 Adverse Events ≥Grade 4 in Severity and Not or Unlikely Related to Investigational Product** **8.4.2.2 Suspected Mild or Moderate Drug-Induced Liver Injury**

Section	Original Text (Original protocol)	Revised Text (Version 2)
	~~8.4.2~~ Other Reasons for Study or Treatment Discontinuation of Subjects ~~8.4.3~~ Subject Discontinuation Notification	**8.4.3** Other Reasons for Study or Treatment Discontinuation of Subjects **8.4.4** Subject Discontinuation Notification
8.4.1.1 Adverse Events ≥Grade 3 in Severity…		**If a subject experiences an AE that is ≥Grade 3 in severity (Section 12.1.4) that is considered possibly, probably, or definitely related to investigational product, the investigational product must be discontinued.**
8.4.1.2 Pregnancy	Whenever the site is notified of a possible pregnancy, the subject should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female subject becomes pregnant, ~~the subject must stop taking~~ investigational product immediately ~~and be withdrawn from the study. The subject~~ must be followed by the Investigator through pregnancy outcome. The mother (and infant) will be followed as considered appropriate by the Investigator and the Medical Monitor. ~~For reporting purposes,~~ pregnancy is not considered an AE.	Whenever the site is notified of a possible pregnancy, the subject should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female subject becomes pregnant, **she must discontinue treatment with** investigational product **and atorvastatin** immediately**, but should continue with the study visit schedule and** must be followed by the Investigator through pregnancy outcome. The mother (and infant) will be followed as considered appropriate by the Investigator and the Medical Monitor. **As described in Section 12.1.8.1**, pregnancy is not considered an AE **for reporting purposes.**
8.4.1.3 Severe Drug-Induced Liver Injury (Paragraph 2)	~~Subjects should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time.~~	**Subjects who discontinue due to significant drug-induced liver injury must be followed until the AE has resolved, stabilized, or is not of clinical concern.**
8.4.1.4 Myonecrosis		**Moderate myonecrosis as defined by creatine kinase ≥10x the untreated baseline levels or ULN. Muscle-related symptoms that do not necessitate mandatory discontinuation of investigational product or atorvastatin are detailed in Section 5.8.**
8.4.2.1 Adverse Events		**If a subject experiences an AE categorized as ≥Grade 4 in severity and not or unlikely related to investigational**

Section	Original Text (Original protocol)	Revised Text (Version 2)
≥Grade 4 in Severity and...		**product, at least a mandatory interruption of investigational product is required.**
8.4.2.2 Suspected Mild or Moderate Drug-Induced Liver Injury	*Deleted Section 8.4.1.3. (Clinical Laboratory Values) of the Original Protocol, and replaced with **Section 8.4.2.2** (new text shown in the right column).* ~~Development of the following clinical laboratory values during the course of the double-blind and LTSE phases of the study mandates investigational product discontinuation:~~ ~~•An aminotransferase (aspartate aminotransferase [AST] or ALT) elevation that is > 3x ULN/baseline/nadir, or~~ ~~•Total bilirubin >1.5 mg/dL (25.7 µmol/L) AND >2x the predose value (average of all pretreatment values), or~~ ~~•When myopathy is diagnosed or suspected (confirm with CPK prior to permanent discontinuation; discontinue if CPK >10x ULN)~~ ~~Note: The mean of all Screening and Baseline values constitute the predose values.~~ ~~If a subject is required to discontinue investigational product due to an increase in aminotransferase or bilirubin, the subject must be followed at appropriate intervals until these parameters have returned to within the normal range or prestudy values, and/or are stable, or there is no ongoing clinical concern.~~	**Because transient fluctuations of ALT or AST are common, and progression to severe drug-induced liver injury or acute liver failure is uncommon, automatic discontinuation of investigational product with an elevation of ALT or AST that is >3x ULN/baseline/nadir or total bilirubin >2x ULN/baseline/nadir, as described in Appendix B, may be unnecessary. If a subject develops signs of a mild or moderate event of drug-induced liver injury, regardless of causality, investigational product should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule. The subject may restart treatment after resolution of the event or return to baseline. Follow-up procedures, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject will be allowed to continue treatment.**
9.2. Concomitant Medications	Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within ~~30 days~~ of Day 1) and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study.	Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within **12 months** of Day 1) and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study.

Section	Original Text (Original protocol)	Revised Text (Version 2)
9.2.3 Management of Changes in Cholesterol	During the double-blind phase of the study, the dose of atorvastatin administration should be as described in this protocol through Week 12. At the Week 12 Visit, Investigators may increase or decrease the dose of atorvastatin as clinically indicated.	During the double-blind phase of the study, the dose of atorvastatin administration should be as described in this protocol through Week 12 **unless tolerability issues develop as referenced in Section 7.4.2**. At the Week 12 Visit, Investigators may increase or decrease the dose of atorvastatin as clinically indicated.
9.2.4 Prohibited Medications *And* Table 3	•Prohibited throughout the double-blind phase of the study:	•Prohibited throughout the double-blind phase of the study: – **Medications contraindicated in the atorvastatin label, including HIV and Hepatitis C protease inhibitors, clarithromycin, and itraconazole (refer to atorvastatin prescribing information in Appendix E for complete list). These medications are also prohibited during the LTSE phase if the subject continues to receive atorvastatin during the LTSE.** *Note: These medications were also added to Table 3.*
9.4.2 Emergency Unblinding Procedures	The ~~DSMC~~ (refer to Section 13.8) will have access to the IWRS and will be able to unblind individual subjects. The ~~DSMC will be provided aggregate data to review~~ during closed sessions.	The **DMC** (refer to Section 13.8) will have access to the IWRS and will be able to unblind individual subjects. The **DMC will review aggregate data** during closed sessions.
9.6.1 Fasting Requirements at Study Visits	All subjects must have been fasting for at least 8 hours prior to Screening Visit 2 (Week -1 Visit) and all subsequent study visits, as all analytes will be assayed in fasting blood or plasma samples (Table 1 and Table 2).	All subjects must have been fasting for at least 8 hours prior to Screening Visit 2 (Week -1 Visit) and all subsequent study visits, as all analytes will be assayed in fasting blood**, serum,** or plasma samples (Table 1 and Table 2).
9.6.2 Grapefruit and Grapefruit Juice	Grapefruit and grapefruit juice consumption should be discouraged following initiation of atorvastatin ~~(please refer to atorvastatin prescribing information [reference: Appendix A])~~.	Grapefruit and grapefruit juice consumption should be discouraged following initiation of atorvastatin **due to possible increases in plasma concentration of atorvastatin** (please refer to atorvastatin prescribing information [**Appendix E]**).

Section	Original Text (Original protocol)	Revised Text (Version 2)
9.7.1 Visit Windows	The Week -1 Visit should occur within ±1 days of the ~~visit day~~.	The Week -1 Visit should occur within ±1 days of the **Randomization/Day 1 Visit**.
		(A row added to in-text table) Week 6, Week 10, and Week 14 (Contact visits) ±4 days
9.7.3 Screening Visit 1 Procedures	Subjects who are statin free (ie, no statin use within 4 weeks of Screening) must return for fasted serum chemistry labs and may proceed to the Randomization/Day 1 Visit once screening labs are available and eligibility is confirmed; subjects who need to wash out statin therapy are required to have a Week -1 Visit 4 weeks after Screening Visit 1. •Record prior (if within ~~6 months~~ of Day 1) and current concomitant medications. •~~Perform a urine-based β-hCG pregnancy test for female subjects of childbearing potential.~~ Perform serum pregnancy test in females of childbearing potential~~, if urine β-hCG pregnancy test is positive~~.	Subjects who are statin free (ie, no statin use within 4 weeks of Screening) must return for fasted serum chemistry labs **at Screening Visit 2**, and may proceed to the Randomization/Day 1 Visit once screening labs are available and eligibility is confirmed; subjects who need to wash out statin therapy are required to have a Week -1 Visit 4 weeks after Screening Visit 1. •Record prior (if within **12 months** of Day 1) and current concomitant medications. **•Obtain serum sample for hepatitis B surface antigen or hepatitis C antibody (and positive HCV ribonucleic acid [RNA]) testing to confirm study eligibility.** •Perform serum pregnancy test in females of childbearing potential.
9.7.5. Randomization/Day 1 Visit Procedures	•Record prior (~~within 30 days of Day 1~~) and current concomitant medications.	•Record prior (**since Screening Visit 1**) and current concomitant medications.
9.7.5	Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1,	Serial blood samples will be obtained for measurement of OCA and its conjugates **30 minutes** prior to dosing and at

Section	Original Text (Original protocol)	Revised Text (Version 2)
Additional Day 1 Procedures for PK Subjects *And* 9.7.13.1 Additional Week 16 Procedures for PK Subjects	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 ~~4-hour~~ sample is collected. ~~Lunch~~ will be provided following collection of the ~~4-hour~~ PK sample; the lunch will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance.	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. **Meal** will be provided following collection of the **1-hour** PK sample; the lunch will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance.
9.7.5 Randomization/Day 1 Visit Procedures *And* Sections 9.7.7, 9.7.9, 9.7.11, 9.7.13, 9.7.15, 9.7.18, 9.7.19, 9.7.20	– ~~Plasma bile acids, 7α-hydroxy-4-cholesten-3-one (C4), and FGF-19; serum IL-6, cytokeratin-18 neoepitope M30 (CK-18-M30), high-sensitivity C-reactive protein (hs-CRP), TNF-α, and Vitamin D;~~ and markers of glucose metabolism ~~(C-peptide, insulin, fasting plasma glucose, and HbA1c)~~	– **PD assessments; markers of inflammation, fibrosis and apoptosis; and markers of glucose metabolism (see Table 4 and Table 9)** – **Vitamin D**
9.7.8 (Week 6 Safety Contact) *And* 9.7.10 (Week 10 Safety Contact) *And* 9.7.12 (Week 14 Safety Contact)	*Note: The numbering of 9.7 subsections is changed in Version 2 compared to that in the Original protocol from Section 9.7.9 onwards due to the addition of new Subsections 9.7.8, 9.7 10, and 9.7.12.*	• **This is a telephone contact with the subject to** – **Review and record AEs** – **Review and record concomitant medications** – **Assess investigational product and atorvastatin compliance**

Section	Original Text (Original protocol)	Revised Text (Version 2)
9.7.18 LTSE Month 3, Month 6, Month 9, Month 15, Month 18, and Month 21 Visit Procedures *(Section 9.7.15 of Original Protocol)*	•Perform a physical examination (only at Month 3 Visit).	•Perform a physical examination (only at Month 3 **and Month 15** Visit**s**).
	•Determine alcohol consumption (using AUDIT questionnaire [only at Month 6 Visit]).	•Determine alcohol consumption (using AUDIT questionnaire [only at Month 6 **and Month 18** Visit**s**]).
	•Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability.	•Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability. – **NOTE: If atorvastatin dose is up-titrated or re-initiated after dose interruption, a telephone safety contact must be conducted 2 weeks following the change in dose to assess for AEs, concomitant medications, and investigational product and atorvastatin compliance.**
	•Obtain blood samples for: – Lipoprotein analyses ~~and~~ reverse cholesterol transport analytes	•Obtain blood samples for: – Lipoprotein analyses – Reverse cholesterol transport analytes **(only at Month 6 and Month 18 Visits)**
9.7.20 LTSE End of Study/Early Termination Procedures		**•Determine alcohol consumption (using AUDIT questionnaire).**
9.7.21 Unscheduled Safety Visits	An increase in aminotransferases (ALT or AST) to >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN) should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the	An increase in aminotransferases (ALT or AST) to >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN) should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities

Section	Original Text (Original protocol)	Revised Text (Version 2)
	abnormalities and to determine if they are increasing or decreasing.	and to determine if they are increasing or decreasing **(Appendix B)**.
10.5 Atorvastatin Tablets	Atorvastatin tablets for oral administration contain 10 mg, 20 mg, 40 mg~~, or 80 mg~~ atorvastatin…	Atorvastatin tablets for oral administration contain 10 mg, 20 mg, **and** 40 mg atorvastatin.
10.5.3 Atorvastatin Dispensation	At subsequent visits, atorvastatin will be dispensed as clinically indicated.	At subsequent visits, atorvastatin will be dispensed as clinically indicated. **For doses higher than 20 mg, subject may take multiple atorvastatin tablets for a total dose of 40 mg or 80 mg, as clinically indicated.**
11.1 Efficacy Assessments (Table 4)	*(Deleted the following row)* ~~Bile acid synthesis and concentrations~~ | ~~C4 (7α hydroxy 4 cholesten 3 one), conjugated and unconjugated bile acids (possible)~~	
11.1.1 Efficacy Laboratory Assessments	The complete list of planned laboratory assessments supporting primary, secondary, and exploratory objectives of the study is shown in Table 4, and includes parameters related to LDL metabolism, lipoprotein metabolism, reverse cholesterol transport, liver biochemistry and markers of liver function, markers of inflammation, glycemic control, and NASH disease severity marker CK-18-M30.	The complete list of planned laboratory assessments supporting primary, secondary, and exploratory objectives of the study is shown in Table 4, and includes parameters related to LDL metabolism, lipoprotein metabolism, reverse cholesterol transport, liver biochemistry and markers of liver function, markers of inflammation, glycemic control, **OCA PD markers,** and NASH disease severity marker**s** CK-18-M30 **and CK-18-M65**.
11.1.2.1 Central Reading of Liver Histology	Kleiner ~~2012~~	Kleiner **2005**
11.2 Pharmacokinetic and Pharmacodynamic Assessments		*Added the following new subsection:* **11.2.1 Pharmacodynamic Assessments**

Section	Original Text (Original protocol)	Revised Text (Version 2)
	~~11.2.1. OCA, Bile Acids, and FGF-19~~	*Original subsection 11.2.1 is now 11.2.2. and is re-named as below* **11.2.2. Pharmacokinetic Assessments**
11.2.1. Pharmacodynamic Assessments		**11.2.1. Pharmacodynamic Assessments** **PD assessments will be collected according to the Schedule of Study Procedures (Table 1 and Table 2) from all subjects to measure C4, FGF-19, and possibly conjugated and unconjugated bile acids (dependent on the results of the C4 and FGF-19 assessments).**
11.2.2 Pharmacokinetic Assessments (Paragraph 1)	~~11.2.1. OCA, Bile Acids, and FGF-19~~ Subjects who participate in the PK ~~and/or PD~~ assessment will provide blood samples for the measurement of OCA and its conjugates~~, C4, FGF-19, and possibly bile acids~~, prior to administration of investigational product (predose) on Day 1 and at the Week 16 Visit.	**11.2.2. Pharmacokinetic Assessments** Subjects who **opt to** participate in the PK assessment will provide blood samples for the measurement of OCA and its conjugates**. The first sample should be collected within 30 minutes** prior to administration of investigational product (predose) on Day 1 and at the Week 16 Visit.
11.2.2 Pharmacokinetic Assessments (Paragraph 2)	*Paragraph 2 deleted:* ~~Instructions regarding the number and type of samples, including the PK assessments, to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a study-specific laboratory manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.~~	
12.1.8.1 Pregnancy and Follow-Up	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue treatment with investigational product immediately (see Section 8.4.1.1) and the Sponsor must be	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue treatment with investigational product **and atorvastatin immediately** (see Section 8.4.1.1) and the

Section	Original Text (Original protocol)	Revised Text (Version 2)
	notified within 24 hours of the Investigator's learning of the pregnancy by completing the Pregnancy Report eCRF in the EDC system. Women who discontinue the study due to pregnancy may not re-enroll in the study at any point.	Sponsor must be notified within 24 hours of the Investigator's learning of the pregnancy by completing the Pregnancy Report eCRF in the EDC system. Women who discontinue the study due to pregnancy may not re-enroll in the study at any point, **but should continue with the study visit schedule and must be followed by the Investigator through pregnancy outcome**.
12.2.6 Laboratory Assessments (Table 9)	Serum chemistry: Albumin, BUN, creatinine, conjugated (direct) bilirubin, total bilirubin, AST, ALT, ALP, GGT, creat~~in~~ine, electrolytes (calcium, chloride, magnesium, phosphorus, potassium, sodium), total protein, bicarbonate, free fatty acids; and blood lipids (total cholesterol, LDL, HDL, and VLDL fractions and TGs)	Serum chemistry: Albumin, BUN, creatinine, conjugated (direct) bilirubin, total bilirubin, AST, ALT, ALP, GGT, creatine **phosphokinase**, electrolytes (calcium, chloride, magnesium, phosphorus, potassium, sodium), total protein, bicarbonate, free fatty acids; and blood lipids (total cholesterol, LDL, HDL, and VLDL fractions and TGs) **Hepatitis virus screening tests: Hepatitis B surface antigen, hepatitis C antibody, and HCV ribonucleic acid [RNA]**
13.6.3.8 Cardiovascular Risk Scores	*New Section 13.6.3.8 Added*	**The cardiovascular risk score includes the FRS and Reynolds scores. Each score is derived from a subject's age, sex, smoking status, total cholesterol and HDL levels, systolic blood pressure, and other factors including family history, BMI, ethnicity, and medications. Cardiovascular scores will be calculated at the time of data analysis. These markers will be summarized by treatment group using descriptive statistics at Baseline and at each on-study evaluation. The change and percentage change from Baseline will also be summarized.**

Section	Original Text (Original protocol)	Revised Text (Version 2)
13.9. Adjudication Committees		**All suspected major adverse cardiovascular events (MACE), and drug-related hepatic injury events that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The 2 committees and event types they are responsible for adjudicating are as follows:** **•Cardiovascular Events Committee (CEC): Adjudicates all suspected MACE (Appendix D)** **•Hepatic Safety Committee: Adjudicates all suspected drug-related hepatic injury events** **Each adjudication committee will have a charter that documents the reporting of events by the study site; definition of the suspected events to be adjudicated; supply of source documentation to the committee; and the entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.** **The adjudication committee members will include experts with relevant adjudication experience; they will not be involved in the study as Investigators, DMC members, or consultants. Any candidate found to have a conflict or whose name is listed on the FDA debarment list will not be offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they will be replaced.** **The adjudication of suspected events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any**

Section	Original Text (Original protocol)	Revised Text (Version 2)
		individual subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.
19. List of References		**American Diabetes Association. Standards of medical care in diabetes-2013. Diabetes Care. 2013;36(Suppl 1):S11-S66.** **Desai CS, Martin SS, Blumenthal RS. Non-cardiovascular effects associated with statins. BMJ 2014;349:g3743** **Kleiner D, Brunt E, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-1321**. **Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. Am Heart J. 2013;166:597-603.** **Rosenson RS, Baker SK, Jacobson TA et al. An assessment by the statin muscle safety task force: 2014 update. J Clin Lipid. 2014;8:S58-S71.** **Simic I, Reiner Z. Adverse effects of statins – myths and reality. Curr Pharm Des. 2015;21:1220-1226.** **Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013;158:526-534.**

Section	Original Text (Original protocol)	Revised Text (Version 2)
Appendix A	APPENDIX A. ~~EUROPEAN AND NICE~~ GUIDANCE FOR THE USE OF STATINS	**APPENDIX A. AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION** GUIDANCE FOR THE USE OF STATINS
Appendix B	For subjects who progress to cirrhosis and decompensation while participating in the study, elevation in liver biochemistry and development of other laboratory and clinical abnormalities may be expected. Clinical ~~outcomes~~ should be reported and recorded as described in Section 12.1.5 and appropriate action should be taken regarding investigational product use and study participation as described in Section 8.4. In subjects with abnormal ALT/AST or bilirubin at baseline, fold increase should be assessed against baseline levels instead of ULN as follows: 3× baseline ALT/AST ~~(and >200 IU/L)~~, or total bilirubin >2× baseline (and >2 mg/dL).	For subjects who progress to cirrhosis and decompensation while participating in the study, elevation in liver biochemistry and development of other laboratory and clinical abnormalities may be expected. Clinical **adverse events (AEs)** should be reported and recorded as described in Section 12.1.5 and appropriate action should be taken regarding investigational product use and study participation as described in Section 8.4. In subjects with abnormal ALT/AST or bilirubin at baseline, fold increase should be assessed against baseline levels instead of ULN as follows: 3× baseline ALT/AST, or total bilirubin >2× baseline (and >2 mg/dL).
Appendix D		**APPENDIX D. STANDARDIZED DEFINITIONS FOR CARDIOVASCULAR ENDPOINT EVENTS**

APPENDIX G. 747-209 PROTOCOL VERSION 3 SUMMARY OF CHANGES

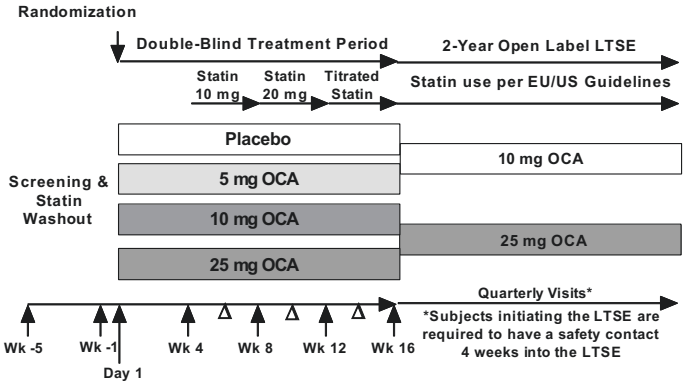
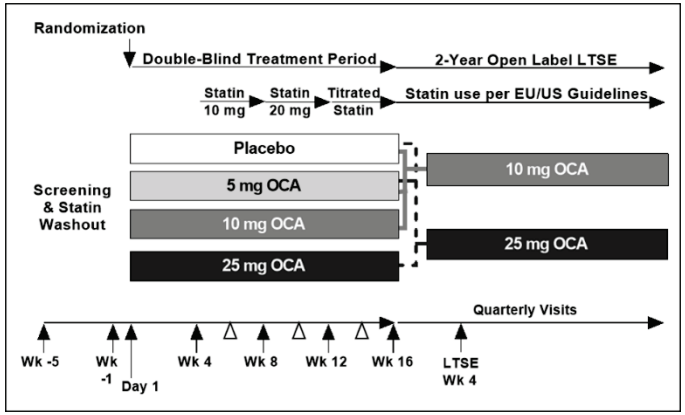
Protocol 747-209 was revised to add a modified randomization scheme to the LTSE in order to maintain the blind of the double-blind phase. The list of conjugates or metabolites of OCA for assessment was expanded to include OCA glucuronide. Additionally, various aspects of the study design and study population were clarified.

Summary of Changes

The following revisions were made to the protocol in Protocol Version 3. Revised and new text in Version 3 is indicated in bold font, and the text deleted from Protocol Version 3 is crossed out in the table below. Minor/editorial changes are not listed individually in the summary table below.

Section	Original Text	Revised Text
Global change	~~Oral~~ temperature	**Body** temperature
Global change	OCA, tauro-OCA, glyco-OCA, total OCA, potentially other conjugates or metabolites not yet identified	OCA, tauro-OCA, glyco-OCA, total OCA, **OCA glucuronide**, potentially other conjugates or metabolites not yet identified
Title Page	~~Version 2: 22 October 2015~~	**The CONTROL Study** **Combination OCA aNd STatin for MonitoRing Of Lipids** **Version 3: 14 June 2016**
Study Personnel Contact Information	Primary Medical Monitor Contact: Roya Hooshmand-Rad, MD, PhD Executive Director, Clinical Research Intercept Pharmaceuticals, Inc. (Intercept) Email: rhooshmand-rad@interceptpharma.com	**The following individual medical monitors may also be contacted through the NASH medical monitor hotline and email address.** Primary **Medical Monitor** Contact: **Emad Basta, MD** **(Lead) Medical Monitor/Medical Expert** **PRA Health Sciences** **Mobile Phone: +1 630 235 6201** **Email CONTROL@PRAHS.com** **NASH Medical Monitor Hotline: +1 844 250 6396** **NASH209@interceptpharma.com**

Section	Original Text	Revised Text
	Secondary Contact: Barbara Scholz, MD Medical Director, Drug Safety Intercept ~~Telephone~~**:** +1 858 353 1350 (Pacific time zone) Email: barbara.scholz@interceptpharma.com	**Email** Secondary Contact**:** Roya Hooshmand-Rad, MD, PhD Executive Director, Medical Safety and Pharmacovigilance Intercept Pharmaceuticals, Inc. (Intercept) **Mobile Phone:** **+1 858 880 6485 (Pacific time zone)** Email: rhooshmand-rad@interceptpharma.com Secondary Contact: Barbara Scholz, MD Medical Director, Drug Safety Intercept **Mobile Phone:** +1 858 353 1350 (Pacific time zone) Email: barbara.scholz@interceptpharma.com
Synopsis Objectives, 6.3 Exploratory Objectives	To evaluate improvement in noninvasive-radiological assessment of fibrosis via transient elastography (TE; at sites where available~~, and evaluated at the end of LTSE~~)	To evaluate improvement in noninvasive-radiological assessment of fibrosis via transient elastography (TE; at sites where available)
Synopsis Methodology, 7.1 Overall Study Design	Statin-treated subjects will be required to stop statin treatment (after signing informed consent) for ~~a total of~~ 5 weeks prior to randomization. <u>Screening Period:</u> Subjects using statins within 30 days of the initial Screening visit (Screening Visit 1) are required to stop statin therapy immediately following this initial visit and must undergo a 4-week statin washout period. ~~One week prior to randomization (Screening Visit 2; Week -1)~~, these subjects will have a pre-randomization visit for assessment of their fasting LDL cholesterol levels.	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 **R**andomization/**Day1**. <u>Screening Period:</u> Subjects using statins within 30 days of the initial Screening visit (Screening Visit 1) are required to stop statin therapy immediately following this initial visit and must undergo a 4-week statin washout period **prior to Screening Visit 2**. **At Screening Visit 2**, these subjects will have a pre-randomization visit for assessment of their fasting LDL cholesterol levels.

Section	Original Text	Revised Text
	Subjects with fasting LDL cholesterol values >200 mg/dL at ~~Week 1~~ will be excluded from the study and their ~~NASH~~ should be managed according to standard of care. Double Blind: Subjects who discontinue atorvastatin during the double-blind phase are eligible to continue OCA during the double-blind phase and enroll into the LTSE at the discretion of the Investigator, provided they continue to meet exclusion criteria #4 (LDL <200 mg/dL). LTSE Phase: During the LTSE phase, all subjects will be treated with OCA. Subjects randomized to placebo or OCA 5 mg during the double-blind phase will receive OCA 10 mg upon entry into and throughout the LTSE phase. Subjects randomized to OCA 10 mg ~~with no tolerability concerns will titrate to OCA 25 mg. Subjects who are randomized to the~~ OCA 25 mg treatment group will continue ~~receiving OCA 25 mg during~~ the LTSE.	Subjects with fasting LDL cholesterol values >200 mg/dL at **Screening Visit 2** will be excluded from the study and their **dyslipidemia** should be managed according to standard of care. Double Blind: Subjects who discontinue atorvastatin during the double-blind phase are eligible to continue OCA during the double-blind phase and enroll into the LTSE at the discretion of the Investigator, provided they continue to meet **the LDLc cutoff of** exclusion criteria #4 (**ie**, LDL**c** <200 mg/dL). LTSE Phase: During the LTSE phase, all subjects will be treated with **open-label** OCA **10 mg or OCA 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.
Synopsis Methodology, 7.1.1 Study Design		
Synopsis Number of Subjects, 7.2 Number of Subjects	8. ~~At least 67% (n = 54) of subjects enrolled in the study will have fibrosis stage 1 and up to 33% (n =~~	9. **A maximum of 20% of subjects will have stage 4 fibrosis.**

Section	Original Text	Revised Text
	~~26) of subjects will have fibrosis stage 2, stage 3, or stage 4~~	
Synopsis, ~~Key~~ Inclusion Criteria 8.2 Subject Inclusion Criteria	6. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below. • ~~Double-b~~arrier method, ie, ~~(a)~~ condom (male or female) or ~~(b)~~ diaphragm~~,~~ with spermicide • Intrauterine device • Vasectomy (partner) • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection) • Abstinence (defined as refraining from heterosexual intercourse)	6. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below. • Barrier method, ie, condom (male or female) **with spermicide** or diaphragm with spermicide • Intrauterine device • Vasectomy (partner) • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection) • Abstinence (defined as refraining from heterosexual intercourse)
Synopsis, ~~Key~~ Exclusion Criteria 8.3 Subject Exclusion Criteria	8. Uncontrolled diabetes defined as HbA1c≥9.~~0~~% within 60 days prior to randomization (Day 1). 9. Administration of any of the following medications as specified below: • Prohibited <u>30 days</u> prior to Day 1: – bile acid sequestrants including cholestyramine • Prohibited <u>3 months</u> prior to Day 1: – nicotinic acid and derivatives, ezetimibe, or – any prescription or over-the-counter medication or herbal remedy with putative NASH efficacy (except Vitamin E or TZDs), – fenofibrate or other fibrates, or	8. Uncontrolled diabetes defined as HbA1c≥9.**5**% within 60 days prior to randomization (Day 1) 9. Administration of any of the following medications as specified below: • Prohibited 30 days prior to Day 1: – bile acid sequestrants including cholestyramine, **and its derivatives** • Prohibited <u>3 months</u> prior to Day 1: – nicotinic acid and derivatives, ezetimibe, or

Section	Original Text	Revised Text
	– Any over-the-counter or health foods used to treat lipids including plant sterols and berberine 10. Evidence of other forms of chronic liver disease including but not limited to: • Positive test result at Screening for hepatitis B surface antigen ~~or~~ hepatitis C <u>antibody</u> (~~and~~ positive ~~hepatitis C virus [~~HCV~~]~~ ribonucleic acid [RNA]) • Primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis or overlap syndrome • Alcoholic liver disease • Wilson's disease or hemochromatosis or iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy • Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level less than normal; exclusion at the Investigator's discretion) • Prior known drug-induced liver injury within 5 years before Day 1 • Known or suspected hepatocellular carcinoma 17. Platelet count <~~100~~,000/mm^3 at any Screening Visit 24. Receipt of any investigational product not being evaluated for the treatment of diabetes or NASH within 30 days prior to Day 1 or within 5 half-lives of the compound ~~(whichever was longer)~~ before Day 1	– any prescription or over-the-counter medication or herbal remedy with putative NASH efficacy (except Vitamin E or TZDs), **or** – **ursodeoxycholic acid, or** – fenofibrate or other fibrates, or – Any over-the-counter or health foods used to treat lipids including plant sterols and berberine 10. Evidence of other forms of **known** chronic liver disease including but not limited to: • Positive test result at Screening for hepatitis B surface antigen • **Active** hepatitis C virus (HCV) infection (positive **for** HCV ribonucleic acid [RNA] at Screening) or history of positive HCV RNA **test result** • Primary biliary cirrhosis **(also known as primary biliary cholangitis)**, primary sclerosing cholangitis, autoimmune hepatitis or overlap syndrome • Alcoholic liver disease • Wilson's disease or hemochromatosis or iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy • Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level less than normal; exclusion at the Investigator's discretion)

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td></td><td>
• Prior known drug-induced liver injury within 5 years before Day 1
• Known or suspected hepatocellular carcinoma
17. Platelet count <**75** 000/mm^3 at any Screening Visit
24. Receipt of any investigational product not being evaluated for the treatment of diabetes or NASH **from Screening Visit 1 to Day 1,** within 30 days prior to Day 1**,** or within 5 half-lives of the compound before Day 1 **(whichever was longer)**
29.→**Acute cholecystitis or acute biliary obstruction**
</td></tr>
<tr><td>Synopsis, Duration of Subject Participation</td><td>Screening period for statin-using subjects: ~~4 week statin washout period + Screening (5 weeks (statin-using subjects only)~~</td><td>Screening period for statin-using subjects: **Up to 5 weeks (including a 4-week statin washout period)**</td></tr>
<tr><td>Synopsis, Criteria for Evaluation
11.1 Efficacy Assessments, Table 4</td><td>
<table>
<tr><th colspan="2">Exploratory Endpoints</th></tr>
<tr><td>OCA pharmacokinetics</td><td>OCA, tauro-OCA, glyco-OCA, total OCA, potentially other conjugates or metabolites not yet identified</td></tr>
<tr><td>Noninvasive radiological liver fibrosis measurements</td><td>By TE (where available~~, and evaluated at the end of LTSE~~)</td></tr>
</table>
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<table>
<tr><th colspan="2">Exploratory Endpoints</th></tr>
<tr><td>OCA pharmacokinetics</td><td>OCA, tauro-OCA, glyco-OCA, total OCA, **OCA glucuronide,** potentially other conjugates or metabolites not yet identified</td></tr>
<tr><td>Noninvasive radiological liver fibrosis measurements</td><td>By TE (where available)</td></tr>
</table>
</td></tr>
<tr><td>List of Abbreviations and Definitions of Terms</td><td>
<table>
<tr><td>PBC</td><td>primary biliary cirrhosis</td></tr>
</table>
</td><td>
<table>
<tr><td>PBC</td><td>primary biliary **cholangitis (also known as primary biliary** cirrhosis**)**</td></tr>
<tr><td>**CAC**</td><td>**Cardiovascular Adjudication Committee**</td></tr>
</table>
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Section	Original Text	Revised Text
5.5 Clinical Experience with Obeticholic Acid	OCA is under investigation for the treatment of multiple chronic liver diseases, including the treatment of NASH, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and biliary atresia. The clinical development program for OCA includes the following 3 studies conducted using subjects with NAFLD or NASH: “ “ • Study D8602001: A~~n ongoing~~ Phase 2 study ~~being~~ conducted by Intercept’s development partner (Sumitomo Dainippon Pharma Co., Ltd) to evaluate the efficacy and safety of 3 doses of OCA versus placebo in NASH. ~~Study D8602001 is ongoing and remains blinded.~~	OCA is under investigation for the treatment of multiple chronic liver diseases, including the treatment of NASH, primary biliary cholangitis (PBC, also called primary biliary **cholangitis (**PBC**, also known as primary biliary** cirrhosis **[Beuers 2015a, Beuers 2015b, Beuers 2015c]**), primary sclerosing cholangitis (PSC), and biliary atresia. The clinical development program for OCA includes the following 3 studies conducted using subjects with NAFLD or NASH: • Study D8602001: **A** Phase 2 study conducted by Intercept’s **Asian** development partner (Sumitomo Dainippon Pharma Co., Ltd) to evaluate the efficacy and safety of 3 doses of OCA versus placebo in NASH **Study D8602001 demonstrated a dose-dependent increase in the percentage of OCA-treated subjects compared to placebo subjects who achieved the primary endpoint (p = 0.053, not significant). The 40 mg OCA dose group achieved statistical significance for the primary endpoint compared to placebo (p = 0.0496). Dose-dependent trends not reaching statistical significance were also observed for several other pre-specified histologic endpoints, including the proportion of subjects with steatosis and inflammation improvement, ballooning resolution, and NASH resolution. In the completer analysis, similar dose-dependent effects were observed, with 51% of patients in the 40 mg dose group compared to 22% in the placebo group meeting the primary endpoint (p = 0.0061). With the exception of dose-dependent pruritus, OCA appeared to be generally safe and well tolerated. The number of pruritus-associated discontinuations were 0, 0, 2, and 5 subjects in the placebo, 10 mg, 20 mg, and 40 mg OCA groups, respectively. Changes in lipid parameters were directionally similar to those observed in the FLINT study. No other meaningful differences in the rate of AEs between the OCA and placebo groups were noted.**

Section	Original Text	Revised Text
5.6.6 Rationale for Timing of Unblinding Process and Implications in LTSE	~~For those subjects continuing into the LTSE: Following completion of all study procedures associated with the double-blind period, subjects will be unblinded via the interactive web response system (IWRS) to determine the open-label OCA dose to be initiated in the LTSE. This will allow double-blind, placebo-treated subjects to initiate OCA at an appropriate dose, and OCA-treated subjects to maintain or increase their dose based on therapeutic response and tolerability rather than forcing fixed dosing to maintain the blind.~~	**As Study 747-209 is a randomized, double-blind study, the double-blind data will not be unblinded until all double-blind data are final and the database is locked. Accordingly, all subjects continuing in the LTSE, investigators, and the Sponsor will remain blinded to subjects' DB treatment regimen. Subjects who were receiving placebo or 5 mg OCA in the DB phase will be randomized to receive either OCA 10 mg or OCA 25 mg in the LTSE. Subjects who were receiving OCA 10 mg or OCA 25 mg in the DB phase will continue on the same dose throughout the LTSE. Using this approach, blinding of the trial will be maintained.**
5.8 Summary of Known Potential Risks with Atorvastatin		**If treatment with statins is initiated, women of childbearing potential must be informed that statin use is contraindicated during pregnancy. Methods of contraception should be reviewed and modified, if necessary, to ensure highly effective methods with failure rates <1% per year, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or history of vasectomy of partner are used.**
7.1.2 Schedule of Study Procedures, Double-Blind Period	[a] Subjects using statins within 4 weeks of Screening are required to stop administering statin therapy after Screening Visit 1, and must ~~undergo a 5-week washout period prior to randomization~~. [b] Screening Visit 2 is required for all subjects. All subjects must have been fasting for at least 8 hours prior to the visit. For subjects undergoing a 4-week washout period, ~~this visit will occur at Week -1~~. For subjects not taking statins at Screening Visit 1, ~~this visit can occur at any time after Screening Visit 1 and up to 1 week prior to randomization~~. ~~For subjects~~	**Added Weeks** row to clarify timing of Screening Visits Modified Visit windows for **Screening Visit 1: Day -35 to Day -7** Modified Visit window for **Screening Visit 2: Day -7 to Day -1** [a] Subjects using statins within 4 weeks of Screening are required to stop administering statin therapy after Screening Visit 1, and must **complete a 4-week statin washout prior to performing assessments at Screening Visit 2**. [b] Screening Visit 2 is required for all subjects. All subjects must have been fasting for at least 8 hours prior to the visit. **The Randomization/Day 1 Visit may occur as soon as screening labs are available and eligibility is confirmed for all subjects.** For subjects undergoing a 4-week washout period, **Screening Visit 2 may occur on day 28 (±1) day of the washout period**. For subjects not taking statins at Screening Visit 1, **Screening Visit 2 can occur at any time**

Section	Original Text	Revised Text
	~~using statins within 4 weeks prior to Screening Visit 1, Screening Visit 2 can occur at any time after 4 weeks have lapsed since the subject's last statin dose.~~ [d] Sitting heart rate, blood pressure, temperature, and respiratory rate [i] and none of the exclusion criteria, may be randomized." [k] Blood samples for all analyses will be collected predose (before administering investigational product) on indicated visit days.	**within 28 days after Screening Visit 1. All Screening assessments must be completed ≤35 days prior to the Randomization/Day 1 Visit.** [d] Sitting heart rate, blood pressure, **body** temperature, and respiratory rate [i] and none of the exclusion criteria, may be randomized. **Subjects randomized to placebo or OCA 5 mg during the double-blind period will be randomized to OCA 10 or 25 mg during the LTSE** [k] Blood samples for all analyses will be collected predose (before administering investigational product **or atorvastatin**) on indicated visit days.
7.1.2 Schedule of Study Procedures, LTSE	Month 1 ~~Contact~~ [a] The first visit after start of LTSE (Month 1 Visit) is relative to Week 16 Visit of the double-blind phase (LTSE Day 1 Visit). ~~This is not a study site visit. The subject should be contacted approximately 1 month after the start of the LTSE, and compliance with OCA treatment instructions, concomitant medications, and AEs should be assessed.~~ [d] Sitting heart rate, blood pressure, temperature, and respiratory rate	Month 1 Added: • Fast ≥8 h Prior to Visit • Vital Signs • Collect Bottles/Atorvastatin Accountability/Compliance • Serum Chemistry/Hematology/Coagulation Parameters • Markers of glucose metabolism, including C-peptide, insulin, fasting plasma glucose, HbA1c • Urine Based β-hCG Pregnancy Test [a] The first visit after start of LTSE (Month 1 Visit) is relative to Week 16 Visit of the double-blind phase (LTSE Day 1 Visit). [d] Sitting heart rate, blood pressure, **body** temperature, and respiratory rate
7.3 Treatment Assignment	Eligible subjects will be randomized into 4 groups in a 1:1:1:1 ratio to receive OCA 5 mg, OCA 10 mg, OCA 25 mg, or placebo during the double-blind phase of the study. Randomization will	Eligible subjects will be randomized into 4 groups in a 1:1:1:1 ratio to receive OCA 5 mg, OCA 10 mg, OCA 25 mg, or placebo during the double-blind phase of the study.

Section	Original Text	Revised Text
	be stratified by LDL concentration (fasting serum LDL cholesterol at Screening Visit 2; ≤125 mg/dL or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4). All subjects will also receive atorvastatin starting at Week 4 at 10 mg daily, escalating to 20 mg at Week 8 (if 10 mg daily is tolerated), with further dose adjustments to be performed as clinically indicated at Week 12, and throughout the LTSE phase. Subjects ~~randomized to placebo or OCA 5 mg~~ will receive OCA 10 mg during the LTSE; ~~subjects randomized to OCA 10 mg or OCA 25 mg will receive OCA 25 mg during the LTSE~~. The study design schematic is shown in Figure 1.	Randomization will be stratified by LDL concentration (fasting serum LDL cholesterol at Screening Visit 2; ≤125 mg/dL or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4). All subjects will also receive atorvastatin starting at Week 4 at 10 mg daily, escalating to 20 mg at Week 8 (if 10 mg daily is tolerated), with further dose adjustments to be performed as clinically indicated at Week 12, and throughout the LTSE phase. Subjects will receive **open-label** OCA 10 mg **or OCA 25 mg** during the LTSE **depending on their double-blind randomized dose (see Section 7.1)**. The study design schematic is shown in Figre 1.
7.4.1 Investigational Product Dose Adjustments	During the LTSE phase, all subjects will be treated with OCA. Subjects randomized to placebo or OCA 5 mg during the double-blind phase will ~~receive OCA 10 mg~~ upon entry into and throughout the LTSE phase. Subjects randomized to OCA 10 mg with ~~no tolerability concerns~~ will ~~titrate to OCA 25 mg~~. Subjects randomized to OCA 25 mg will continue to receive ~~this dose~~ throughout the LTSE. Subjects may continue with atorvastatin therapy as clinically indicated.	During the LTSE phase, all subjects will be treated with OCA. Subjects randomized to placebo or OCA 5 mg during the double-blind phase will **be re-randomized in a 1:1 ratio through IWRS to OCA 10 mg or OCA 25 mg** upon entry into and throughout the LTSE phase. Subjects randomized to OCA 10 mg will **continue to receive OCA 10 mg throughout the LTSE**. Subjects randomized to OCA 25 mg will continue to receive **OCA 25 mg** throughout the LTSE. Subjects may continue with atorvastatin therapy as clinically indicated.
8.4.1.3 Severe Drug-Induced Liver Injury	Subjects who develop significant drug-induced liver injury, which is considered to be causally related to the investigational product, should be discontinued from investigational product and should not be rechallenged. Significant injury as described in Appendix B, ~~or~~ evidence of functional hepatic impairment as indicated by rising bilirubin or INR. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued. Severe drug induced-liver injury that is not considered related to investigational product must be discussed with the Sponsor before ~~resuming treatment~~. Subjects who discontinue due to significant drug-induced liver injury must be followed until the AE has resolved, stabilized, or is not of clinical concern.	**If a subject develops signs and symptoms of a severe drug-induced liver injury, regardless of causality, investigational product and atorvastatin should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule.** Subjects who develop significant drug-induced liver injury, which is considered to be causally related to the investigational product **or atorvastatin**, should be discontinued from investigational product **or atorvastatin, as appropriate** and should not be rechallenged. Significant injury as described in Appendix B, **and includes** evidence of functional hepatic impairment as indicated by rising bilirubin or INR. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued.

Section	Original Text	Revised Text
		Severe drug induced-liver injury that is not considered related to investigational product **or atorvastatin** must be discussed with the Sponsor before **investigational product or atorvastatin is reinitiated. Follow-up procedures for subjects resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject is to be allowed to continue treatment.** Subjects who discontinue due to significant drug-induced liver injury must be followed until the AE has resolved, stabilized, or is not of clinical concern.
9.1 Investigational Product **and Atorvastatin** Treatment Regimen	~~The~~ investigational products ~~are either~~ OCA or placebo.	**While placebo, OCA, and atorvastatin are all study medications provided by the Sponsor, for the purposes of this protocol,** investigational product **refers to** OCA or placebo**, and study medication, where used, refers to atorvastatin.**
9.1.2 LTSE	Following completion of Week 16 Visit procedures, ~~subjects who are participating in the LTSE will be unblinded via the IWRS~~. ~~Subjects who were receiving OCA during the double-blind phase will continue to receive either OCA 10 mg or OCA 25 mg once daily during the LTSE. Subjects randomized to placebo or 5 mg OCA during the double-blind phase will initiate dosing at OCA 10 mg in the LTSE. Subjects randomized to OCA 10 mg during the double-blind phase will titrate to OCA 25 mg on Day 1 of the LTSE. Subjects randomized to OCA 25 mg during the double-blind phase will continue to receive OCA 25 mg.~~	Following completion of Week 16 Visit procedures, **all subjects will be treated with open-label OCA 10 mg or OCA 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.**
9.2.5 Standard of Care and Other Concomitant Medications	Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigational product, ensuring at least 4 hours between doses of the BAS and/or antacids and the investigational product (ie, BAS should be administered 4 hours before or 4 hours after investigational product administration).	Subjects taking BAS **(including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants)** or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigational product, ensuring at least 4 hours between doses of the BAS and/or antacids and the investigational product (ie, BAS should be

Section	Original Text	Revised Text
		administered 4 hours before or 4 hours after investigational product administration). **Taken concomitantly, OCA and warfarin may decrease INR, thus INR should be monitored and the dosage of warfarin adjusted, as needed, to maintain the target INR range.** **The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate, showed weak effect of OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.**
9.4 Randomization and Blinding	The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide patient data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned and investigational product (OCA or placebo) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind. The subjects, Investigator, and study site staff will be blinded to the subject's treatment allocation ~~during the subject's participation~~ in the double-blind phase of the study.	The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide patient data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned and investigational product (OCA or placebo) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind. The subjects, Investigator, and study site staff will be blinded to the subject's treatment allocation in the double-blind phase of the study **until all subjects have completed the double-blind phase of the study and the database locked**. **In the LTSE phase, all subjects will be treated with open-label OCA 10 mg or OCA 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 and subjects randomized to OCA 10 mg or OCA 25 mg during the double-blind phase will continue on the same dose throughout the LTSE.**
9.4.2 Emergency Unblinding Procedures	Randomization codes and corresponding treatment assignments will be made available to the Investigator for emergency use only through the IWRS system. When possible, the Medical Monitor	Randomization codes and corresponding treatment assignments will be made available to the Investigator **and the Medical Monitor** for emergency use only through the IWRS system.

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document the case in the subject's source record. Subsequently, the Investigator should contact the Medical Monitor to explain any premature unblinding of treatment assignment (eg, accidental unblinding or unblinding due to a serious AE [SAE]). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. ~~Similarly, if the Medical Monitor breaks the blind for the purpose of evaluating an emergent safety issue or for regulatory reporting purposes, the~~ Medical Monitor will document within study correspondence the rationale, circumstances, and the person(s) being informed about the unblinding.</td><td>When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document the case in the subject's source record. Subsequently, the Investigator should contact the Medical Monitor to explain any premature unblinding of treatment assignment (eg, accidental unblinding or unblinding due to a serious AE [SAE]). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. The Medical Monitor will document within study correspondence the rationale, circumstances, and the person(s) being informed about the unblinding.</td></tr>
<tr><td>9.7.1 Visit Windows</td><td>~~Screening Visit 1~~ should occur ≤35 days prior to the Day 1 Visit. Subjects who are taking statins at the time of screening or within ~~4 weeks~~ of Screening Visit 1 are required to stop statin therapy for 4 weeks, and provide a fasting blood sample at Screening Visit 2 ~~(Week -1 Visit)~~ to confirm eligibility. Subjects who have not taken statins within ~~4 weeks~~ of Screening Visit 1 are not required to enter into the washout period and may proceed to Screening Visit 2 ~~(Week -1)~~ to provide a fasting blood sample. ~~The Week -1 Visit should occur within ±1 days of the Randomization/Day1 Visit.~~
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening Visit 1</td><td>Visit(s) are to occur ≤5 weeks (35 days) ~~before~~ Day 1.</td></tr>
<tr><td>LTSE Visits: Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, and Month 21</td><td>±1 week (7 days); the LTSE visits are relative to LTSE Day 1 (ie, Week 16 of double-blind phase)</td></tr>
</table></td><td>All Screening assessments should occur ≤35 days prior to the Randomization/Day 1 Visit. Subjects who are taking statins at the time of screening or within 30 days of Screening Visit 1 are required to stop statin therapy for 4 weeks (28 (±1) days), and provide a fasting blood sample at Screening Visit 2 to confirm eligibility. Subjects who have not taken statins within 30 days of Screening Visit 1 are not required to enter into the washout period and may proceed to Screening Visit 2 to provide a fasting blood sample. The Randomization/Day 1 Visit may occur as soon as all screening labs are available and eligibility is confirmed.
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening Visit 1</td><td>Visit(s) are to occur ≤5 weeks (35 days) prior to Day 1.</td></tr>
</table></td></tr>
</table>

Section	Original Text	Revised Text
		LTSE Visits: **Month 1,** Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, and Month 21 | ±1 week (7 days); the LTSE visits are relative to LTSE Day 1 (ie, Week 16 of double-blind phase)
9.7.3 Screening Visit 1 Procedures ~~(≤35 Days Before Day 1)~~	The Screening Visit assessments must be performed ~~within~~ ≤5 weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects who are statin-free (ie, no statin use within ~~4 weeks~~ of Screening) must return for fasted serum chemistry labs at Screening Visit 2, and may proceed to the Randomization/Day 1 Visit once screening labs are available and eligibility is confirmed; subjects who need to wash out statin therapy are required to "~~**have a Week -1 Visit 4 weeks after Screening Visit 1**~~." Additional Screening Visit 1 procedure for subjects currently taking statins: • Subjects who are currently taking statins, defined as statin use within ~~4 weeks~~ of Screening, will be instructed to discontinue statin therapy following Screening Visit 1. ~~These subjects must complete a 5-week statin washout prior to being randomized.~~ After 4 weeks of statin washout, subjects will return for Screening Visit 2~~/Week -1 Visit~~ to provide blood samples for fasted serum chemistry.	The Screening Visit assessments must be performed ≤5 weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects who are statin-free (ie, no statin use within **30 days** of Screening) must return for fasted serum chemistry labs at Screening Visit 2, and may proceed to the Randomization/Day 1 Visit once screening labs are available and eligibility is confirmed; subjects who need to wash out statin therapy are required to **return for Screening Visit 2 following the washout period**. Additional Screening Visit 1 procedure for subjects currently taking statins: • Subjects who are currently taking statins, defined as statin use within **30 days** of Screening, will be instructed to discontinue statin therapy following Screening Visit 1. After 4 weeks of statin washout, subjects will return for Screening Visit 2 to provide blood samples for fasted serum chemistry.
9.7.4 Screening Visit 2~~/Week -1~~ Visit-Procedures	Subjects who were receiving statin therapy at the time of screening. • Verify that subjects have completed a 4-week washout period. ~~All Subjects~~:	**All subjects will return for Screening Visit 2 to confirm eligibility criteria and provide blood samples for fasted serum chemistry.** **For s**ubjects who were receiving statin therapy at the time of screening. • Verify that subjects have completed a 4-week washout period.

Section	Original Text	Revised Text
		For all subjects:…
9.7.14 Additional Procedures at Week 16/LTSE Day 1	Subject who ~~will~~ continue into the LTSE phase after completing the procedures listed for the Week 16 Visit… • ~~Dispense investigational product as instructed~~	Subject**s** who continue into the LTSE phase after completing the procedures listed for the Week 16 Visit… • **Record the visit in IWRS, randomize the subject to one of the open-label treatment groups, and dispense open-label investigational product according to IWRS instructions.**
9.7.16 LTSE Visits	~~LTSE Visits~~ will occur every 3 months (eg, at Months ~~3~~, 6, 9, and 12) ~~following completion of the Week 16/LTSE Day 1 Visit~~. The visit procedures described below will repeat annually for the duration of the LTSE. For example, once a subject completes a year (Month 12 Visit) in the LTSE, their next visit should be 3 months later and the procedures described for the Month 3 LTSE Visit should be followed.	**LTSE Visits should occur within ±1 week of the visit day and the timing of all visits should be relative to the double-blind Week 16 Visit (ie, the start of the LTSE; LTSE Day 1). For example, if the Month 6 Visit occurred 1 week late, the Month 9 Visit should still be approximately 9 months after the Week 16 Visit.**
9.7.16 LTSE Visits	~~LTSE Visits should occur within ±1 week of the visit day and the timing of all visits should be relative to the double-blind Week 16 Visit (ie, the start of the LTSE; LTSE Day 1). For example, if the Month 6 Visit occurred 1 week late, the Month 9 Visit should still be approximately 9 months after the Week 16 Visit.~~	**The first LTSE visit following LTSE Day 1 will occur at LTSE Month 1. The next** visit will occur **at LTSE Month 3 and** every 3 months **thereafter** (eg, at Months 6, 9, and 12) for the duration of the LTSE. The **quarterly** visit procedures described below will repeat annually for the duration of the LTSE. For example, once a subject completes a year (Month 12 Visit) in the LTSE, their next visit should be 3 months later and the procedures described for the Month 3 LTSE Visit should be followed.
9.7.17 LTSE Month 1 ~~Contact~~**/Visit Procedures**	~~Approximately 1 month into the LTSE, the subject should be contacted to assess compliance with OCA treatment, review and record concomitant medications, and assess and record AEs. This is not a clinic visit. This contact is not repeated in subsequent years of participation.~~	• **Verify that the subject has fasted for at least 8 hours.** – Record fasting status in the source and eCRF. – If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is

Section	Original Text	Revised Text
		required prior to all study visits, but water is permitted. • **Assess and record vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure).** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability. Following product accountability, redispense the same bottle of investigational product for use until the next visit.** • **Collect used bottles of atorvastatin, assess atorvastatin compliance, and perform atorvastatin accountability. Following atorvastatin accountability, if the subjects is continuing with the same dose of atorvastatin, redispense the same bottle for use until the next visit.** • **NOTE: If atorvastatin dose is up-titrated or re-initiated after dose interruption, a telephone safety contact must be conducted 2 weeks following the change in dose to assess for AEs, concomitant medications, and investigational product and atorvastatin compliance.** • **Obtain blood samples for:** • **Serum chemistry (will include basic lipid panel and liver biochemistry panel), hematology, and coagulation** • **Markers of glucose metabolism** • **CPK, if myopathy suspected**

Section	Original Text	Revised Text
		• **Perform a urine based β-hCG pregnancy test in female subjects of childbearing potential. Perform serum pregnancy test in females of childbearing potential if urine β-hCG pregnancy test is positive.** • **Reiterate dosing instructions for investigational product and advise the subject:** – Take the investigational product at approximately the same time each day – NOT to take investigational product or atorvastatin (if applicable) or on the morning of the next visit – To bring the investigational product and atorvastatin (if applicable) bottle(s); s/he will dose at the clinic – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.
10 Study Medication Materials and Management	~~STUDY MEDICATION MATERIALS AND MANAGEMENT~~	**INVESTIGATIONAL PRODUCT AND STUDY MEDICATION**
10.1 Investigational Product (OCA or Placebo) LTSE Phase:	~~5 mg,~~ 10-mg and 25-mg OCA tablets for the LTSE Phase will be supplied as white ~~or yellow~~ tablets. • White OCA tablets are round and debossed with "INT" on one side and "3547" on the other side. • ~~5 mg yellow tablets: Round and debossed with "INT" on one side and "5" on the other side.~~	10-mg and 25-mg OCA tablets for the LTSE Phase will be supplied as white ~~or yellow~~ tablets. • White OCA tablets are round and debossed with "INT" on one side and "3547" on the other side.

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<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>~~• 10 mg yellow tablets: Triangular and debossed with "INT" on one side and "10" on the other side.~~
~~• 5 mg yellow tablets: Oval and debossed with "INT" on one side and "25" on the other side.~~</td><td></td></tr>
<tr><td>10.3 Investigational Product Storage</td><td>Investigational product should be stored ~~at the clinical study sites~~ in the containers in which they are received from the Sponsor's supplier, at 15-25°C ~~and protected from excess humidity~~.</td><td>Investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15-25°C.</td></tr>
<tr><td>11.1.2.1 Central Reading of Liver Histology</td><td>All biopsy assessments, including determination of study eligibility based on NASH diagnosis and fibrosis staging during Screening, will be performed centrally by an independent pathologist. Key features of NASH (ie, steatosis, lobular inflammation, and hepatocellular ballooning) will be graded in accordance with the NASH CRN criteria for scoring (Kleiner 2005). Fibrosis staging for eligibility will also be performed in accordance with NASH CRN criteria for fibrosis staging.</td><td>All biopsy assessments, including determination of study eligibility based on NASH diagnosis and fibrosis staging during Screening, will be performed centrally by an independent pathologist. The central pathologist must confirm histological presence of NASH and a minimum NAS of 4 with a score of at least 1 in each component of NAS. Key features of NASH (ie, steatosis, lobular inflammation, and hepatocellular ballooning) will be graded in accordance with the NASH CRN criteria for scoring (Kleiner 2005) as summarized in Table 5. Fibrosis staging for eligibility will also be performed in accordance with NASH CRN criteria for fibrosis staging.
Table 5: NASH CRN Scoring System for Determining Eligibility and Primary Histological Endpoint Assessment
<table>
<tr><th colspan="2">NAFLD Activity Score (NAS)</th><th colspan="2">Fibrosis Staging</th></tr>
<tr><th>Parameter</th><th>Scoring Criteria</th><th>Parameter</th><th>Staging Criteria</th></tr>
</table>
</td></tr>
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<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Steatosis</td><td>0 = <5%
1 = 5% - 33%
2 = >33% - 66%
3 = >66%</td><td>Stage 0</td><td>No Fibrosis</td></tr>
<tr><td>Lobular Inflammation</td><td>0 = No Foci
1 = <2 Foci per 200 × field
2 = 2-4 Foci per 200 × field
3 = > 4 Foci per 200 × field</td><td>Stage 1
Stage 1a
Stage 1b
Stage 1c</td><td>Perisinusoidal or Periportal
Mild, zone 3, persinusoidal
Moderate, zone 3, perisinusoidal
Portal / periportal</td></tr>
<tr><td rowspan="3">Ballooning</td><td rowspan="3">0 = None
1 = Few balloon cells
2 = Many cells / prominent ballooning</td><td>Stage 2</td><td>Perisinusoidal and portal / periportal</td></tr>
<tr><td>Stage 3</td><td>Bridging fibrosis</td></tr>
<tr><td>Stage 4</td><td>Cirrhosis</td></tr>
</table>
In addition to the primary scoring system of NASH CRN, biopsy samples will also be scored based on modified Ishak
</td></tr>
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Section	Original Text	Revised Text
		scoring (Ishak 1995) for all subjects. Any extra biopsy tissue may undergo exploratory histological evaluations.
11.2.2 Pharmacokinetic Assessments	The first sample should be collected within 30 minutes prior to administration of investigational product (predose) on Day 1 at the Week 16 Visit.	The first sample should be collected within 30 minutes prior to administration of investigational product (predose) on Day 1 **and prior to administration of investigational product or atorvastatin** at the Week 16 Visit.
12.1.2 Relationship to Investigational Product or Study Medication		**If the relationship between a SAE and the atorvastatin is determined to be "definite," "probable," or "possible," the event will be considered to be related to atorvastatin for the purpose of assessing expedited safety reporting and reporting to the manufacturer.**
12.1.4.1 Severity of Pruritus (as and AE)		**Since pruritus is a subjective symptom and the occurrence and magnitude of which are not readily measured by objective tools, clinical judgment needs to be applied in the management of each subject. Managing OCA-related pruritus may help improve tolerance in those subjects who experience problematic pruritus and may otherwise discontinue from the study prematurely. General guidance for the management of subjects experiencing significant pruritus includes:** • **Drug holiday: A drug holiday is defined as an Investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (ie, non-daily dosing does not constitute a drug holiday). For subjects with severe pruritus, instruct the subject to stop taking investigational product until the pruritus subsides to an acceptable level, at which time it should be restarted. Details of drug holidays and/or nondaily dosing regimens should be recorded in the CRF.** • **Prescribe BAS. Subjects taking BAS (including colestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) should be**

Section	Original Text	Revised Text
		instructed to stagger their dosing of investigational product, ensuring at least 4 hours between doses of the BAS and investigational product. • **Other therapies may be tried as deemed clinically appropriate.** • **Less frequent dosing of investigational product (eg, on alternate days) may be tried, after which subjects may return to their original daily dose as soon as tolerated.**
12.1.8.1 Pregnancy and Follow-Up	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue treatment with investigational product and atorvastatin immediately (see Section 8.4.1.1) and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing the Pregnancy ~~Report~~ eCRF in the EDC system~~. Entering the pregnancy report into the EDC system will automatically notify the Sponsor of the pregnancy.~~ The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and the Sponsor. Women who discontinue the study due to pregnancy may not re-enroll in the study at any point, but should continue with the study visit schedule and must be followed by the Investigator through pregnancy outcome. Similarly, if a subject's pregnancy is terminated early (planned or unplanned), the subject will also be removed from the study. Completing the Pregnancy Report ~~in the EDC~~ is not a substitute for reporting an AE/SAE ~~when~~ an AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 17.1 must also be followed.	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue treatment with investigational product and atorvastatin immediately (see Section 8.4.1.1) and the Sponsor must be notified within 24 hours of the Investigator's **awareness** of the pregnancy by completing the Pregnancy eCRF in the EDC system **and downloading and completing the Pregnancy Report Form**. **The Pregnancy Report Form must be emailed to sae@interceptpharma.com or faxed to +1-800-497-8521.** The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and the Sponsor. Women who discontinue the study due to pregnancy may not re-enroll in the study at any point, but should continue with the study visit schedule and must be followed by the Investigator through pregnancy outcome. Similarly, if a subject's pregnancy is terminated early (planned or unplanned), the subject will also be removed from the study. Completing the Pregnancy Report **Form** is not a substitute for reporting an AE/SAE **if** an AE/SAE has occurred **related to or concurrent with the pregnancy**. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 1.7.1 must also be followed.

Section	Original Text	Revised Text
12.2.4 Electrocardiogram	Investigative sites must retain a copy of all 12-lead ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the ~~subject's initials,~~ Subject ID number, date, and time. Full instructions will be provided for forwarding the 12-lead ECGs for central reading.	Investigative sites must retain a copy of all 12-lead ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Subject ID number, date, and time. Full instructions will be provided for forwarding the 12-lead ECGs for central reading.
12.2.6 Laboratory Assessments	Except for Screening, subjects will be instructed to attend each study visit in a fasted state, and subjects should remain fasted until their blood samples have been collected.	Except for Screening **Visit 1**, subjects will be instructed to attend each study visit in a fasted state, and subjects should remain fasted until their blood samples have been collected.
13.6.3.7 Pharmacokinetic Analysis	The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, and potentially other conjugates or metabolites not yet identified. PK analysis will be done using non-compartmental methods.	The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, **OCA glucuronide** and potentially other conjugates or metabolites not yet identified. PK analysis will be done using non-compartmental methods.
13.7.5 Adjudicated Cardiovascular Events		**Adjudicated cardiovascular events include core MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes are defined in Appendix D and will be included in the Cardiovascular Adjudication Committee Charter for adjudication. Undetermined cause of death will be classified as a cardiovascular death by the Cardiovascular Adjudication Committee.** **Summaries of adjudicated cardiovascular events will include the incidence of TEAEs and the incidence of serious TEAEs. All summaries of incidence will include the associated exact binomial 95% CI.**
13.9 Adjudication Committees	• Cardiovascular ~~Events~~ Committee (~~CEC~~): Adjudicates all suspected MACE	• Cardiovascular **Adjudication** Committee (CAC): Adjudicates all suspected MACE**, including all deaths**
16.4 Subject Confidentiality	All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and	All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and

Section	Original Text	Revised Text
and Data Protection	confidentiality of all subjects will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All data shall be secured against unauthorized access. The Investigator will maintain a list of subject names and identifying information (eg, subjects' hospital numbers, unique subject numbers). This list will not be collected by the Sponsor. The written information sheet will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by the Sponsor or designee will be identified by unique subject number/randomization code/~~subject initials/~~site number, only.	confidentiality of all subjects will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. **All reports and communications relating to subjects in this study that are disclosed to an authorized third party will identify subjects only by protocol and assigned number and will be shared in a secure manner.** All data shall be secured against unauthorized access. The Investigator will maintain a list of subject names and identifying information (eg, subjects' hospital numbers, unique subject numbers). This list will not be collected by the Sponsor. The written information sheet will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by the Sponsor or designee will be identified by unique subject number/randomization code/ site number, only.
19 List of References		**Beuers U, Gershwin ME, Gish RG, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Dig Liver Dis. 2015a;47(11):924-6.** **Beuers U, Gershwin ME, Gish RG, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Gastroenterology. 2015b;149(6):1627-9.** **Beuers U, Gershwin ME, Gish RG, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015c;62(5):1620-2.**

Section	Original Text	Revised Text
Appendix D	***Appendix D included Major Adverse Cardiovascular Event Definitions from Chapters 1 through 7 of "Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials," dated August 20, 2014***	***Appendix D was updated to add definitions from Chapters 8 through 10 of "Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials," dated August 20, 2014***

APPENDIX H. 747-209 PROTOCOL VERSION 4 SUMMARY OF CHANGES

Protocol 747-209 was revised to include the following information:

- Incorporation of the evaluation the bioanalytical concentrations of atorvastatin and its metabolites.
- Updating the maximum percentage of subjects with stage 4 fibrosis from 20% to 30%.
- Removing the obeticholic acid (OCA) glucuronide component of PK as that bioanalysis will be conducted in another study.
- Additional clarifications.

Summary of Changes

The following revisions were made to the protocol in Protocol Version 4. Revised and new text in Version 4 is indicated in **bold** font, and the text deleted from Protocol Version 3 is crossed out in the table below. Minor/editorial changes are not listed individually in the summary table below.

Section	Original Text (Version 3)	Revised Text (Version 4)	Key Change Reasons / Justification for Change
Study Personnel Contact Information	Investigators are encouraged to call the ~~NASH medical monitor hotline~~ at ~~+1 844 250 6396~~ or send an email to the NASH medical monitor at ~~NASH209@intercept pharma~~.com with safety questions as these lines of contact are monitored 24 hours a day. ~~The following individual medical monitors may also be contacted through the NASH medical monitor hotline and email address~~.	Investigators are encouraged to call the **PRA Medical Support Center phone number for the United States and Canada** at +1 **866 326 5053** or send an email to the NASH medical monitor at **CONTROL@prahs**.com with safety questions as these lines of contact are monitored 24 hours a day.	The PRA Medical Support Center phone number and email address were updated.

Section	Original Text (Version 3)	Revised Text (Version 4)	Key Change Reasons / Justification for Change
Study Personnel Contact Information	~~NASH Medical Monitor Hotline~~ ~~Email~~ ~~+1 844 250 6396~~ ~~NASH209@interceptpharma.com~~	*Deletion*	Removed the NASH Medical Monitor Hotline Email (no longer applicable).
Study Personnel Contact Information	Primary Medical Monitor Contact: Phone: Email Secondary Contact: Mobile Phone: Email	Emad Basta, MD (Lead) Medical Monitor/Medical Expert PRA Health Sciences +1 866 326 5053 CONTROL@~~PRAHS~~.com ~~Roya Hooshmand Rad~~, MD PhD ~~Executive~~ Director, ~~Medical Safety and Pharmacovigilance~~ Intercept Pharmaceuticals, Inc. (Intercept) +1 ~~858 880 6485~~ (Pacific time zone) ~~rhooshmand rad~~ @interceptpharma.com	Primary Medical Monitor Contact: Phone: Email Secondary Contact: Mobile Phone: Email	Emad Basta, MD (Lead) Medical Monitor/Medical Expert PRA Health Sciences +1 866 326 5053 CONTROL@**prahs**.com **Tolga Baykal, MD, PhD** **Medical Director, Clinical Development** Intercept Pharmaceuticals, Inc. (Intercept) +1 **619 643 8886** (Pacific time zone) **tolga.baykal**@interceptpharma.com	Updated email address. Tolga Baykal was added as secondary contact.
Synopsis Objectives: Exploratory Objectives 6.3 Exploratory Objectives	*Insertion*	• **To evaluate the bioanalytical concentrations of atorvastatin and its metabolites**	New exploratory objective for the determinations of the concentrations of atorvastatin and its metabolites.
Synopsis Number of Subjects (Planned)	Approximately 80 subjects with biopsy-confirmed NASH and evidence of liver fibrosis, but no hepatic decompensation, who meet eligibility criteria, will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups. A maximum of ~~20~~% of subjects will have stage 4 fibrosis.	Approximately 80 subjects with biopsy-confirmed NASH and evidence of liver fibrosis, but no hepatic decompensation, who meet eligibility criteria, will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups. A maximum of **30**% of subjects will have stage 4 fibrosis.	The rapid rate of enrollment of subjects with stage 4 fibrosis allowed patients already in screening to be enrolled after the initial maximum of 20% was met (the overall number of subjects remains at ~ 80).

Section	Original Text (Version 3)		Revised Text (Version 4)		Key Change Reasons / Justification for Change
Synopsis Statistical Methods 11.1, Efficacy Assessments Table 4, List of Planned Assessments	OCA pharmacokinetics	OCA, tauro-OCA, glyco-OCA, total OCA~~, OCA glucuronide~~, potentially other conjugates or metabolites not yet identified	OCA pharmacokinetics	OCA, tauro-OCA, glyco-OCA, total OCA, potentially other conjugates or metabolites not yet identified	Removal of OCA glucuronide as that bioanalysis will be conducted in another study.
	Insertion		Exploratory Endpoints		Addition of the determination of the concentration of atorvastatin and its metabolites to characterize atorvastatin concentrations with and without OCA.
			Atorvastatin bioanalytical concentrations	**Atorvastatin and its metabolites**	
Synopsis Analysis Populations 13.1, Analysis Sets	Pharmacokinetic Population: The PK Population will include all OCA subjects who consent to participate in the PK assessments and have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours before the visit and must not have any major protocol deviations that potentially affect exposure levels.		Pharmacokinetic Populations**:** The **OCA** PK Population will include all OCA subjects who consent to participate in the PK assessments and have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours before the visit and must not have any major protocol deviations that potentially affect exposure levels. **The Atorvastatin PK Population will include all subjects who consent to participate in the PK assessments and have at least one confirmed fasted analyzable sample.**		Differentiation of OCA PK Population and incorporation of the Atorvastatin PK Population.
7.1.2, Schedule of Study Procedures Table 1, Schedule of Study Procedures: Double-Blind Period	[s] At selected investigational sites, subjects will have the option to provide blood samples for measurement of ~~OCA~~ PK. PK samples will be collected within 30 minutes prior to dosing and again 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.		[s] At selected investigational sites, subjects will have the option to provide blood samples for measurement of PK **for OCA (Day 1 and Week 16), and for atorvastatin (Week 16)**. PK samples will be collected within 30 minutes prior to dosing and again 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.		Clarification on the PK sampling of OCA and incorporation of atorvastatin PK sampling.
7.2, Number of Subjects	Approximately 80 subjects who meet the eligibility criteria, including biopsy-confirmed NASH and evidence of liver fibrosis, but no hepatic decompensation, will be included in this study. A maximum of ~~20~~% of subjects will have stage 4 fibrosis.		Approximately 80 subjects who meet the eligibility criteria, including biopsy-confirmed NASH and evidence of liver fibrosis, but no hepatic decompensation, will be included in this study. A maximum of **30**% of subjects will have stage 4 fibrosis.		The rapid rate of enrollment of subjects with stage 4 fibrosis allowed patients already in screening to be enrolled after the initial maximum of 20%

Section	Original Text (Version 3)	Revised Text (Version 4)	Key Change Reasons / Justification for Change
			was met (the overall number of subjects remains at ~ 80).
9.7.13.1, Additional Week 16 Procedures for PK Subjects	Following collection of the Week 16 fasted samples indicated above, subjects who are participating in the PK assessment will each receive a single dose of their assigned investigational product with water. Serial blood samples will be obtained for measurement of OCA and its conjugates 30 minutes prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose.	Following collection of the Week 16 fasted samples indicated above, subjects who are participating in the PK assessment will each receive a single dose of their assigned **double-blind** investigational product with water. Serial blood samples will be obtained for measurement of OCA and its conjugates**, and atorvastatin and its metabolites,** 30 minutes prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose.	Clarification of study phase. Incorporation of PK sampling for atorvastatin.
11.2, Pharmacokinetic and Pharmacodynamic Assessments	Parent OCA and its major conjugates (glyco-OCA and tauro-OCA), C4, and FGF-19 concentrations will be determined for OCA PK and FXR activity in OCA-treated subjects. Samples will be obtained for possible assessment of conjugated and unconjugated bile acids.	Parent OCA and its major conjugates (glyco-OCA and tauro-OCA), C4, and FGF-19 concentrations will be determined for OCA PK and FXR activity in OCA-treated subjects. **Concentrations of atorvastatin and its metabolites will be assessed in PK sampled subjects.** Samples will be obtained for possible assessment of conjugated and unconjugated bile acids.	Addition of the determination of the concentration of atorvastatin and its metabolites.
11.2.2, Pharmacokinetic Assessments	Subjects who opt to participate in the PK assessment will provide blood samples for the measurement of OCA and its conjugates. The first sample should be collected within 30 minutes prior to administration of investigational product (predose) on Day 1 and prior to administration of investigational product or atorvastatin at the Week 16 Visit. Subjects will then receive a single dose of investigational product with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose.	Subjects who opt to participate in the PK assessment will provide blood samples for the measurement of OCA and its conjugates**, and atorvastatin and its metabolites**. The first sample should be collected within 30 minutes prior to administration of investigational product (predose) on Day 1 and prior to administration of investigational product or atorvastatin at the Week 16 Visit. Subjects will then receive a single dose of investigational product with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates**, and atorvastatin and its metabolites,** at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose.	Incorporation of atorvastatin PK and sampling.

Section	Original Text (Version 3)	Revised Text (Version 4)	Key Change Reasons / Justification for Change
12.1.4.1, Severity of Pruritus (as an AE)	•Drug holiday: A drug holiday is defined as an Investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (ie, non-daily dosing does not constitute a drug holiday). ~~For subjects with severe pruritus, instruct the subject to stop taking investigational product until the pruritus subsides to an acceptable level, at which time it should be restarted.~~ Details of drug holidays and/or nondaily dosing regimens should be recorded in the CRF.	•Drug holiday: A drug holiday is defined as an Investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (ie, non-daily dosing does not constitute a drug holiday). Details of drug holidays and/or nondaily dosing regimens should be recorded in the CRF**. Per Section 8.4.1.1, subjects with pruritus ≥Grade 3 in severity and possibly, probably, or definitely related to investigational product must discontinue investigational product.**	Instructions for severity of pruritus were removed. The instructions for the handling of ≥Grade 3 in severity are provided.
12.2.6, Laboratory Assessments Table 10, List of Laboratory Analytes to be Tested	Subset of Subjects PK analytes: OCA, tauro-OCA, glyco-OCA, ~~OCA glucuronide~~ and possible other conjugates or metabolites not yet identified	Subset of Subjects PK analytes: OCA, tauro-OCA, glyco-OCA, and possible other conjugates or metabolites not yet identified **Atorvastatin and its metabolites**	Removal of OCA glucuronide. Addition of atorvastatin and its metabolites.
	[a] NMR-based panel will be used for ~~(a)~~ LDL, HDL, and VLDL cholesterol concentrations, particle sizes, and particle concentrations~~, and (b)~~ ApoA1, ApoB, ApoE, ApoCII, ApoCIII ~~and~~ Lp(a) concentrations. Serum chemistry panel will be used for LDL, HDL, VLDL, TG, and total cholesterol concentration.	[a] NMR-based panel will be used for LDL, HDL, and VLDL cholesterol concentrations, particle sizes, and particle concentrations. ApoA1, ApoB, ApoE, ApoCII, ApoCIII**,** Lp(a) **and PCSK9** concentrations **will be measured using appropriate methods at central or specialty laboratories**. Serum chemistry panel will be used for LDL, HDL, VLDL, TG, and total cholesterol concentration.	Clarification of methods to be used for the determination of ApoA1, ApoB, ApoE, ApoCII, ApoCIII, Lp(a), and PCSK9 concentrations.
13.6.3.7, Pharmacokinetic Analysis	The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, ~~OCA glucuronide~~, and potentially other ~~conjugates or metabolites~~ not yet identified. PK analysis will be ~~done~~ using non-compartmental ~~methods~~. ~~The~~ values will be summarized by active treatment group using descriptive statistics. Only samples that have a confirmed fasting of approximately 8 hours or more before their visit will be included in the analysis. Further details regarding specific parameters ~~and methods~~ will be described in the SAP.	The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA**, atorvastatin and its metabolites**, and potentially other **analytes** not yet identified. PK analysis will be **conducted** using **standard** non-compartmental **methodologies**. **For the analysis of OCA and its conjugates**, values will be summarized by active treatment group using descriptive statistics. Only samples that have a confirmed fasting of approximately 8 hours or more before their visit will be included in the analysis.	Incorporation of clarifications for OCA and atorvastatin PK analysis.

Section	Original Text (Version 3)	Revised Text (Version 4)	Key Change Reasons / Justification for Change
		Further details regarding **the methods for calculating PK and the** specific parameters **to be reported** will be described in the SAP.	