Center For Experimental Therapeutics
School of Medicine
University of Pennsylvania Health System
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MEMORANDUM

our copy
IB, phase II report, FDA letter was sent to IRB, but copies not included in our copy submission packet

To: Joseph Sherwin, Ph.D.
Director, Regulatory Affairs
36th and Walnut Streets, Mellon Bank Building
Mezzanine Level
Philadelphia, PA 19104

From: Daniel J. Rader, MD

Date: December 2, 2002

Title: **A Phase I/II Open Label, Dose-Escalation Study to Determine the Safety, Tolerability and Efficacy of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor BMS-201038 in Patients with Homozygous Familial Hypercholesterolemia (Protocol No. UP 1001)**

Sponsor: Doris Duke Charitable Foundation

I am writing to request full-board approval of the above-referenced protocol. Please find attached the following documents:

- Original and 3 copies of this cover letter, full protocol, consent form, face sheet, and protocol summary
- 15 copies of the protocol summary, face sheet, and consent form
- 1 copy of the Investigational Brochure. Please note that the most recent IB is dated 10/13/97. The IB does not include information concerning the safety from the phase II study performed by Bristol-Myers Squibb (BMS). A summary of this report is included and was forwarded to the FDA by BMS in 6/02. We are in the process of updating the IB to include this data that will be forwarded to the IRB as soon as it is available. The proposed study will only be performed at The University of Pennsylvania. All investigators are familiar with all safety data.
- 1 copy of two recruitment tools (patient letter and doctor letter)

The intervention, investigational drug BMS-201038 (IND# 50,820), was transferred to me by Bristol-Myers Squibb on August 21, 2002. I submitted documentation to the FDA on 11/14/02 (see attached letter) to request an amendment to the IND to allow a new indication of homozygous familial hypercholesterolemia in both adolescent and adult patients. We had a teleconference with the FDA on 11/25/02 to discuss minor changes to the protocol, which have been incorporated in the attached documents. We will forward all future information concerning the IND to the IRB once it becomes available.

If you have any questions regarding the contents of this package, please contact LeAnne Bloedon, MS, RD at 215-573-1190, or myself. I thank the Committee for considering this request.

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(For Committee Use Only)

Date:Nov. 15, 2002 Appendix A Protocol # _____

UNIVERSITY OF PENNSYLVANIA
IRB PROTOCOL "FACE SHEET" (Page 1 of 2)

Submit the original protocol and 15 copies for full review or one copy of materials for exempted/expedited review to the Director for Regulatory Affairs, Suite 230, 3508 Market/3357 prior to the initiation of any work involving human subjects or human material. Please limit the title to 2 lines of 50 characters each if possible and answer all items below.

Project Title: **A Phase I/II Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability and Efficacy of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor BMS-201038 in Patients with Homozgyous Familial Hypercholesterolemia (Protocol # UP 1001)**

Funding Agency or Sponsor: **Doris Duke Charitable Foundation** Grant #:**Distinguished Clinical Scientist Award**

Address: 650 Fifth Ave, 19th floor, New York, NY 10019

Principal Investigator: **Daniel Rader, MD**
Title: **Associate Professor of Medicine**
Campus Mailing Address & Mailcode: **654 BRB II/III Labs, 421 Curie Blvd, Philadelphia, PA 19104**
Telephone: **215-573-4176** Responsible Org. (4 digits): # **4624**
SS # or PennCard ID #: **186-52-8751** E-Mail Address **rader@mail.med.upenn.edu**
Other Investigators **L. Bloedon, MS, RD; M. Cuchel, MD, PhD; P. Szapary, MD; M. Wolfe, BS**

PLEASE ANSWER THE FOLLOWING QUESTIONS:

1. ☐YES ☒ NO Is this application for a fellowship/stipend only?

2. ☐YES ☒ NO This project is to be undertaken as part of a previously approved Training, Center, or Program grant. Grant Number: _____
   Project Title: _____
   Director: _____

3. ☐YES ☒ NO Does the project involve the administration of personality tests, inventories, or questionnaires? If YES, provide the name and one copy of the standard tests/questionnaire or 3 copies of any proposed instrument: _____

4. ☒YES ☐ NO Does the project involve the use or drawing of human blood, blood products, tissues or body fluids? If YES, contact the Office of Environmental Health and Radiation Safety, 215-898-4453.

   4a. ☒YES ☐ NO Did you attend the Occupational Exposure to Bloodborne Pathogens Program within the last year?

5. ☐YES ☒ NO Does the project involve administration of ionizing radiation to subjects for other than clinical purposes? If YES, you must contact the Environmental Health and Radiation Safety Office, 215-898-7187.

6. ☐YES ☒ NO Does the project involve gene therapy (administration of recombinant vectors) to human

7. ☒ YES ☐ NO Does the project involve the testing of investigational drugs or devices? If YES, provide: Name of Drug or Device: BMS-201038 IND# or IDE# 50,820 Name of Manufacturer: Bristol-Myers Squibb and 1 copy of an **unreturnable** Drug/Device Brochure

   If this protocol involves the administration of medications to humans for research purposes (not part of general clinical practice), you **must obtain an authorization from the Penn Investigational Drug Service** (IDS) at 215-349-8817.
   Authorization number: _____ (must obtain from IDS staff).

8 ☐ YES ☒ NO Does the proposed study involve the use of electrical apparatus at HUP other than routine patient care equipment? If yes, contact the Director Clinical Engineering at 215-662-2330 for authorization.

9. ☐ YES ☒ NO Will this study involve additional work to the Nursing staff?

10. ☐ YES ☒ NO Do you, your spouse or any dependent children have any proprietary interest (i.e. any property or financial interest including stock in the sponsor, patents, trademarks, copyrights or licensing, supplemental research grants or consulting arrangements) in the tested drug, device or research procedure which is the subject of this study? **If yes, please describe in detail, the nature of the interest(s) in a separate attachment.** Please discuss how these conflicts will be managed during the period of the trial. Include language disclosing such interests in the consent form for use by research subjects.

    In addition, for industry sponsored trials please submit the documentation submitted to the sponsor as required by 21CFR54.1.

11. . Human Subjects involved in the proposed activity include: ☒ minors ☐ fetuses, ☐ abortuses ☐ pregnant women, ☐ prisoners, ☐ mentally retarded subjects, ☐ mentally disabled or cognitively impaired subjects, ☐ HIV-positive subjects, or ☐ None of the above special populations.

I certify that I have provided the IRB with all information relative to the known side effects and prior adverse events reported for the drug(s), devices or procedures which is the subject of this study and will inform the IRB immediately of any known change in this risk information.

Signatures: Principal Investigator: David Rader

*Department Chairperson: A.C. Schaffer Dept./Org Code:

Department Chairperson: _____ Dept./Org Code:

Faculty Sponsor (if required):

*The signature of each department chairperson with faculty involved, is required.
A Dean's signature must be obtained if the investigator is also the chairperson.

Clinical Protocol

Study Title: A Phase I/II Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability and Efficacy of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor BMS-201038 in patients with Homozygous Familial Hypercholesterolemia (Protocol No. UP 1001)

Principal Investigator: Daniel J. Rader, MD

Sub-Investigators: Jesse Berlin, PhD
LeAnne Bloedon, MS, RD
Marina Cuchel, MD, PhD
Philippe Szapary, MD
Megan Wolfe, BS

Department of Medicine, Center for Experimental Therapeutics, and the General Clinical Research Center University of Pennsylvania Medical Center Philadelphia, PA

Date: December 2, 2002

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1.0 OVERVIEW

1.1 Protocol Summary

Objectives: To determine the safety, dosing regimen and efficacy of MTP inhibitor, BMS-201038, in patients with homozygous Familial Hypercholesterolemia (hoFH). The primary objective is to evaluate the safety and tolerability of four doses of BMS-201038 given as an initial dose and then force-titrated up for an additional three doses over a 16 week period. Secondary objectives include evaluating the pharmacodynamics of BMS-201038 as determined by changes in a host of lipid-related laboratory measures.

Study Sites: The only site will be The University of Pennsylvania Medical Center in Philadelphia, PA, USA.

Subjects: Males and females at least 13 years old with clinically diagnosed homozygous familial hypercholesterolemia (hoFH). A minimum of 8 subjects will be enrolled in the study.

Study Design and Duration: This is a single site, open-label, dose-escalation phase I/II clinical trial that will evaluate the safety, tolerability and pharmacodynamics of BMS-201038 assessed by clinical laboratory data and adverse events. There will be a minimum of 8 subjects with hoFH enrolled in the study. All subjects will initially receive 0.03 mg/kg of BMS-201038 every day for 4 weeks. If none of the stopping rules apply, dosage will be increased to 0.1 mg/kg/d for the next 4 weeks, followed by 0.3 mg/kg/d and 1.0 mg/kg/d, each for 4 weeks duration. There are 15 visits during the entire 22 week study duration.

Outcome Measures: Toxicity will be measured in terms of physical findings on the clinical exam, electrocardiogram, pulmonary function tests, laboratory parameters (see Appendix A), vital signs, and any signs or symptoms reported by the subject. Toxicity will be assessed at screening, baseline and on days 7, 14, 28, 35, 42, 56, 63, 70, 84, 91, 98, 112, and 140 after study drug administration. In addition, research personnel will call each subject 24-72 hours following initiation of each new dose to inquire about reported short-term side effects.

Efficacy will be measured by analyzing changes in the following parameters at visits 1, 2, 5, 8, 11, 14, and 15: Total cholesterol (TC), LDL-cholesterol (directly measured), VLDL-cholesterol, HDL-cholesterol, triglycerides (TG), apoA-I, apoA-II, apoB, apo-CIII, apoE, and Lp(a).

1.2 Protocol Schematic

Screening Visit (Visit 1, -14 days)

Sign Informed Consent, full physical exam, medical history, clinical laboratory tests, electrocardiogram, vitals, urine pregnancy test, dietary counseling

↓

Baseline Visit (Visit 2, Day 0)

Abbreviated physical exam, electrocardiogram, vitals, dietary counseling and compliance, clinical laboratory data, drug administration (0.03 mg/kg/d), adverse events, concomitant medications, urine pregnancy test, NMRS testing, pulmonary function tests

↓

Follow-up Visits (Visits 3, 4, 6, 7, 9, 10, 12, 13; Days 7, 14, 35, 42, 63, 70, 91, 98)

Abbreviated physical exam, vitals, clinical laboratory data, adverse events, concomitant medications, urine pregnancy test

↓

End of Treatment Phase Visits (Visits 5, 8, 11, 14; Days 28, 56, 84, 112)

Abbreviated physical exam (full exam at visit 14 only), electrocardiogram, vitals, dietary counseling and compliance, clinical laboratory data, drug administration: visit 5, 0.1 mg/kg/d; visit 8, 0.3 mg/kg/d; visit 11, 1.0 mg/kg/d; adverse events, concomitant medications, urine pregnancy test, NMRS testing, pulmonary function tests

↓

Final Visit (Visit 15, Day 140)

Abbreviated physical exam, electrocardiogram, vitals, clinical laboratory data, adverse events, concomitant medications, NMRS testing, pulmonary function tests

2.0 Background & Significance:

2.1 Homozygous FH

Homozygous familial hypercholesterolemia (hoFH) is a serious life-threatening genetic disease caused by homozygosity or compound heterozygosity for mutations in the low density lipoprotein (LDL) receptor (1). Total plasma cholesterol levels are generally over 500 and markedly premature atherosclerotic vascular disease is the major consequence. Untreated, most patients develop atherosclerosis before age 20 and generally do not survive past age 30 (2). Currently there are no effective medical therapies for hoFH. The current standard of care is to perform LDL apheresis, a physical method of purging the plasma of LDL. Apheresis, while effective, must be repeated once a week, and there is a substantial rate of rebound of LDL cholesterol levels (3). Although anecdotally this procedure probably does delay the onset of atherosclerosis, it is laborious, expensive, and does not prevent the eventual development of atherosclerosis at a very premature age in these patients. Therefore, there is a tremendous unmet medical need for new medical therapies for hoFH. This disease formerly qualifies as an orphan disease in that it occurs with a frequency of approximately one in a million individuals, indicating that there are between 200 and 300 patients with homozygous FH in the U.S. (2).

2.2 Microsomal Transfer Protein (MTP)

Another rare genetic disease called abetalipoproteinemia is associated with extremely low levels of cholesterol and absent LDL in the blood (4). The genetic defect in this disorder is mutations in the microsomal transfer protein (MTP) (5,6). This protein is responsible for transferring lipids, particularly triglycerides, onto the assembling chylomicron and very low density lipoprotein (VLDL) particles in the intestine and the liver, respectively. In the absence of functional MTP, chylomicrons and VLDL are not effectively assembled or secreted and cannot be detected in the blood. VLDL serves as the metabolic precursor to LDL and the inability to secrete VLDL from the liver results in the absence of LDL in the blood. The finding that MTP is the genetic ideology of abetaliproteinemia led to the concept that pharmacologic inhibition of MTP might be a strategy for reducing cholesterol levels in humans (7). As a result, MTP inhibitors were developed by several pharmaceutical companies.

2.3 MTP Inhibitor, BMS-201038

Bristol-Myers Squibb (BMS) developed BMS-201038 as a potent inhibitor of MTP in vitro (IND 50,820). Studies in animals indicated that it effectively reduced plasma cholesterol levels (Investigator's Brochure). Of substantial importance to this protocol, a study was performed in the rabbit model of homozygous FH and BMS-201038 was found to be remarkably effective in reducing cholesterol levels in rabbits that lack a functional LDL receptor (8). This study in the best accepted animal model for the homozygous FH indicated that MTP inhibition by BMS-201038 might be effective in substantially reducing cholesterol levels in patients with hoFH.

BMS-201038 has been tested extensively in phase I and phase II trials in humans (Investigator's Brochure). It was found to be extremely effective in reducing plasma cholesterol and LDL cholesterol levels in humans (full analysis of efficacy data will be complete soon and forwarded to the FDA). Preliminary analysis of the phase II data reveals LDL cholesterol decreased by 65% in patients who received 25 mg BMS-201038 over four weeks. However, two issues have prevented this drug from being developed for large scale clinical use. First, patients taking higher doses of BMS-201038 (25 mg per day) developed steatorrhea (Investigator's Brochure). Second, an increase in liver transaminases, again primarily at higher doses, apparently due to some increase in the lipid content in the liver, was observed. Bristol-Myers Squibb concluded that these two effects made it unlikely that BMS-201038 could be developed as a drug for large scale use. However, we feel, and investigators at BMS and elsewhere fully concur, that BMS-201038 may be a very effective and reasonably safe medical therapy for lowering cholesterol in patients with hoFH. The current protocol is designed as a phase I/II protocol that would be the first evaluation of the safety, tolerability and pharmacodynamics of BMS-201038 in patients with hoFH.

2.4 Pharmacology

Previous in vitro and in vivo data of BMS-201038 has been performed exclusively by BMS and is described in the Investigator's Brochure.

2.5 Toxicology

All toxicity studies with BMS-201038 have been conducted by BMS. Toxicity data is included in the Investigator's Brochure.

3.0 Study Objectives

To determine the safety, dosing regimen and efficacy of MTP inhibitor, BMS-201038, in patients with hoFH. The primary objective is to evaluate the safety and tolerability of four doses of BMS-201038 given as an initial dose and then force-titrated for an additional three doses over a 16 week period. Secondary objectives include evaluating the pharmacodynamics of BMS-201038. The specific endpoints of interests include:

a. % change in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and very low density lipoprotein (VLDL) cholesterol concentrations at the end of each 4-week dose period compared to the baseline value of each parameter and at the end of the previous dose phase(s).
b. Changes in other plasma lipoproteins: apolipoproteins (A-I, A-II, B, C-III, E) and Lp(a)

4.0 Study Design

This is a single site, open-label, dose-escalation phase I/II clinical trial that will evaluate the safety, tolerability and pharmacodynamics of BMS-201038 assessed by clinical laboratory data and adverse events. There will be a minimum of 8 subjects with hoFH enrolled in the study. All subjects will initially receive 0.03 mg/kg of BMS-201038 every day for 4 weeks. If none of the stopping rules apply, dosage will be increased to 0.1 mg/kg/d for the next 4 weeks, followed by 0.3 mg/kg/d and 1.0 mg/kg/d, each for 4 weeks duration. There are 15 visits during the entire 22 week study duration.

5.0 Source of Subjects

Subjects will be recruited from a database consisting of patients with hoFH who were/are being treated by physicians at the University of Pennsylvania Health System or who completed a previous hoFH-related clinical trial. The rest of subjects will also be recruited via local IRB-approved web site announcements targeting patients with hoFH throughout the nation and around the world.

6.0 Study Population

A minimum of 8 subjects will be enrolled at the University of Pennsylvania. Subjects will be selected based on the following study criteria:

6.1 Inclusion Criteria:

1. Males and females ≥ 13 years of age
2. Clinical diagnosis of hoFH **AND** *one* of the following (a, b, or c):
   a. documented functional mutation in both LDL receptor alleles
   OR
   b. skin fibroblast LDL receptor activity < 20% normal
   OR
   c. TC > 500 mg/dL AND TG < 300 mg/dL AND both parents have documented TC > 250 mg/dL
3. Body weight ≥ 40 kg
4. Negative screening pregnancy test if female of child-bearing potential
5. Subjects must be willing to comply with all study-related procedures
6. Subjects must be willing and able to go off all lipid-lowering medications, dietary supplements (psyllium preparations) and LDL apheresis within 4 weeks prior to the baseline visit until the end of the study

6.2 Exclusion Criteria:

1. Uncontrolled hypertension defined as: systolic blood pressure > 180 mmHg, diastolic blood pressure > 95 mmHg
2. History of chronic renal insufficiency (serum creatinine >2.5 mg/dL)
3. History of liver disease or abnormal LFTs at screening (>3x upper limit normal)
4. Any major surgical procedure occurring less than 3 months prior to the screening visit
5. Cardiac insufficiency defined by the NYHA classification as functional Class III or Class IV
6. History of a non-skin malignancy within the previous 5 years
7. History of alcohol or drug abuse
8. Participation in an investigational drug study within 6 weeks prior to the screening visit
9. Serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the study.

7.0 Study Procedures

A detailed study time-table and list of all procedures to be performed at each visit is included in Appendix A.

7.1 Screening Visit (-14 Days)

Potential subjects will be screened first by a telephone interview with research personnel. Subjects who meet initial study requirements will be invited for a screening visit (visit 1) at the General Clinical Research Center (GCRC). During this visit, they will review and sign an IRB-approved consent form. A study physician or nurse practitioner will obtain medical history and perform a physical examination. Nursing will obtain an electrocardiogram and measure weight, height, waist circumference, sitting blood pressure and heart rate. In addition, subjects will have blood drawn (after following a 12-hour fast) for evaluating fasting lipids, safety laboratory parameters and a complete blood count as described in Appendix A. In addition, subjects will provide a urine sample for a standard urine analysis and pregnancy test (females of child-bearing potential only). These laboratory parameters are included to assure the subject meets eligibility criteria and that he/she is in good health. Research staff will call each subject once clinical data has been reviewed to notify him/her if they may continue with the study.

7.1.1 Dietary Counseling

Subjects will receive dietary counseling at the screening visit instead of returning once eligibility is confirmed in order to decrease the number of study visits since many of the volunteers will be traveling great distances. It is important for subjects to follow the research diet per instructions based on the activity of MTP. MTP is expressed in the intestine and is involved in the production of chylomicrons, which carry lipids in circulation. When MTP is absent or inhibited in the presence of a lipid-containing diet, steatorrhea results secondary to fat malabsorption. This can lead to secondary malabsorption of other nutrients, as well as weight loss. These effects can be eliminated if a fat-poor diet is followed as seen in patients with abetalipoproteinemia, a genetic condition characterized by MTP deficiency (9). A fat-poor diet, however, can lead to deficiencies in fat-soluble vitamins (vitamins A, D, E and K) and the essential fatty acids, linoleic acid and alpha linolenic acid. The negligible fat diet described below is designed to prevent the symptoms of lipid malabsorption and provide all essential nutrients to prevent deficiencies while maintaining a healthy weight.

Subjects will meet with the registered dietitian at the screening visit for initial dietary instruction and then at each subsequent visit to monitor dietary compliance, weight maintenance and discuss potential adherence problems. Subjects will be instructed to start following the research diet beginning immediately after the screening visit until they complete the study. The dietitian will provide diet instructions that are tailored to each individual for healthy weight maintenance.

Subjects will be instructed on how to include at least 3 g, but no more than 5 g total fat (mixed between linoleic acid and alpha linolenic acid sources) per day in order to provide enough essential fatty acids to prevent deficiency. In addition, subjects will be provided a standard multi-vitamin and be instructed to take one per day starting the day of the screening visit until completion of the study. The multivitamin will supply 100% of the current Dietary Reference Intake (DRI) based on age and gender for all essential vitamins and minerals (includes fat-soluble vitamins). The registered dietitian will call subjects 3-5 days after the screening visit to assess compliance and assist with potential problems regarding diet adherence.

7.2 Baseline visit (Day 0)

Subjects will return to the GCRC 1- 2 weeks after the screening visit for the baseline visit. Subjects will receive study drug and be instructed to take a once daily dosage that is equivalent to 0.03 mg/kg body weight. Enough study drug will be supplied to cover the next four weeks with an extra 7 day supply. Clinical assessments will be performed as described in Appendix A. Blood and urine will be drawn for parameters listed in Appendix A after a 12-hour fast. Subjects will be asked about possible changes in their medical history and medication usage. Subjects will meet with the dietitian to monitor dietary compliance and discuss potential adherence problems.

7.3 Follow-up Visits

Subjects will return to the GCRC 7, 14 and 28 (+/- 3 days) days after each initiation of a new dosage of BMS-201038 (see Appendix A for a more detailed time schedule). Research personnel will call subjects 24-72 hours following initiation of each dose in order to inquire about possible tolerability problems and monitor short-term adverse events. Subjects will come back to the GCRC 28 days (+/-3 days) after subjects have stopped the last dosage for a final visit. This design allows us to capture potential adverse events that may be related to the study drug while considering subject needs and lifestyle. The procedures that will be performed at every visit are described in detail in Appendix A. The Data and Safety Monitoring Plan section (Section 9.7) describes how adverse events will be handled and rules regarding dose escalation and patient removal.

7.4 Measures of Clinical Toxicity

Toxicity will be measured in terms of physical findings on the clinical exam, electrocardiogram, pulmonary function tests, NMRS testing, laboratory parameters (see Appendix A), vital signs,

and any signs or symptoms reported by the subject. All toxicity measures will be assessed at baseline (day 0), at the end of each dose-treatment (days 28, 56, 84, 112) and at the final visit (day 140). Specific toxicity measures (see Appendix A) will also be included on days 7, 14, 35, 42, 56, 63, 70, 91, 98, and 140 days after study drug administration. In addition, research personnel will call each subject 24-72 hours following initiation of each dose to inquire about reported short-term side effects.

7.5 Measures of Efficacy

Efficacy will be measured by analyzing changes in the following parameters at visits 1, 2, 5, 8, 11, 14, and 15: Total cholesterol, LDL-cholesterol (directly measured) VLDL-cholesterol, HDL-cholesterol, triglycerides, apoA-I, apoA-II, apoB, apo-CIII, apoE, and Lp(a).

7.6 Bioassays

Please see Appendix A for a complete schedule and explanation of all laboratory tests performed as a part of this study.

In our ongoing clinical research studies, our group routinely employs a variety of assays of lipids and lipoproteins in the CDC-certified lipid laboratory at the University of Pennsylvania using a COBAS FARA II high speed automated selective chemistry system. All blood samples will be collected in the GCRC, centrifuged and the plasma kept at –70°C prior to analysis in batches.

Test	Type of Assay	Manufacturer	Catalog #	Lower Limit	Low CV	High CV
Cholesterol	Enzymatic	Wako Diagnostics	276-64909	1 mg/dl	2.35	3.22
Triglycerides	Enzymatic	Wako Diagnostics	995-86108	1 mg/dl	1.81	2.90
HDL-Chol.	Enzymatic	Raichem	82051	1 mg/dl	2.2	2.5
ApoA-I*	ImmunoTurbidometric	Wako Diagnostics	991-27201	1 mg/dl	1.2	1.5
ApoA-II*	ImmunoTurbidometric	Wako Diagnostics	416-27301	5 mg/dl	1.5	3.2
ApoB*	ImmunoTurbidometric	Wako Diagnostics	993-27401	1 mg/dl	2.5	1.7
ApoCIII	ImmunoTurbidometric	Wako Diagnostics	411-35801	1.1mg/dl	1.2	3.2
ApoE	ImmunoTurbidometric	Wako Diagnostics	417-35901	0.5mg/dl	5.0	1.6
Lp(a)	ImmunoTurbidometric	Wako Diagnostics	1742-101	1 mg/dl	4.26	2.24

All non-lipid laboratory parameters (see Appendix A) will be analyzed by Pepper Laboratories at the Hospital of the University of Pennsylvania (HUP). This laboratory is both CLIA and CAP certified.

8.0 Study Drug

8.1 Drug administration and labeling

BMS-201038 will be supplied as powder from Bristol Myers Squibb. The investigational pharmacist at the GCRC will weigh study drug based on the required dose and subject's body weight and package it into a standard gelatin capsule. Each bottle will be labeled with the patient's unique identification number, name, date dispensed, storage conditions, and directions for use. The initial dosage will be 0.03 mg/kg/d of BMS-201038 or placebo, followed by daily administration of 0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg. Drug will be taken with water once daily in the morning. Subjects will be instructed to bring their bottles of study drug to the GCRC at every clinic visit after enrollment. On the day subjects are coming to the clinic for a scheduled visit, they will be instructed to take that day's dosage in the clinic. Missed doses should be taken only if they can be taken $\geq$ 12 hours prior to the next scheduled dose.

8.2 Drug storage and Drug accountability

The investigational pharmacist at the GCRC will ensure that all study drug is stored in a secured area, under recommended storage conditions (86° F) and in accordance with applicable regulatory requirements, and will be dispensed by qualified staff members. The pharmacist will maintain accurate records regarding study drug administration and return.

8.3 Compliance

Study drug compliance will be monitored by pill count. Research personnel will record study drug compliance in the appropriate section of the Case Report Form (CRF).

8.4 Dose Selection

Because this study will include adolescents of varying body size and weight, the dose will be based on weight rather than as a fixed dosing. BMS-201038 has been studied in phase I trials at doses as low as 5 mg in adults. Therefore, we chose a very low dose (0.03 mg/kg body weight) as the starting dose for this trial, fully expecting this dose to be very safe but also unlikely to be efficacious with regard to cholesterol lowering. There are at least two major reasons for starting at a dose of 0.03 mg/kg body weight. First, particularly since adolescents

will be included, to ensure a high level of safety and tolerability at the initial starting dose in this study. Second, we hypothesize that the steatorrhea and liver lipid accumulation may be reduced by the initiation of a very low dose of the drug with a gradual up titration. The remaining three doses were chosen by calculating ½ log units of the previous dose. We picked an upper dose of 1 mg/kg based on data from the animal study by Wetterau (8) revealing greater than 80% LDL cholesterol reduction using 10 mg/kg, with an ED_{50} of 1.9 mg/kg.

9.0 Safety

9.1 Potential Risks

BMS-201038 has been studied in humans up to one phase II clinical trial. Healthy volunteers with primary hypercholesterolemia were randomized in a 1:1 ratio to receive a once-daily dose of BMS-201038 25 mg every day x 4 weeks or matched placebo every day x 4 weeks. Safety was measured based on adverse events (AEs), percent hepatic fat by Nuclear Magnetic Resonance Spectroscopy (NMRS) of the liver, and the results of vital sign measurements, electrocardiograms, physical examinations and clinical laboratory tests. There were no deaths or serious AEs. In the treated group, gastrointestinal and hepatobiliary related AEs were the most common and thought to be related to treatment. Diarrhea and nausea/vomiting were notably increased in the active group and hepatobiliary AEs were seen only in the active group. Hepatic fat content increased by an average of 20.6% in the active group compared to essentially no change in the placebo group. Following 6 weeks off drug, the reversibility of the fat accumulation was demonstrated as the mean percent fat decreased to 2.9% above baseline in the treated group and the placebo group remained unchanged.

Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal pain, weight loss) were at least in part due to the presence of a lipid-containing diet and can most likely be eliminated by restricting fat content in the diet as explained in section 7.1.1. In this study, we propose to include minimal fat (< 5 g per day) to avoid gastrointestinal effects, while providing enough lipids to supply essential fatty acids. In addition, subjects will receive a daily multi-vitamin to provide 100% of the dietary reference intakes (DRI's) of fat-soluble vitamins as well as all vitamins and minerals.

The increase in hepatic fat content seen in the phase II study was minimal, and is comparable to the level of fatty liver seen in various conditions (e.g. alcoholism, obesity, diabetes, hepatitis C, use of certain medications). In addition, the effects of the drug on hepatic content were

almost completely reversed by 6 weeks after drug was discontinued. Steatosis is usually asymptomatic or associated with a mild increase in animo transferases. In the population of hoFH that is at very high risk of morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD), minimal fatty liver will most likely not result in significant adverse clinical effects. Stopping rules, as explained in sections 9.7.1.1.1-9.7.1.1.3, have been included for specific hepatic laboratory parameters to protect subjects against risk of hepatic toxicity. We will perform NMRS testing of the liver at baseline, at the end of each dose-treatment phase (4, 8, 12, and 16 weeks) and at the final visit to provide information to assist in determining the appropriate dosage for future studies.

As with any blood test, there may be some minor discomfort, minor bruising, and/or fainting associated with the drawing of blood. There is also a very small chance (less than 1%) of infection at the needle puncture site.

9.2 Potential Benefits

The primary benefit is the potential of BMS-201038 to significantly lower LDL cholesterol and thus reduce atherosclerosis. BMS-201038 has been shown to reduce LDL cholesterol by as much as 80% in humans. We feel the benefits of this medication far outweigh the potential risks (steatorrhea and minimal fatty liver) in a very high risk population for ASCVD and associated ASCVD mortality with limited available medical therapy. Thus, BMS-201038 has the potential to serve as an orphan drug.

9.3 Adverse events

All observed or volunteered adverse events regardless of suspected causal relationship to study drug will be recorded on the adverse event source document and transcribed onto the case report form. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing illnesses will be recorded. In addition, abnormal objective test findings (e.g., electrocardiogram changes, abnormal laboratory test results) that result in a change in study drug dosage or in discontinuation of the drug, or require intervention or diagnostic evaluation to assess the risk to the patient/subject, will be recorded as adverse events. Clinically significant changes in physical examination findings will also be recorded as adverse events. All adverse events will be graded according to the National Cancer Institute's Common Toxicity Criteria (CTC), version 2.0 (4/30/99).

9.4 Non-serious Adverse Events

Any AE that is not designated as Serious, as defined in Section 8.3 below, must be recorded on the Non-serious AE page of the CRF. All non-serious adverse events will be reported to the University of Pennsylvania IRB according to standard operating procedures.

9.5 Serious adverse events

All serious adverse events (as defined below) regardless of treatment group or suspected relationship to study drug will be immediately reported to the University of Pennsylvania IRB and the FDA.

A serious adverse event is any adverse drug experience occurring at any dose that:

1. results in death;
2. is life-threatening;
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity; or
5. results in congenital anomaly/birth defect.

9.6 Pregnancy

If a subject or Investigator suspects that the subject may be pregnant prior to study drug administration, the study drug must be withheld until results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must be withdrawn from the study. If pregnancy is suspected while the subject is receiving study drug, the study drug must immediately be withdrawn until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject withdrawn from the trial. Protocol required procedures for study discontinuation will be performed on the subject unless contraindicated by pregnancy. Other appropriate follow-up procedures will be considered if indicated.

9.7 Data and Safety Monitoring Plan

This trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) as outlined in the International Conference on Harmonization (ICH) document "Good Clinical Practice: Consolidated Guideline" and the Declaration of Helsinki. All data will first be collected on original source documents by research personnel. Data will be transferred onto case report

forms (CRFs) as instructed by internal standard operating procedures. CRFs will not contain any subject identifiers. Original source documents, CRFs, and other study documentation will be maintained in a locked file cabinet in the research coordinator's office until archived.

The monitoring of a clinical trial is necessary to ensure the protection of the subject's rights, the safety of subjects enrolled in the trial and the integrity and quality of the resulting data. For this type of clinical trial, The University of Pennsylvania routinely employs monitoring services from an outside, self-employed Clinical Research Associate (CRA) that is not an employee of the University of Pennsylvania. This individual will be hired at a later date.

Monitoring visits will be conducted periodically throughout the study. The first monitoring visit will occur no more than 2 weeks after the first subject is randomized. Subsequent monitoring visits will occur based on enrollment, but will typically be scheduled for every 2-3 months. At each visit, the monitor will review the Regulatory Binder, source documents and CRFs. The monitor will provide a written report to the PI and DSMB detailing findings after each visit that will be filed in the Regulatory Binder.

9.7.1 Data and Safety Monitoring Board (DSMB)

A DSMB will be established to assure the safety of participants in this trial as well as the validity and integrity of the data generated. The DSMB will review laboratory data and adverse events on an ongoing basis. The DSMB will assess safety via complete blood and urine analyses, physical exams, capturing of adverse events and concomitant medications and other clinical data (e.g. vitals, anthropometric measures, electrocardiograms). Membership of the DSMB will be comprised of at least three physicians (one lipid expert, one expert in hepatology, and one pediatric specialist with a strong pharmacokinetic background) not affiliated with any aspect of this study. The DSMB will meet (may be via teleconference) at least one time per month after the first person has initiated treatment and more frequently as needed. The DSMB will also meet in the event of grade 3 or 4 toxicity as described in the sections below. Reports detailing what was discussed at these meetings will be forwarded to the Principal Investigator. A copy of reports relating to safety will be provided to the data monitor. The following dose escalation and removal rules will be instated and mandated by the DSMB:

9.7.1.1 Rules Governing Dose Escalation for Grade 3 Toxicity

9.7.1.1.1 Individuals

Dose escalation may occur if the subject tolerates therapy without evidence of grade 3 toxicity (as defined by the NCI's Common Toxicity criteria, version 2, 1999, Appendix B). If an individual experiences a grade 3 toxicity, he/she will come back for confirmation (e.g. repeat lab test) as soon as possible. If evidence of grade 3 toxicity is confirmed, dosage will be decreased to 1½ times the previous dose for an additional 4 weeks following the visit schedule per standard protocol (see Section 9.5.1.1.3, "Removal of Subjects from Study: Addressing Grade 4 Toxicity" for specific guidelines relating to specific grade 4 adverse events). If grade 3 toxicity is discovered at 7, 14, or 28 days after the reduction in dose, the dosage will be further decreased to the previous pre-escalated dose (0.03, 0.1, 0.3 mg/kg/d) for an additional 4 weeks per standard protocol. If grade 3 toxicity is detected at any visit (7, 14, or 28 days post dose) at this dosage, the subject will discontinue drug, but will come back 4 weeks after drug has been discontinued for a final safety visit. If there is no evidence of grade 3 toxicity at any of the visits during a four week period where dosage has been lowered, then the subject will escalate to the next dosage per standard protocol and follow the study visit schedule per protocol.

9.7.1.1.2 Remaining Subjects

When a volunteer experiences grade 3 or 4 toxicity, the remaining subjects (at all doses) will remain following the dosing regimen per protocol. If two people experience the same grade 3 or 4 toxicity at the same dose level, or if 4 subjects (50%) experience any grade 3 or 4 toxicity at any dose level, the DSMB will meet to determine if the dosing regimen should be altered for remaining subjects.

9.7.1.1.3 Removal of Subjects From Study: Addressing Grade 4 Toxicity

Every effort within the bounds of safety and patient choice will be made to have subjects complete the study. With regards to hepatoxicity, if a volunteer experiences confirmed grade 4 toxicity, he/she will discontinue study drug and come back 4 weeks after drug has been discontinued for a final visit (equivalent to visit 15, day 140). Grade 4 toxicity regarding hepatoxicity is defined below:

1. If either ALT or AST levels are greater than 20.0 x ULN on two separate occasions and at least 24 hours apart;

2. If alkaline phosphatase is > 20.0 x ULN on two separate occasions and at least 24 hours apart;
3. If total bilirubin is > 10.0 x upper limit of normal on two separate occasions and at least 24 hours apart;

Other rules for removing volunteers from the study not relating to hepatoxicity include:

4. Clinically significant laboratory abnormality or SAE that will impede the patient from continuing in the study;
5. Demonstrated non-compliance with study protocol; or
6. Patient chooses to discontinue from the study

10.0 Consent Procedures

Before study initiation, this protocol, the informed consent form, and any advertisements for subject recruitment will be submitted for review and approval to the University of Pennsylvania Institutional Review Board (IRB). The investigator will obtain written informed consent from each subject enrolled in the study, in accordance with the U.S. Food and Drug Administration (FDA) regulations 21 CFR parts 50.20-50.27. It is the responsibility of the investigator to ensure that informed consent is obtained from the subject or his/her guardian or legal representative before any activity or treatment is undertaken which is not part of routine care.

11.0 Database Management

A study specific database will be created by the Biostatistics Analysis Center (BAC). The BAC is a research facility within the Biostatistics Unit of the Center for Clinical Epidemiology and Biostatistics (CCEB) at the University of Pennsylvania School of Medicine. The BAC will be responsible for creating the case report forms and the Access database that will be used specifically for this project.

All the data generated from the trial will be backed up daily on the server. The data will be double entered into the database, without identifying information and the database itself will be password protected.

12.0 Statistical Analysis

All analyses will be performed by the appointed biostatistician using SAS software (Version 8.0, SAS Institute; Cary, NC). The primary endpoint of this study is to establish safety and tolerability

of BMS-201038 in this population with regards to laboratory and clinical parameters. This will be done using paired Student's t-tests for continuous variables and Fisher's Exact tests for proportions.

Secondary objectives include evaluating the pharmacodynamics of BMS-201038 as determined by changes in a host of lipid-related laboratory measures. Our primary efficacy variable will be percent reduction in LDL-C, comparing the effect of each dose to baseline and LDL-C values at the end of previous dose phases. This will again be done using a paired Student's t-test. Because we will be making multiple time point comparisons, all t-tests will be adjusted using Bonferoni methods. Since this is a pilot study, formal sample size calculations are not needed. However, based on enrolling 8 patients with hoFH for this study, we would be able to detect LDL-C reductions of at least 30% as shown below. For doses 0.1, 0.3, and 1.0 mg/kg, we expect to see LDL-C reductions in the ranges of 0-15%, 15-35%, and 35-80%, respectively based on data from previous phase I and II studies in healthy volunteers with normal cholesterol concentrations (see IND 50,820). For our purposes, we will assume that all subjects will advance and complete the 0.3 mg/kg dose. We expect to see at least a 30% reduction in LDL-C at that dose. Based on previous data, we expect that the SD at baseline and week 8 will be 20%. Using a two-tailed alpha of 0.05 and an 80% power, we would need 6 completed subjects at that dose level. With the sample size of 8 completing the entire study, paired comparison would have over 80% power to detect reductions of 24% in LDL-C. Thus, with 8 subjects we will have sufficient numbers upon which to gauge safety and efficacy, and to more precisely estimate sample size for future studies of this agent in this high-risk population.

Appendix A

Study Visits & Procedures

Procedure	Visit 1	Visit 2	Visits 5, 8, 11, 14	Visits 3, 4, 6, 7, 9, 10, 12, 13	Visit 15
	-2 Weeks	**Week 0**	**Days 28, 56, 84, 112**	**Days 7, 14, 35, 42, 63, 70, 91, 98**	**Day 140**
Informed consent	X				
Medical History (screen) Physical exam[1]	X	X	X	X	X
Electrocardiogram	X	X	X		X
Blood pressure, heart rate, weight, height & waist measures	X	X	X	X	X
Dietary counseling & compliance	X	X	X		
Comprehensive Metabolic Lab Panel, TSH, INR and CBC[2]	X	X	X	X	X
Fat-soluble vitamin levels[3]		X	X		X
Fatty acid profile[4]		X	X		X
Full fasting Lipid profile[5]	X	X	X		X
Urinalysis[6]	X	X	X	X	X
Drug administration		X[7]	X[8]		
Adverse Events		X	X	X	X
Concomitant medications	X	X	X	X	X
Urine pregnancy test[9]	X	X	X	X	
Drug Compliance			X	X	
NMRS of the liver		X	X		X
Pulmonary Function Tests[10]		X	X		X

[1] A full physical exam (genitourinary) will be performed at visits 1 and 14 and abbreviated exams will be performed at visits 2-13, and 15.

[2] Comprehensive Metabolic panel includes: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, TSH (only at visits 2 and 15), INR and total bilirubin. CBC includes: white blood cell count, hemoglobin, hematocrit, platelet count, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

[3] Vitamins A, E and D will be assessed by measuring serum concentrations of the individual vitamins. Levels of vitamin K will be monitored indirectly by evaluating the INR.

[4] Fatty acid profile includes serum levels of linoleic acid and alpha linolenic acid

[5] Full fasting lipid panel includes: Total Cholesterol, LDL-Cholesterol (directly measured) VLDL-Cholesterol, HDL-Cholesterol, Triglycerides, apoA-I, apoA-II, apoB, apoE, Lp(a). Apolipoproteins will be measured at visits 2, 5, 8, 11, 14 and 15 only

[6] Urinalysis includes urinary color, turbidity, pH, glucose, bilirubin, ketones, blood, protein, WBC's

[7] Study drug will be initiated at 0.03 mg/kg body weight

[8] Drug will be escalated if none of the stopping rules apply as follows: visit 5, 0.1 mg/kg; visit 8, 0.3 mg/kg; visit 11, 1 mg/kg. Study drug will not be administered at visit 14 as this is the last day of treatment

[9] Potential childbearing females only

[10] Spirometry with DLCO will be performed to include: forced vital capacity; forced expiratory volume during 1 second; forced expiratory flow, 25-75%; and carbon monoxide lung diffusion

Appendix B

COMMON TOXICITY CRITERIA (CTC)

Adverse Event	Grade 0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever <38°C (<100.4°F)	urticaria, drug fever ≥38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					

Adverse Event	Grade 0	1	2	3	4
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing - Other (Specify. _____)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or ≤25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges:					
children (≤18 years)	*90% cellularity average*				
younger adults (19-59)	60 - 70% cellularity average				
older adults (≥60 years)	50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	<LLN - 500/mm^3	200 - <500/mm^3	50 - <200/mm^3	<50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	<LLN - 10.0 g/dL <LLN - 100 g/L <LLN - 6.2 mmol/L	8.0 - <10.0 g/dL 80 - <100 g/L 4.9 - <6.2 mmol/L	6.5 - <8.0 g/dL 65 - <80 g/L 4.0 - <4.9 mmol/L	<6.5 g/dL <65 g/L <4.0 mmol/L
For leukemia studies or bone marrow infiltrative/ myelophthisic processes, if specified in the protocol.	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Also consider Haptoglobin, Hemoglobin.					

Adverse Event	Grade 0	1	2	3	4
Leukocytes (total WBC)	WNL	<LLN - 3.0 x 10^9/L <LLN - 3000/mm^3	≥2.0 - <3.0 x 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9/L ≥1000 - <2000/mm^3	<1.0 x 10^9/L <1000/mm^3
For BMT studies, if specified in the protocol.	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9/L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol.		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9/L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3	-
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol.		*≥75 - <100%LLN*	*≥50 - <75%LLN*	*≥25 - <50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9/L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3
For BMT studies, if specified in the protocol.	WNL	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9/L ≥100 - <500/mm^3	<0.1 x 10^9/L <100/mm^3
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	<LLN - 75.0 x 10^9/L <LLN - 75,000/mm^3	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥10.0 - <50.0 x 10^9/L ≥10,000 - <50,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
For BMT studies, if specified in the protocol.	WNL	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥20.0 - <50.0 x 10^9/L ≥20,000 - <50,000/mm^3	≥10.0 - <20.0 x 10^9/L ≥10,000 - <20,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT studies, if specified in the protocol.	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					

Adverse Event	Grade 0	1	2	3	4
Transfusion: pRBCs	none	-	-	yes	-
For BMT studies, if specified in the protocol.	none	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
For pediatric BMT studies, if specified in the protocol.	*none*	*≤15mL/kg in 24 hours elective or planned*	*>15 - ≤30mL/kg in 24 hours elective or planned*	*>30mL/kg in 24 hours*	*hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin*
Also consider Hemoglobin					
Blood/Bone Marrow - Other (Specify. _____)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-
Note: Grade palpitations only in the absence of a documented arrhythmia.					
Prolonged QTc interval (QTc >0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-

Adverse Event	Grade 0	1	2	3	4
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia - Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T - wave flattening or changes	asymptomatic, ST - and T - wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥10% but <20% of baseline value, shortening fraction ≥24% but <30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥20% of baseline value; <24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥0.03 - <0.05 ng/mL	≥0.05 - <0.1 ng/mL	≥0.1 - <0.2 ng/mL	≥0.2 ng/mL
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to >150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by >20 mmHg (diastolic) or to >150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis

Note: For pediatric patients, use age and sex appropriate normal values >95th percentile ULN.

Adverse Event	Grade 0	1	2	3	4
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting).					
Notes: Angina or MI is graded as Cardiac-ischemia/infarction in the CARDIOVASCULAR (GENERAL) category.					
For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	with physiologic consequences	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Notes: Injection site reaction is graded in the DERMATOLOGY/SKIN category.					
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General - Other (Specify. _____)	none	mild	moderate	severe	life-threatening or disabling

Adverse Event	Grade 0	1	2	3	4
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also consider Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg
Partial thromboplastin time (PTT)	WNL	>ULN - ≤1.5 x ULN	>1.5 - ≤2 x ULN	>2 x ULN	-
Phlebitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	>ULN - ≤1.5 x ULN	>1.5 - ≤2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT studies, if specified in the protocol,	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin, Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Note: See Appendix III for performance status scales.					

Adverse Event	Grade 0	1	2	3	4
Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10^9/L)	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	>40.0°C (>104.0°F) for <24hrs	>40.0°C (>104.0°F) for >24hrs
Also consider Allergic reaction/hypersensitivity.					
Note: The temperature measurements listed above are oral or tympanic.					
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain	<5%	5 - <10%	10 - <20%	≥20%	-
Also consider Ascites, Edema, Pleural effusion (non-malignant).					
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure
Also consider Ascites, Edema, Pleural effusion (non-malignant).					
Weight loss	<5%	5 - <10%	10 - <20%	≥20%	-
Also consider Vomiting, Dehydration, Diarrhea.					
Constitutional Symptoms - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-

Adverse Event	Grade 0	1	2	3	4
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
Also consider Allergic reaction/hypersensitivity.					
Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					
Rash/dermatitis associated with high-dose chemotherapy or BMT studies.	none	faint erythema or dry desquamation	moderate to brisk erythema ona patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	None	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity.					
Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					

Adverse Event	Grade 0	1	2	3	4
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound-infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fasciitis
Wound-non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin - Other (Specify. _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	absent	-	present	-	-
Also consider Hyperglycemia, Hypokalemia.					
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon

Adverse Event	Grade 0	1	2	3	4
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis), Hypotension.					
Diarrhea patients without colostomy:	none	increase of <4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	None	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
For pediatric BMT studies, if specified in the protocol		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If the adverse event is radiation-related, grade either under Dysphagia-esophageal related to radiation or Dysphagia-pharyngeal related to radiation.					
Dysphagia-esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	Dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula-esophageal.					
Dysphagia-pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula-pharyngeal.					
Fistula-esophageal	none	-	-	present	requiring surgery
Fistula-intestinal	none	-	-	present	requiring surgery

Adverse Event	Grade 0	1	2	3	4
Fistula-pharyngeal	none	-	-	present	requiring surgery
Fistula-rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Notes: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginitis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally >1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Notes: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia-esophageal related to radiation or Dysphagia-pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Amylase is graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					

Adverse Event	Grade 0	1	2	3	4
Proctitis	none	increased stool frequency, occasional blood-streaked stools or rectal discomfort (including hemorrhoids) not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea requiring parenteral support; rectal bleeding requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain due to radiation.					
Notes: Fistula is graded separately as Fistula-rectal/anal.					
Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva; may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
For BMT studies, if specified in the protocol	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Adverse Event	Grade 0	1	2	3	4
HEMORRHAGE					
Notes: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (<50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider Platelets, Transfusion: pRBCs, and Transfusion: platelets in addition to grading severity by grading the site or type of bleeding. If the site or type of Hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS Hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage-Other (Specify site, _____). Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, Hemorrhage - Other (Specify site, _____). Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Note: Expected blood loss at the time of surgery is not graded as an adverse event.					
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention

Adverse Event	Grade 0	1	2	3	4
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring <2 pads per day	requiring ≥2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage - Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	normal	≥2 - <3 mg/100 mL	≥3 - <6 mg/100 mL	≥6 - <15 mg/100 mL	≥15 mg/100 mL
GGT (γ - Glutamyl transpeptidase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hepatic enlargement	absent			present	-
Note: Grade Hepatic enlargement only for treatment related adverse event including Veno-Occlusive Disease.					
Hypoalbuminemia	WNL	<LLN - 3 g/dL	≥2 - <3 g/dL	<2 g/dL	-
Liver dysfunction/ failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hepatic - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)

Adverse Event	Grade 0	1	2	3	4
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C) Also consider Neutrophils. Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L) Also consider Neutrophils. Notes: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC Note: This adverse event criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia Also consider Neutrophils.	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
Infection/Febrile Neutropenia - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH <normal, but ≥7.3	-	pH <7.3	pH <7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH >normal, but ≤7.5	-	pH >7.5	pH >7.5 with life-threatening physiologic consequences
Amylase	WNL	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	<LLN - 16 mEq/dL	11 - 15 mEq/dL	8 - 10 mEq/dL	<8 mEq/dL

Adverse Event	Grade 0	1	2	3	4
CPK (creatine phosphokinase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5 x ULN	>5 - 10 x ULN	>10 x ULN
Hypercalcemia	WNL	>ULN - 11.5 mg/dL >ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dL >2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dL >3.1 - 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Hypercholesterolemia	WNL	>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
Hyperglycemia	WNL	>ULN - 160 mg/dL >ULN - 8.9 mmol/L	>160 - 250 mg/dL >8.9 - 13.9 mmol/L	>250 - 500 mg/dL >13.9 - 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis
Hyperkalemia	WNL	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypermagnesemia	WNL	>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
Hypernatremia	WNL	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10 x ULN	>10 x ULN
Hyperuricemia	WNL	>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
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Hyperkalemia.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dL <LLN - 2.0 mmol/L	7.0 - <8.0 mg/dL 1.75 - <2.0 mmol/L	6.0 - <7.0 mg/dL 1.5 - <1.75 mmol/L	<6.0 mg/dL <1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dL <LLN - 3.0 mmol/L	40 - <55 mg/dL 2.2 - <3.0 mmol/L	30 - <40 mg/dL 1.7 - <2.2 mmol/L	<30 mg/dL <1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dL <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dL 0.4 - <0.5 mmol/L	0.7 - <0.9 mg/dL 0.3 - <0.4 mmol/L	<0.7 mg/dL <0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dL <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dL ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dL ≥0.3 - <0.6 mmol/L	<1.0 mg/dL <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Metabolic/Laboratory - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling

Adverse Event	Grade 0	1	2	3	4
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia (tenderness or pain in muscles) is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline >2 SD*	*inability to work/frank mental retardation*

Adverse Event	Grade 0	1	2	3	4
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Note: Syncope (fainting) is graded in the NEUROLOGY category.					
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This adverse event is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability (children <3 years of age)	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	none	mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum	severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)	severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia

Adverse Event	Grade 0	1	2	3	4
Mood alteration-anxiety, agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy-cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy-motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus	absent	present	-	-	-
Also consider Vision-double vision.					
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA). Vasovagal episode, CNS cerebrovascular ischemia.					

Adverse Event	Grade 0	1	2	3	4
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision-blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-

Adverse Event	Grade 0	1	2	3	4
Vision-night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual - Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Adverse Event	Grade 0	1	2	3	4
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flare is graded in the SYNDROME category.					
Pain - Other (Specify, _____)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation

Adverse Event	Grade 0	1	2	3	4
Carbon monoxide diffusion capacity (DL_{CO})	≥90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme-Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Notes: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Adverse Event	Grade 0	1	2	3	4
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmodic	severe symptoms requiring narcotic	-
Creatinine	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or <0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or >3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and dip stick reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase >2 x normal but <hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	requiring frequent in/out catheterization (≥4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture

Adverse Event	Grade 0	1	2	3	4
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy - Other (Specify type, _____) excludes metastasis from initial primary	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Feminization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	oligospermia (low sperm count)	azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function - Other (Specify, _____)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					

Adverse Event	Grade 0	1	2	3	4
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) is graded in the COAGULATION category.					
Tumor flare	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Also consider Hypercalcemia.					
Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.					
Tumor lysis syndrome	absent	-	-	present	-
Also consider Hyperkalemia, Creatinine.					
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded in the RENAL/GENITOURINARY category.					
Syndromes - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Appendix I

Adverse Event Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

Adverse Event:	Date of Treatment:		Course Number:
Date of onset:			Grade at onset:
Date of first change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Did adverse event resolve? If so, date of resolution of adverse event:	Yes_____	No_____	
Date of last observation (if prior to recovery):			
Reason(s) observations stopped (if prior to recovery):			
Was patient retreated?	Yes_____	No_____	
If yes, was treatment delayed for recovery?	Yes_____	No_____	
Date of next treatment?			
Dose reduced for next treatment?	Yes_____	No_____	

Additional Comments:

_____

_____

If module is being activated for new adverse event not currently in CTC, please provide definitions for adverse event grading:

Grade 0 = _____

Grade 1 = _____

Grade 2 = _____

Grade 3 = _____

Grade 4 = _____

Appendix II

Infection Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

1. Use the Common Toxicity Criteria definitions to grade the severity of the infection.
2. Specify type of infection from the following (CHOOSE ONE):

   BACTERIAL FUNGAL PROTOZOAL VIRAL UNKNOWN

3. Specify site of infection from the following (CHOOSE ALL THAT APPLY):

   BLOOD CULTURE POSITIVE
   BONE INFECTION
   CATHETER (intravenous)
   CATHETER (intravenous), tunnel infection
   CENTRAL NERVOUS SYSTEM INFECTION
   EAR INFECTION
   EYE INFECTION
   GASTROINTESTINAL INFECTION
   ORAL INFECTION
   PNEUMONIA
   SKIN INFECTION
   UPPER RESPIRATORY INFECTION
   URINARY TRACT INFECTION
   VAGINAL INFECTION
   INFECTION, not otherwise specified (Specify site, _____)

4. Specify organism, if known: _____.
5. Prophylactic antibiotic, antifungal, or antiviral therapy administration

   Yes_____ No_____

   If prophylaxis was given prior to infection, please specify below:

   Antibiotic prophylaxis _____

   Antifungal prophylaxis _____

   Antiviral prophylaxis _____

   Other prophylaxis _____

Appendix III

Performance Status Scales/Scores

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

Appendix IV

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for adverse event occurring greater than 90 days after radiation therapy.

	Grade				
Adverse Event	0	1	2	3	4
Bladder- Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/ generalized telangiectasia/ intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 mL)	Necrosis/contracted bladder (capacity <100 mL)/severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus- Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/ perforation; fistula
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthalmitis; blindness
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia >110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25 - 35 mg%; creatinine 1.5 - 2.0 mg%; creatinine clearance >75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea >36 - 60 mg%; creatinine clearance >50 - 74%	Severe albuminuria; severe hypertension; persistent anemia (<10 g%); severe renal failure; urea >60 mg%; creatinine >4 mg%; creatinine clearance <50%	Malignant hypertension; uremic coma/urea >100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis

Appendix IV (continued)

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for adverse event occurring greater than 90 days after radiation therapy.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/ continuous O_2/assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth, good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis
Radiation - Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

Appendix V

BMT-Specific Adverse Events

Summary of BMT-Specific Adverse Events that may be used **if specified by the protocol.** These differ from the standard CTC and may be more relevant to the transplant setting. They are listed here for the convenience of investigators writing transplant protocols. They are also included in the CTC document.

	Grade				
Adverse Event	0	1	2	3	4
Bilirubin associated with graft versus host disease for BMT studies .	normal	≥2 - <3 mg/100 mL	≥3 - <6 mg/100 mL	≥6 - <15 mg/100 mL	≥15 mg/100 mL
Diarrhea associated with graft versus host disease (GVHD) for BMT studies.	none	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
Diarrhea for pediatric BMT studies.		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Hepatic enlargement	absent	-	-	present	-
Leukocytes (total WBC) for BMT studies.	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9/L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3
Leukocytes (total WBC) for pediatric BMT studies (using age, race and sex normal values).		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia for pediatric BMT studies (using age, race and sex normal values).	mm^3	*≥75-<100%LLN*	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC) for BMT studies.	WNL	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9/L ≥100 - <500/mm^3	<0.1 x 10^9/L <100/mm^3
Platelets for BMT studies.	WNL	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥20.0 - <50.0 x 10^9/L ≥20,000 - <50,000/mm^3	≥10.0 - <20.0 x 10^9/L ≥10,000 - <20,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
Rash/dermatitis associated with high-dose chemotherapy or BMT studies.	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies.	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms.	macular or papular eruption or erythema with pruritus or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation

Appendix V (Continued)

BMT-Specific Adverse Events

Summary of BMT-Specific Adverse Events that may be used if **specified by the protocol**. These differ from the standard CTC and may be more relevant to the transplant setting. They are listed here for the convenience of investigators writing transplant protocols. They are also included in the CTC document.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Stomatitis/pharyngitis (oral/pharyngeal mucositis) for BMT studies.	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Transfusion: Platelets for BMT studies.	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Transfusion: pRBCs for BMT studies.	none	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Transfusion: pRBCs for pediatric BMT studies.	*none*	*≤15mL/kg in 24 hours elective or planned*	*>15 - ≤30mL/kg in 24 hours elective or planned*	*>30mL/kg in 24 hours*	*hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin*
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) for BMT studies.	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies.	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure

Appendix VI

BMT Complex/Multicomponent Events

	Grade				
Adverse Event	0	1	2	3	4
Note: The grading of Complex/Multicomponent Events in bone marrow transplant will be defined in the protocol. The grading scale must use the CTC criteria for grading the specific component events (adverse events).					
Failure to engraft	absent	mild	moderate	severe	life-threatening
Also consider Hemoglobin, Neutrophils/granulocytes (ANC/AGC), Neutrophils/granulocytes (ANC/AGC) for BMT studies, if specified in the protocol, Platelets, Platelets for BMT studies, if specified in the protocol					
Graft versus host disease	absent	mild	moderate	severe	life-threatening
Also consider Fatigue, Rash/desquamation, Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for patients without colostomy, Diarrhea for patients with colostomy, Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for pediatric BMT studies, if specified in the protocol, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol					
Stem cell infusion complications	absent	mild	moderate	severe	life-threatening
Also consider Allergic reaction/hypersensitivity, Conduction abnormality/Atrioventricular heart block, Nodal/junctional arrhythmia/dysrhythmia, Prolonged QTc interval (QTc >0.48 seconds), Sinus bradycardia, Sinus tachycardia, Supraventricular arrhythmias (SVT/atrial fibrillation/flutter), Vasovagal episode, Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia), Cardiovascular/Arrhythmia - Other (Specify, _____), Hypertension, Hypotension, Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10^9/L), Rigors/chills, Sweating (diaphoresis), Rash/desquamation, Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Urticaria (hives, welts, wheals), Diarrhea for patients without colostomy, Diarrhea for patients with colostomy, Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for pediatric BMT studies, if specified in the protocol, Nausea, Vomiting, Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hemoptysis, Alkaline phosphatase, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, GGT, SGOT (AST), SGPT (ALT), Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L), Infection without neutropenia, Hyperkalemia, Hypernatremia, Hypokalemia, Depressed level of consciousness, Seizures, Abdominal pain, Headache, Creatinine, Hemoglobinuria					
Veno-Occlusive Disease (VOD)	absent	mild	moderate	severe	life-threatening
Also consider Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Depressed level of consciousness, Hepatic pain, Renal failure, Hepatic enlargement					

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PROTOCOL SUMMARY

A Phase I/II Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability and Efficacy of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor BMS-201038 in patients with Homozygous Familial Hypercholesterolemia (Protocol No. UP 1001)

Principal Investigator: Daniel J. Rader, MD

Sub-investigators: Jesse Berlin, PhD; LeAnne Bloedon, MS, RD; Marina Cuchel, MD, PhD; Philippe Szapary, MD; Megan Wolfe, BS

Background/Significance:
Homozygous familial hypercholesterolemia (hoFH) is a serious life-threatening genetic disease caused by homozygosity or compound heterozygosity for mutations in the low density lipoprotein (LDL) receptor. This disease formerly qualifies as an orphan disease in that it occurs with a frequency of approximately one in a million individuals, indicating that there are between 200 and 300 patients with hoFH in the United States. Total plasma cholesterol levels are generally over 500 and markedly premature atherosclerotic vascular disease is a major consequence. Untreated, most patients develop atherosclerosis before age 20 and generally do not survive past age 30. Currently there are no effective medical therapies for hoFH. BMS-201038 has the potential to be effective in significantly lowering cholesterol levels and thus reduce atherosclerosis in patients diagnosed with hoFH. BMS-201038 has been studied in phase I and phase II trials in healthy volunteers and has been shown to significantly reduce cholesterol levels by as much as 80%. In addition, a study was performed in the rabbit model of hoFH and BMS-201038 was found to be remarkably effective in reducing cholesterol levels in rabbits that lack a functional LDL receptor. This study, in the best accepted animal model for hoFH, indicated that MTP inhibition by BMS-201038 might be effective in substantially reducing cholesterol levels in patients with hoFH. Efficacy data from the phase II clinical trial that was performed by BMS is still being analyzed, but preliminary analysis indicates patients with primary hypercholesterolemia (LDL cholesterol > 160 mg/dL) assigned to BMS-201038 25 mg x 4 weeks reduced LDL cholesterol by an average of 65% compared to baseline.

Objectives: To determine the safety, dosing regimen and efficacy of MTP inhibitor, BMS-201038, in patients with homozygous Familial Hypercholesterolemia (hoFH). The primary objective is to evaluate the safety and tolerability of four doses of BMS-201038 given as an initial dose and then force-titrated up for an additional three doses over a 16 week period. Secondary objectives include evaluating the pharmacodynamics of BMS-201038 as determined by changes in a host of lipid-related laboratory measures.

Study Sites: The only site will be The University of Pennsylvania Medical Center in Philadelphia, PA, USA.

Subjects: Males and females at least 13 years old with clinically diagnosed homozygous familial hypercholesterolemia (hoFH) that meet entry criteria. A minimum of 8 subjects will be enrolled in the study.

Inclusion Criteria:
1. Males and females ≥ 13 years of age
2. Clinical diagnosis of hoFH **AND** *one* of the following (a, b, or c):
   a. documented functional mutation in both LDL receptor alleles
   OR
   b. skin fibroblast LDL receptor activity < 20% normal

OR

c. TC > 500 mg/dL AND TG < 300 mg/dL AND both parents have documented TC > 250 mg/dL

3. Body weight ≥ 40 kg
4. Negative screening pregnancy test if female of child-bearing potential
5. Subjects must be willing to comply with all study-related procedures
6. Subjects must be willing and able to go off all lipid-lowering medications, dietary supplements (psyllium preparations) and LDL apheresis within 4 weeks prior to the baseline visit until the end of the study

Exclusion Criteria:

1. Uncontrolled hypertension defined as: systolic blood pressure > 180 mmHg, diastolic blood pressure > 95 mmHg
2. History of chronic renal insufficiency (serum creatinine >2.5 mg/dL)
3. History of liver disease or abnormal LFTs at screening (>3x upper limit normal)
4. Any major surgical procedure occurring less than 3 months prior to the screening visit
5. Cardiac insufficiency defined by the NYHA classification as functional Class III or Class IV
6. History of a non-skin malignancy within the previous 5 years
7. History of alcohol or drug abuse
8. Participation in an investigational drug study within 6 weeks prior to the screening visit
9. Serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the study.

Study Design and Duration: This is a single site, open-label, dose-escalation phase I/II clinical trial that will evaluate the safety, tolerability and pharmacodynamics of BMS-201038 assessed by clinical laboratory data and adverse events. There will be a minimum of 8 subjects with hoFH enrolled in the study. All subjects will initially receive 0.03 mg/kg of BMS-201038 every day for 4 weeks. If none of the stopping rules apply, dosage will be increased to 0.1 mg/kg/d for the next 4 weeks, followed by 0.3 mg/kg/d and 1.0 mg/kg/d, each for 4 weeks duration. There are 15 visits during the entire 22 week study duration.

Outcome Measures: Toxicity will be measured in terms of physical findings on the clinical exam, electrocardiogram, pulmonary function tests, NMRS of the liver, laboratory parameters (see Appendix A), vital signs, and any signs or symptoms reported by the subject. Toxicity will be assessed at screening, baseline and on days 7, 14, 28, 35, 42, 56, 63, 70, 84, 91, 98, 112, and 140 days after study drug administration. In addition, research personnel will call each subject 24-72 hours following initiation of each new dose to inquire about reported short-term side effects.

Efficacy will be measured by analyzing changes in the following parameters at visits 1, 2, 5, 8, 11, 14, and 15: Total cholesterol (TC), LDL-cholesterol (directly measured), VLDL-cholesterol, HDL-cholesterol, triglycerides (TG), apoA-I, apoA-II, apoB, apo-CIII, apoE, and Lp(a).

Data and Safety Monitoring Board (DSMB)

A DSMB will be established to assure the safety of participants in this trial as well as the validity and integrity of the data generated. The DSMB will review laboratory data and adverse events on an ongoing basis. The DSMB will assess safety via complete blood and urine analyses, physical exams, capturing of adverse events and concomitant medications and other clinical data (e.g. vitals, anthropometric measures, electrocardiograms). Membership of the DSMB will be comprised

of at least three physicians (one lipid expert, one expert in hepatology, and one pediatric specialist with a strong pharmacokinetic background) not affiliated with any aspect of this study. The DSMB will meet (may be via teleconference) at least one time per month after the first person has initiated treatment and more frequently as needed. The DSMB will also meet in the event of grade 3 or 4 toxicity as described in the sections below. The following dose escalation and removal rules will be instated and mandated by the DSMB:

Rules Governing Dose Escalation for Grade 3 Toxicity

Individuals

Dose escalation may occur if the subject tolerates therapy without evidence of grade 3 toxicity (as defined by the NCI's Common Toxicity criteria, version 2, 1999, Appendix B). If an individual experiences a grade 3 toxicity, he/she will come back for confirmation (e.g. repeat lab test) as soon as possible. If evidence of grade 3 toxicity is confirmed, dosage will be decreased to 1½ times the previous dose for an additional 4 weeks following the visit schedule per standard protocol (see Section 9.5.1.1.3, "Removal of Subjects from Study: Addressing Grade 4 Toxicity" for specific guidelines relating to specific grade 4 adverse events). If grade 3 toxicity is discovered at 7, 14, or 28 days after the reduction in dose, the dosage will be further decreased to the previous pre-escalated dose (0.03, 0.1, 0.3 mg/kg/d) for an additional 4 weeks per standard protocol. If grade 3 toxicity is detected at any visit (7, 14, or 28 days post dose) at this dosage, the subject will discontinue drug, but will come back 4 weeks after drug has been discontinued for a final safety visit. If there is no evidence of grade 3 toxicity at any of the visits during a four week period where dosage has been lowered, then the subject will escalate to the next dosage per standard protocol and follow the study visit schedule per protocol.

Remaining Subjects

When a volunteer experiences grade 3 or 4 toxicity, the remaining subjects (at all doses) will remain following the dosing regimen per protocol. If two people experience the same grade 3 or 4 toxicity at the same dose level, or if 4 subjects (33%) experience any grade 3 or 4 toxicity at any dose level, the DSMB will meet to determine if the dosing regimen should be altered for remaining subjects.

Removal of Subjects From Study: Addressing Grade 4 Toxicity

Every effort within the bounds of safety and patient choice will be made to have subjects complete the study. With regards to hepatoxicity, if a volunteer experiences confirmed grade 4 toxicity, he/she will discontinue study drug and come back 4 weeks after drug has been discontinued for a final visit (equivalent to visit 15, day 140). Grade 4 toxicity regarding hepatoxicity is defined below:

1. If either ALT or AST levels are greater than 20.0 x ULN on two separate occasions and at least 24 hours apart;
2. If alkaline phosphatase is > 20.0 x ULN on two separate occasions and at least 24 hours apart;
3. If total bilirubin is > 10.0 x upper limit of normal on two separate occasions and at least 24 hours apart;

Other rules for removing volunteers from the study not relating to hepatoxicity include:

4. Clinically significant laboratory abnormality or SAE that will impede the patient from continuing in the study;
5. Demonstrated non-compliance with study protocol; or
6. Patient chooses to discontinue from the study

Protocol Schematic

Screening Visit (Visit 1, -14 days)

Sign Informed Consent, full physical exam, medical history, clinical laboratory tests, electrocardiogram, vitals, urine pregnancy test, dietary counseling

↓

Baseline Visit (Visit 2, Day 0)

Abbreviated physical exam, electrocardiogram, vitals, dietary counseling and compliance, clinical laboratory data, drug administration (0.03 mg/kg/d), adverse events, concomitant medications, urine pregnancy test, NMRS of the liver, pulmonary function tests

↓

Follow-up Visits (Visits 3, 4, 6, 7, 9, 10, 12, 13; Days 7, 14, 35, 42, 63, 70, 91, 98)

Abbreviated physical exam, vitals, clinical laboratory data, adverse events, concomitant medications, urine pregnancy test

↓

End of Treatment Phase Visits (Visits 5, 8, 11, 14; Days 28, 56, 84, 112)

Abbreviated physical exam (full exam at visit 14 only), electrocardiogram, vitals, dietary counseling and compliance, clinical laboratory data, drug administration: visit 5, 0.1 mg/kg/d; visit 8, 0.3 mg/kg/d; visit 11, 1.0 mg/kg/d; adverse events, concomitant medications, urine pregnancy test, NMRS of the liver, pulmonary function tests

↓

Final Visit (Visit 15, Day 140)

Abbreviated physical exam, electrocardiogram, vitals, clinical laboratory data, adverse events, concomitant medications, NMRS of the liver, pulmonary function tests

Appendix A

Study Visits & Procedures

Procedure	Visit 1	Visit 2	Visits 5, 8, 11, 14	Visits 3, 4, 6, 7, 9, 10, 12, 13	Visit 15
	-2 Weeks	**Week 0**	**Days 28, 56, 84, 112**	**Days 7, 14, 35, 42, 63, 70, 91, 98**	**Day 140**
Informed consent	X				
Medical History (screen) Physical exam[1]	X	X	X	X	X
Electrocardiogram	X	X	X		X
Blood pressure, heart rate, weight, height & waist measures	X	X	X	X	X
Dietary counseling & compliance	X	X	X		
Comprehensive Metabolic Lab Panel, TSH, INR and CBC[2]	X	X	X	X	X
Fat-soluble vitamin levels[3]		X	X		X
Fatty acid profile[4]		X	X		X
Full fasting Lipid profile[5]	X	X	X		X
Urinalysis[6]	X	X	X	X	X
Drug administration		X[7]	X[8]		
Adverse Events		X	X	X	X
Concomitant medications	X	X	X	X	X
Urine pregnancy test[9]	X	X	X	X	
Drug Compliance			X	X	
NMRS of the liver		X	X		X
Pulmonary Function Tests[10]		X	X		X

[1] A full physical exam (genitourinary) will be performed at visits 1 and 14 and abbreviated exams will be performed at visits 2-13, and 15.

[2] Comprehensive Metabolic panel includes: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, TSH (only at visits 2 and 15), INR and total bilirubin. CBC includes: white blood cell count, hemoglobin, hematocrit, platelet count, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

[3] Vitamins A, E and D will be assessed by measuring serum concentrations of the individual vitamins. Levels of vitamin K will be monitored indirectly by evaluating the INR.

[4] Fatty acid profile includes serum levels of linoleic acid and alpha linolenic acid

[5] Full fasting lipid panel includes: Total Cholesterol, LDL-Cholesterol (directly measured) VLDL-Cholesterol, HDL-Cholesterol, Triglycerides, apoA-I, apoA-II, apoB, apoE, Lp(a). Apolipoproteins will be measured at visits 2, 5, 8, 11, 14 and 15 only

[6] Urinalysis includes urinary color, turbidity, pH, glucose, bilirubin, ketones, blood, protein, WBC's

[7] Study drug will be initiated at 0.03 mg/kg body weight

[8] Drug will be escalated if none of the stopping rules apply as follows: visit 5, 0.1 mg/kg; visit 8, 0.3 mg/kg; visit 11, 1 mg/kg. Study drug will not be administered at visit 14 as this is the last day of treatment

[9] Potential childbearing females only

[10] Spirometry with DLCO will be performed to include: forced vital capacity; forced expiratory volume during 1 second; forced expiratory flow, 25-75%; and carbon monoxide lung diffusion

University of Pennsylvania

Principal Investigator:
Daniel Rader, MD
Center for Experimental Therapeutics
Tel: 215-573-4176

24-Hour Emergency Number: 215/662-6059
(Ask for the Medical Resident on Call)

CONSENT TO PARTICIPATE AS A SUBJECT IN AN INVESTIGATIONAL STUDY

TITLE: A Phase I/II Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability and Efficacy of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor BMS-201038 in Patients with Homozygous Familial Hypercholesterolemia (Protocol # UP 1001)

Sponsor:

Introduction

You are invited to participate in a research study that will last approximately 22 weeks. Before you give your consent to volunteer, please read the following information and ask as many questions as necessary to be sure that you understand what your participation would involve. Approximately 8 subjects will be participating in this study. This study is only being conducted at The University of Pennsylvania.

Purpose

The purpose of this study is to examine how a new cholesterol lowering medication called BMS-201038, is handled by the body and its effects on lowering low density lipoprotein (LDL) cholesterol (known as "the bad cholesterol") in males and females with homozygous familial hypercholesterolemia (hoFH), a condition resulting in very high levels of LDL cholesterol. BMS-201038 has been shown to lower LDL cholesterol by as much as 80% in healthy people with high cholesterol. This medication is an "investigational" drug, which means that the drug has not been approved by the U.S. Food and Drug Administration (FDA) or any other regulatory agency in the world. This drug has not been approved as a prescription or over-the-counter medication because it is still being studied for the treatment of high cholesterol. You are being asked to participate in this study because you have homozygous familial hypercholesterolemia. If you decide to participate, you will receive BMS-201038 in different doses over a period as long as 16 weeks.

Procedures

Your participation in this research study will last approximately 22 weeks and you will need to visit the General Clinical Research Center (GCRC) at the Hospital of the University of Pennsylvania approximately 15 times during the study.

Screening (Visit 1) The purpose of this visit is to explain the study to you and see if you meet the requirements to be in the study. Research staff will measure your blood pressure, heart rate, height, weight and waist circumference. A physician or Nurse Practitioner will ask you questions about your past medical history and current medications. This individual will also perform a physical exam. In addition, an electrocardiogram (also known as an EKG) will be performed, which provides a tracing of your heart's activity. You will have a small amount of blood drawn (about 2 tablespoons) for safety and lipid (cholesterol and triglycerides) labs after a 12- hour fast (nothing to eat or drink except water 12 hours before your scheduled appointment). You will also be asked to provide a small urine sample for a simple urinalysis. If you are a female who is capable of becoming pregnant, a standard pregnancy test will also be performed on this urine sample.

You will meet with the dietitian at the GCRC to discuss the diet that must be followed starting the day of your screening visit until the end of the study. It is important for study volunteers to follow this diet. The medication works to lower cholesterol by stopping the action of a protein that is involved with absorbing fat from food and packaging cholesterol in the blood. Since this medication is expected to stop the action of this protein, fat that you eat would not be allowed to be absorbed and would cause extreme diarrhea. If you remove most of the fat from your diet, you should not have diarrhea. Therefore, the dietitian will instruct you on how to remove fat (except a small amount) from your diet. She will instruct you on how to provide a small amount so that you get enough fatty acids that are needed for normal processes in the body. The dietitian will design the diet so that you maintain your weight and get all of your nutrients. Because fat-soluble vitamins (vitamins A, D, E and K, nutrients needed to perform normal functions in the body), from food need fat to be absorbed, you will need to take a multivitamin every day. Research personnel will provide you with multi-vitamins starting at the screening visit. You will receive multi-vitamins at specific visits throughout the study.

Once all clinical data has been reviewed, research staff will contact you and let you know if you qualify for the study.

Baseline (Visit 2) If you qualify for the study, you will be asked to return to the GCRC in approximately 2 weeks after the screening visit for the baseline visit. The baseline visit will last approximately 1 hour. Research staff will ask you if your medications or medical history have changed since the screening visit. You will have an electrocardiogram performed to trace your heart's activity. You will have blood drawn (a little less than 2 ½ tablespoons) after a 12 hour fast (nothing to eat or drink except water) for safety and lipid (cholesterol and triglyceride) labs and labs relating to the use of the medication. The study physician or Nurse Practitioner will perform a brief physical exam. You will be asked to provide a urine sample for routine safety labs and a standard pregnancy test (females capable of becoming pregnant only). Research staff will measure your blood pressure, heart rate, and weight. You will be asked if you are having any problems with your diet. At this visit, you will be given BMS-201038 in the amount of 0.03 mg per kilogram of body weight per day for 4 weeks. You will need to take the medicine once a day with water in the morning. Please bring the study medication bottle(s) containing any remaining pills with you to every future visit.

Follow-up Visits 3, 4, 6, 7, 9, 10, 12, 13 You will be asked to come back to the GCRC on the following days (+/- 3 days) from the baseline visit (when you first started taking the study medication): 7, 14, 35, 42, 63, 70, 91, and 98. You will have a brief physical exam performed by either the study physician or Nurse Practitioner. At these visits, research personnel will measure your heart rate, sitting blood pressure, and weight. Research personnel will ask you if you have experienced any unusual symptoms since we last saw you or added, removed or changed any medications. You will have blood drawn after a 12 hour fast (nothing to eat or drink except water) for safety labs and labs related to lipids. You will be asked to provide a urine sample for routine safety labs and a standard

pregnancy test (females capable of becoming pregnant only). Research personnel will collect your bottle of study medication and provide you with additional study medication.

Follow-up Visits 5, 8, 11, 14

You will be asked to come back to the GCRC on the following days (+/- 3 days) from the baseline visit (when you first started taking the study medication): 28, 56, 84, and 112. You will have a brief physical exam (a full physical exam will be performed at visit 14 only) performed by either the study physician or Nurse Practitioner. At these visits, research personnel will measure your heart rate, sitting blood pressure, and weight. Research personnel will ask you if you have experienced any unusual symptoms since we last saw you or added, removed or changed any medications. In addition, research staff will ask you about potential problems with following the research diet. You will have blood drawn after a 12 hour fast (nothing to eat or drink except water) for safety labs and labs related to lipids. You will be asked to provide a urine sample for routine safety labs and a standard pregnancy test (females capable of becoming pregnant only). You will have an electrocardiogram performed to trace your heart's activity. Research personnel will collect your bottle of study medication and provide you with additional study medication. At visits 5, 8, and 11, you will increase the dosage of study medication. At visit 5, you will take 0.1 mg study medication per kilogram of body weight per day for 4 weeks. At visit 8, you will increase dosage to 0.3 mg study medication per kilogram of body weight for another 4 weeks and at visit 11, you will increase the dosage to 1.0 mg per kilogram of body weight per day for the final 4 weeks. If you experience any side effects with the medication, the study physician will talk to you about whether to decrease the dosage or discontinue the medication.

Final Visit (Visit 15)

You will come back to the GCRC 4 weeks after visit 14 for the last visit. At this visit, you will have a brief physical exam. Research personnel will measure heart rate, sitting blood pressure and weight. You will have an electrocardiogram performed to trace the activity of your heart. Research personnel will ask you if you have experienced any unusual symptoms since we last saw you or added, removed or changed any medications. You will have blood drawn after a 12 hour fast (nothing to eat or drink except water) for safety labs and labs related to lipids. You will be asked to provide a urine sample for routine safety labs. Research personnel will collect your bottle of study medication.

The total amount of blood you will have drawn during the entire 22 weeks is approximately 360 ml (1 ½ cups), which is less than the standard Red Cross blood donation (2 pints, which is equal to 2 cups).

Risks

There are some potential risks and discomforts that you may reasonably expect as part of the study. BMS-201038 was studied in healthy volunteers with high cholesterol and caused an increase in liver function tests in some subjects. Some subjects were also found to have some fat built up in their liver, which at high levels can be serious. Levels of fat found in the study were not at a dangerous level. There were no deaths or serious side effects that occurred in this study. Some subjects taking this medication also reported stomach pain, diarrhea, nausea, and fatigue (being tired). It is believed these results occurred because the amount of fat in the diet was not restricted. We believe that by following the poor fat diet described in this consent form, there should not be significant symptoms of those described above.

As with any blood test, there may be some minor discomfort, minor bruising, and/or fainting associated with the drawing of blood. There is also a very small chance (less than 1%) of infection at the needle puncture site.

Costs and Financial Risks
There will be no cost to you for any visits or procedures required by this study.

Benefits
No direct medical benefit is assured from your participation in this study. If this study shows a positive effect in lowering cholesterol with BMS-201038, volunteers may benefit. While there may be no therapeutic benefit to you in this study, your participation will provide new information about the use of BMS-201038 in patients with homozygous familial hypercholesterolemia.

Alternatives
The alternative to this study is not to participate. There are treatments (LDL apheresis) and medications that are used to lower cholesterol in patients with hoFH that are available through your physician.

Compensation
We will compensate you for reasonable travel and lodging expenses that you need to spend in order to take part in this study. In order to compensate you for your time and effort, you will receive $25 for completing visit 1 and $50 each for completing all remaining visits. For completing the entire study, you will receive an additional $150. Therefore, if you attend and complete all 15 visits, you will be paid $875.

Confidentiality
You understand that every attempt will be made by the investigators to maintain all information collected in this study strictly confidential, except as may be required by court order or by law. You further understand that authorized representatives of the University of Pennsylvania, as well as the Food and Drug Administration (FDA), may have access to and may copy, both your medical records and records from your participation in this study. This access is necessary to insure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this research, you will not be identified by name.

Significant New Findings
You will be told of any significant new knowledge that is obtained during the course of this research, which may affect your health and/or relate to your willingness to continue participation. To find out more about any aspect of this study, you may contact the persons whose name, address and telephone number appears below.

Daniel J. Rader, MD
University of Pennsylvania
654 BRB II/III
421 Curie Blvd
Philadelphia, PA 19104
215-573-4176

Disclaimer/Withdrawal
You agree that your participation in this study is completely voluntary and that you may withdraw at any time without prejudicing your present or future care. You also understand that should your physician find it necessary, and/or in your best interest, he/she may withdraw you from the study.

Injury/Complications
You understand that in the event of any physical injury or illness resulting from the study, medical treatment will be provided to you. Financial compensation for injury or illness is not available from the University of Pennsylvania. No other compensation, including compensation for wages lost as a result of injury, hospitalization or professional services, will be provided. You or your third party payer, if any, may be billed for medical expenses associated with this study only if they are deemed medically necessary and if such expenses would have been incurred independent of the study.

Subject Rights
If you wish further information regarding your rights as a research subject, you may contact the Director in the Office of Regulatory Affairs at the University of Pennsylvania at 215-898-2614. You also understand that if you have questions pertaining to your participation in this particular research study, you may contact Dr. Rader by calling the telephone number listed at the top of page one. You have been given the opportunity to ask questions and have had them answered to your satisfaction.

Conclusion: You have read and understand the consent form. You agree to participate in this research study. Upon signing below, you will receive a copy of the consent form.

Name of Subject	Signature of Subject	Date
Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

Dear Doctor:

At the University of Pennsylvania we are currently conducting a phase I/II study to investigate the safety and the efficacy of a new drug that should be able to substantially reduce plasma cholesterol levels in patients with homozygous familial hypercholesterolemia. This drug is an inhibitor of the microsomal triglyceride transfer protein (MTP), a key protein involved in the intracellular packaging and secretion of apoB containing particles. Treatment with MTP inhibitors has been very successful in reducing cholesterol levels in Watanabe-heritable hyperlipidemic rabbits, the best accepted animal model for familial hypercholesterolemia.

The drug used in this protocol has been tested in phase I and phase II trials in humans and found to be very effective in reducing plasma total and LDL cholesterol. However, gastrointestinal side effects (primarily steatorrhea and increase in liver transaminases apparently due to increased hepatic lipid content) have been associated with treatment at higher doses and have prevented this drug from being developed for large scale clinical use. Never the less, we think that it may be a very effective and safe medical therapy for lowering cholesterol in patients with homozygous familial hypercholesterolemia.

We are writing to inform you that your patient (Mr/Ms SoandSo) has volunteered to participate in our study.
OR
On reviewing our clinical records we found that Mr/MS SoandSo, one of our patients, is a potential candidate for our study. We are writing to ask permission to contact him/her with the intention of recruiting him/her, if suitable.
We will of course keep you fully informed.

If you have any questions or would like to request additional information about the study, please contact at @mail.med.upenn.edu or call .

Sincerely,

Daniel J. Rader, MD
Director, Preventive Cardiology & Lipid Research Center
University of Pennsylvania Health System

Dear (patient name),

We are currently conducting a study to investigate a new medication that should be able to reduce plasma cholesterol levels substantially in patients with homozygous familial hypercholesterolemia. This drug is part of a new family of drugs called MTP inhibitors. Treatment with this drug has been very successful in reducing cholesterol levels in an animal model for familial hypercholesterolemia and in people with high cholesterol.

Your doctor, Dr. So and So, gave us permission to contact you to see if you would be interested in participating in our research study.
OR
We are contacting you because you have already participated in one of our previous studies and may be a candidate for this study.

The study will involve fifteen visits to the General Clinical Research Center (GCRC) at the University of Pennsylvania Hospital during a six month period. After the screening visit, if you are willing to participate and if you qualify for the study, you will be asked to stop all your cholesterol-lowering medication and LDL apheresis. You will be also asked to start on a low fat diet that you will have to follow for all the duration of the study. At the baseline visit you will start the new drug at a very low dose. After each month, the dose will be increased. You will be asked to come to GCRC for the screening and baseline visits, after one, two and four weeks from the beginning of each new dose of the drug and for a final visit 4 weeks after the treatment ended. You will be very carefully monitored on this study. Each study visit involves a physical exam, drawing a small amount of blood and obtaining urine samples. At the beginning and end of the study, and at the end of each dose period participants will also undergo tests to monitor lung and liver function.
Compensation will be provided for time and travel to all enrolled participants.

If you are interested in hearing more about this exciting study, as well as finding out if you qualify, please contact at @mail.med.upenn.edu or call .
If you would like to speak to me personally about this study, please call the above number and I will return your call at my earliest convenience. We understand that it may not be convenient for you to participate at this time and your decision will not affect in any way the care that you may receive from us.

Thank you for your potential interest in this exciting study and we hope to hear from you soon.

Sincerely,

Daniel J. Rader, MD
Director, Preventive Cardiology and Lipid Research Center
University of Pennsylvania Health System