Study Protocol and Statistical Analysis Plan

A Phase I-II Trial of Daratumumab for the treatment of patients with AL amyloidosis

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Statistical plan pages 15-16

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Index

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Version 9: 9/21/17
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1.0 OBJECTIVES

Primary:

1.1 Safety and tolerability of infusion of daratumumab in AL amyloidosis, specifically with respect to infusion reactions

Secondary:

1.2 Determine hematologic response rate of single agent daratumumab
1.3 Determine organ responses with respect to cardiac biomarkers and proteinuria
1.4 Determine time to next treatment

Exploratory:

1.5 Assess Health Related Quality of Life as reported in SF-36

2.0 BACKGROUND

AL amyloidosis is a variant plasma cell disorder in which clonal bone marrow plasma cells produce immunoglobulin light chains that misfold into fibrils that are deposited in visceral organs, leading to organ dysfunction and failure. Untreated, the disease has a median survival of only about one year. Oral treatment with melphalan and dexamethasone has had varying efficacy in different centers[1,2]. More intensive treatment with high dose intravenous melphalan with autologous stem cell transplantation (HDM/SCT) produces complete hematologic responses (CR) in about 40% of patients and partial responses in a similar proportion; these are frequently accompanied by stabilization or improvement in organ function[3]. However, less than 30% of referred patients are eligible for HDM/SCT and treatment-related mortality (TRM) is high in inexperienced centers. While hematologic responses can be durable after HDM/SCT, 28% of patients do relapse at a median of 4 years[4]. Thus, we continue to seek more effective regimens for patients who are ineligible for or who have relapsed after first line of therapy.

The advent of novel agents in the treatment of multiple myeloma has changed the therapeutic landscape of plasma cell dyscrasias. Clinical trials at Boston Medical Center incorporating proteasome inhibitors such as bortezomib and ixazomib, as well as immunomodulatory agents including thalidomide[5], lenalidomide[6], and pomalidomide have shown promising activity in AL amyloidosis.

Daratumumab is a human CD38-directed monoclonal antibody, recently FDA approved, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including proteasome inhibitor (PI) and immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD. Daratumumab led to an overall hematologic response of 29% in heavily pretreated, relapsed or refractory patients with myeloma. The median time to response was 1 month (range, 0.9 to 5.6 months) and the median duration of response was 7.4 months (range: 1.2 to 13.1+ months)[8.] Results were similar in an open-label dose escalation trial of daratumumab monotherapy in patients with relapsed or refractory myeloma. Given the above, daratumumab has become a drug of interest in the field of AL amyloidosis, a disease that shares a similar pathophysiology to multiple myeloma; both are clonal plasma cell dyscrasias expressing CD38 on their surface.

Given these promising results of daratumumab monotherapy in myeloma, we propose a study of daratumumab in the treatment of patients with AL amyloidosis who are in need of a second line of therapy.

3.0 DRUG INFORMATION

3.1 Daratumumab (IND-948)

a. DESCRIPTION: Daratumumab is a human CD38-directed monoclonal antibody currently FDA approved for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. Daratumumab is a human IgG1k monoclonal antibody that binds the CD38 glycoprotein, a protein expressed on the surface of plasma cells. It antagonizes the function of CD38 via complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), and through apoptosis of CD38-expressing cells via cross-linking (de Weers, Journal of Immunology, 2011).

b. SAFETY: Based on clinical trial data collected from patients with relapsed refractory multiple myeloma, the most common adverse events reported were infusion related, predominantly during the first infusion and up to 24 hours thereafter. Severe reactions, such as bronchospasm, dyspnea, hypoxia, and hypotension were rare (<2% each). Less serious and more common reactions (≥5%) included nasal congestion, cough, chills, rhinitis allergic, throat irritation, dyspnea and nausea. The incidence of any grade infusion reaction was 46% with the first infusion of daratumumab, 5% with the second infusion, and 4% with subsequent infusions. Of note, there were no grade 3 or higher reactions upon subsequent infusions. The median time to a reaction was approximately 1.5 hours while the incidence of infusion interruption due to an adverse event was 37%. Reactions could occur up to 48 hours following completion of the infusion. Common adverse events (≥10%) included, but not limited to: fatigue, cough, back pain, arthralgias, nausea and diarrhea. Serious adverse events were reported in up to 33% of patients and these included pneumonia (6%), general physical health deterioration (3%) and fever (3%). No grade 4 events were reported.

As of 11/15/18, daratumumab has been administered to approximately 4,407 patients in the setting of clinical trials, with an estimated world-wide post-marketing exposure of 34,316 person-years. HBV reaction, including fatal cases, has been observed in association with daratumumab. The overall frequency of HBV reactivation is daratumumab clinical trials, including serious and non-serious reports is 0.2%.

c. PHARMACOLOGY

Formulation: Daratumumab is administered intravenously.

Administration:
Infusion rates for daratumumab administration:

	Dilution volume	Initial rate (1st hour)	Rate increment[a]	Maximum rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusion[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Consider incremental escalation of the infusion rate only in the absence of infusion reactions.
[b] Use a dilution volume of 500 mL only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.
[c] Use a modified initial rate for subsequent infusions (i.e. third infusion onwards) only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions.
Otherwise, continue to use instructions for the second infusion.

Daratumumab will be administered at the FDA-approved dose of 16mg/kg as an intravenous infusion. Weight from screening visit will be used for initial dosing and throughout treatment period but will be recalculated for weight change ≥ 10%. It will be administered weekly from weeks 1 to 8, followed by every 2 weeks from weeks 9 to 24, and then every 4 weeks thereafter until progression or unacceptable toxicities, for up to 24 months of total study therapy.

The first infusion of daratumumab (in 1000 mL) will be administered at an initial rate of 50 mL/hour to be escalated hourly by 50 mL/hour to a maximum rate of 200 mL/hour.

The second infusion of daratumumab will be administered in 500 mL if no grade 1 or greater reactions have occurred throughout the first 3 hours of the first infusion. The second infusion will be administered at an initial rate of 50 mL/hour to be escalated hourly by 50 mL/hour to a maximum rate of 200 mL/hour

The third and subsequent doses will be administered in 500 mL at a starting rate of 100 mL/hour to be escalated hourly by 50 mL/hour to a maximum rate of 200 mL/hour as long as no ≥ Grade 1 infusion reactions occur during a final infusion rate of ≥ 100 mL/hr in the first two infusions.

Infusion reactions of any grade will lead to the temporary interruption or slowing of the infusion, as well as management of symptoms. Depending on the grade/severity of the reaction, this may require the permanent discontinuation of the drug.

Refer to section 8 for management of infusion reactions.

Supplier: Janssen Scientific Affairs, LLC

4.0 STAGING CRITERIA

Staging defined by NT-proBNP and troponin T cut-offs of < 332 pg/mL and <0.035 ng/mL, respectively, as thresholds: Stage I, both under threshold; and Stage II, either troponin or NT-proBNP (but not both) over threshold and stage III, both elevated. If troponin T is not available, troponin I may be used, but threshold is <0.1 ng/mL.

Stage IIIb cardiac disease is defined as NT-proBNP of > 8500 pg/mL (see exclusion criteria, section 5.2)

5.0 RECRUITMENT AND CONSENTING

The investigators will recruit participants from within their own practice. It is standard of care that patients scheduled for visits within the hematology/oncology clinics are "pre-screened" to determine if they may be "potentially eligible" for any available clinical trials. This is not specific for this study.

A screening consent is not obtained, as the pre-screening review is conducted prior to their appointment.

No data will be collected. The medical records are reviewed and a screening note is placed in the medical record to indicate that the patient may or may not be "potentially eligible" for a clinical trial. If the patient is potentially eligible, the physician will discuss the study at the visit. No procedures are performed for screening until after consent is obtained.

No data will be retained prior to obtaining consent. No data is collected during the "pre-screening". During the pre-screen, if a patient is determined to be not potentially eligible for any available clinical trials, the patient would not be considered as a "screen fail" as they have not undergone a full screening.

If potentially eligible, the investigator will inform the potential participant within his/her practice that he/she may be eligible for the research study. If the patient agrees to discuss and receive information about the study, an IRB-approved Informed Consent Form will be presented to the patient by a member of the research staff who will verbally outline the details of the procedures, risks, benefits, alternatives, costs, etc. The patient will be given the opportunity to bring the consent home and discuss with family members and/or other physicians and to ask any and all questions of the investigator and/or research staff. Once the patient is satisfied that all questions have been answered, if he/she wishes to participate, the consent form will be signed and dated by the patient and the person obtaining consent. Copies of the signed Informed Consent Form will be given to the patient and placed in the appropriate medical record. The original copy will be placed in the research chart.

For participants that live out of state, after the initial consent discussion in clinic, further discussions may take place via telephone with the research nurse and/or investigator to be sure all questions are answered to the patient's satisfaction. If the patient agrees to participate, (s)he may sign, print and date the consent document and fax it to the research office. The investigator will sign the consent on the day (s)he receives it, as confirmation that the consenting process has taken place. A copy of the document with both signatures will be given to the patient and placed in the appropriate medical record. The participant will be instructed to bring the document with their original signature to the next visit. In addition, when the patient returns to begin screening and/or treatment, a clean copy of the current consent is again presented to the patient for signature. The treating investigator will sign and a copy will be given to the patient. This signed consent as well as the original wet-ink signature pages (participant and investigator) will be kept in the research chart.

Potential participants who are non-English speaking will be consented using the Short Form (if IRB approved). A hospital translator or a translator on the phone line will be used throughout the consent process and throughout their participation in the study.

The consent process that has taken place will be documented in the medical record.

6.0 ELIGIBILITY CRITERIA

6.1 Eligibility Criteria

- Histological diagnosis of primary systemic (AL) amyloidosis:
  a. At least one tissue demonstrating positive Congo Red staining with characteristic apple green birefringence AND/OR characteristic appearance of fibrils on electron microscopy **AND**

  b. Evidence of a clonal plasma cell dyscrasia:
     i. Monoclonal protein in the serum and/or urine by immunofixation electrophoresis **AND/OR**
     ii. Abnormal serum free light chain assay **AND/OR**
     iii. Clonal plasma cell population in the bone marrow demonstrated by immunohistochemistry, flow cytometry or in situ hybridization **AND**

  c. Evidence of organ involvement other than carpal tunnel syndrome. Confirmation of tissue diagnosis at all sites of organ dysfunction is encouraged, but not required.

- Must have received at least one prior treatment regimen of proven efficacy in the treatment of AL amyloidosis. If prior treatment included ASCT, at least 6 months must have elapsed between ASCT and study drug.

- Must be ≥ 18 years of age.

- Must have a performance status of 0-2 by ECOG criteria (see Section 10.4)

- Must have adequate hepatic function as evidenced by serum bilirubin values < 2.0 mg/dL; ALT and/or AST < 3xULN (bilirubin < 3 mg/dL allowed if related to Gilbert's syndrome).

- Must have an absolute neutrophil count ≥1000/mm^3, hemoglobin ≥7.5 g/dL, and platelet count ≥50×10^9/L

6.2 Exclusion Criteria:

- Renal Insufficiency (CrCL <20mL/min), calculated by Cockcroft-Gault Equation
  CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72)
  *Equation parameters such as **Sex** have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (1), represent the values that will be used.*
  The default unit of measure for weight is kilograms. Please verify that the correct unit of measure has been selected.
  http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault

- Mayo clinic cardiac biomarker stage IIIb (see appendix 14.3)

- Evidence of significant cardiovascular conditions as specified below:
  – NT-ProBNP > 8500 ng/L (Mayo Stage IIIb patients are excluded)

  - New York Heart Association (NYHA) classification IIIB or IV heart failure (see Section 10.5)
  - Unstable Angina, Severe uncontrolled Arrhythmia refractory to medical management, prolonged QTc interval > 500 msec, symptomatic orthostatic hypotension refractory to medical management, or supine systolic blood pressure < 90 mm Hg.
  - LVEF <30% by Echocardiogram

- Overt multiple myeloma (>30% bone marrow plasmacytosis, extensive (>2) lytic lesions, or hypercalcemia).

- Eligible for autologous stem cell transplant procedure (unless patient refuses)

- Any form of secondary or familial (ATTR) amyloidosis

- Active infection

- Prior treatment with daratumumab

- The presence or history of another malignancy is not allowed except for the following:

    - adequately treated basal cell or squamous cell skin cancer,
    - in situ cervical cancer,
    - adequately treated Stage I or II cancer from which the patient is currently in complete remission, any other cancer from which the patient has been disease-free for 5 years.

- Seropositive for human immunodeficiency virus (HIV)

- Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

- Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy)

- Pregnant or nursing women. Women and men of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

- Chronic smokers or those with known COPD with a FEV1 <50% of predicted normal. Note that FEV1 testing is required for chronic smokers or patients suspected of having COPD.

- Known moderate or severe persistent asthma within the past 2 years or currently has uncontrolled asthma of any classification

7.0 TREATMENT PLAN

Drug	Dose[c]	Frequency	Route of Administration
Daratumumab	16 mg/kg body weight	Weekly, weeks 1-8	IV infusion
Daratumumab	16 mg/kg body weight	Every 2 weeks, weeks 9-24[a]	IV infusion
Daratumumab	16 mg/kg body weight	Every 4 weeks ,week 25[b] onwards, for up to 24 months of total study therapy	IV infusion

[a] First dose of the every-2-week dosing schedule is given at week 9
[b] First dose of the every-4-week dosing schedule is given at week 25
[c] Weight from screening visit will be used for initial dosing and throughout treatment period but will be recalculated for weight change ≥ 10%.

Infusion rates for daratumumab administration

	Dilution volume	Initial rate (1st hour)	Rate increment[a]	Maximum rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusion[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Consider incremental escalation of the infusion rate only in the absence of infusion reactions.
[b] Use a dilution volume of 500 mL only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.
[c] Use a modified initial rate for subsequent infusions (i.e. third infusion onwards) only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.

7.1 Week 1 and Week 2 infusions (i.e., the first two doses)

The following premedications should be administered approximately 30-60 minutes prior to infusion

- Acetaminophen 650 mg po
- Diphenhydramine 25-50 mg po/iv
- Methylprednisolone 100 mg iv for first two doses (C1 D1 and C1 D8)
- Loratadine10 mg po
- Famotidine 20 mg iv
- Montelukast 10 mg po
- Ondansetron 4mg iv

The following should be administered at the 2 hour infusion point, (even if there is no reaction)

- Diphenhydramine 25 mg po/iv
- Famotidine 20 mg iv
- Methylprednisolone 40 mg iv

The following medications should be administered post-infusion to reduce the risk of delayed infusion reactions:

- Methylprednisolone 20 mg (or equivalent) orally for 2 days, 24 and 48 hours following the infusion start time
- Montelukast 10 mg orally for 2 days, 24 and 48 hours following the infusion start time (only for first 4 infusions)

7.2 <u>ALL subsequent doses (i.e. starting with week 3 dose):</u>

The following premedications should be administered approximately 30-60 minutes prior to infusion.

- Acetaminophen 650 mg po
- Diphenhydramine 25-50 mg po/iv or Claritin 10 mg po
- Methylprednisolone 60 mg iv
- Famotidine 20 mg iv
- Ondansetron 4mg iv (as needed)
- Montelukast po 10 mg (optional following the first dose)

The following medications should be administered post-infusion to reduce the risk of delayed infusion reactions:

- Methylprednisolone 20 mg (or equivalent) orally for 2 days, 24 and 48 hours following the infusion start time
- Montelukast 10 mg orally for 2 days, 24 and 48 hours following the infusion start time (only for first 4 infusions) (optional)

7.3 Additional Information

Patients with a history of chronic obstructive disease or asthma will undergo pulmonary function testing for the determination of their forced expiratory volume in one second (FEV1) prior to daratumumab exposure. In addition, this population of patients should be considered for short and long-acting bronchodilators in addition to inhaled corticosteroids post-infusion.

Patients will be initiated on antiviral prophylaxis (acyclovir or valcyclovir) to prevent herpes zoster reactivation within one week of starting daratumumab and will be continued for 3 months following the completion of treatment.

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to

RBCs can mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Blood bank must be notified if a patient has received daratumumab and of this interference with serological testing. Order type and screen and blood bank phenotype on patients prior to starting daratumumab.

HBV Serology:

All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment v11.0 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

HBV DNA tests:

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Section 9). Where required by local law, the results of HBV testing may be reported to the local health authorities

Management of Hepatitis B Virus Reactivation:

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation.
For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

7.4 Criteria For Removal From Protocol Treatment:

7.4.1 Hematologic progression of disease.

7.4.2 Organ progression in the absence of hematologic response

7.4.3 Complete hematologic response, with continuation of the study drug per the discretion of the treating investigator

7.4.4 Unacceptable toxicity.

7.4.5 The patient may withdraw from the study at any time for any reason.

7.4.6 Development of overt multiple myeloma.

7.4.7 Completion of 24 months of daratumumab.

7.5 All patients will be followed until initiation of next treatment.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

See Section 3.0 for potential toxicities associated with daratumumab. In all patients experiencing such toxicities, an attempt should be made to distinguish between drug toxicity, associated medical illness, or disease (amyloid)-related symptomology.

Dose delay is the primary method for managing daratumumab-related toxicities.

Infusion-related reactions:
Infusion reactions of any grade will lead to the temporary interruption or slowing of the infusion, as well as management of symptoms. Depending on the grade/severity of the reaction, this may require the permanent discontinuation of the drug.

For Grade 1-2 infusion reactions, daratumumab can be resumed at half the rate at which the reaction occurred. Further escalation of the rate is still possible providing the patient does not experience any further reactions.

For Grade 3 reactions, the infusion can be restarted at half the rate once the intensity of the reaction has decreased to a Grade 2 level or lower. Further escalation of the rate is still possible providing the patient does not experience any further reactions. The above instructions can be repeated if another Grade 3 reaction occurs. Permanent discontinuation of daratumumab should be undertaken if a third Grade 3 or greater reaction occurs.

For Grade 4 reactions (life threatening), daratumumab should be discontinued permanently.

Non-reaction Daratumumab-Related Toxicity Management
The criteria for a dose delay are:
- Grade 4 hematologic toxicities
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Daratumumab Delays
Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. If more than 2 consecutive planned doses of daratumumab are missed due to adverse events, treatment should be permanently discontinued. If 2 consecutive doses of daratumumab are missed for any reason other than adverse events, this should be brought to the attention of the Sponsor at the earliest possible time and study treatment should be discontinued, unless, upon consultation with the sponsor and the review of data, continuation is agreed upon.

No dosage adjustments are required for patients with pre-existing renal dysfunction. According to prior pharmacokinetic studies, no dosage adjustments are required for mild hepatic dysfunction (Total Bili 1.0-1.5x ULN or AST > ULN). Daratumumab has not been studied in patients with moderate or severe hepatic dysfunction (Total Bili > 1.5 x ULN). These patients will be excluded from the study (see exclusion criteria section 5.2).

9.0 STUDY CALENDAR

	Screening	Prior to each dose	Monthly (CxD1)	Every 3 Month beginning C4,D1	End of Study TreatmentVisit[5]
PHYSICAL[9]					
History & Physical Exam, including liver assessment	X		X[7]	X	X
Height	X				
ECOG Performance Status (see 10.4)	X	X		X	X
Vital Signs & Weight		X		X	
Adverse Event Monitoring		X		X	X
SF-36 (QOL)	X			X	
LABORATORY-Serum					
Complete Blood Count with Differential	X	X		X	X
Beta-HCG[1]	X				
Chemistry including: BUN, creatinine, glucose, sodium, potassium, chloride, bicarb, cholesterol, CK, calcium, total protein, LDH, magnesium, phosphorous, triglycerides, uric acid, TSH, amylase	X	X		X	X
BUN / Serum Creatinine	X	X		X	X
Creatinine Clearance [3]	X				
Hepatic Function Testing: ALT/AST, Bilirubin, Albumin, Alkaline Phosphatase	X	X		X	X
β-2 Microglobulin / C-reactive protein	X			X	X
Cardiac enzymes: BNP/ Troponin I/NT ProBNP	X	X		X	X
Serum free light chain assay	X	X[8]		X	X
SPEP, SIFE, Immunoglobulins	X			X	X
Coombs test; IAT (anti globulin test)	X				
Coagulation profile: PTT, INR, D-dimer, Factor X	X			X	X
HBV serology testing[10]	X				
HBV DNA testing[11]	X				X
Type And Screen and blood bank phenotype [6]	X				
Daratumumab-specific Immunofixation (patients with Kappa disease only)	X			X	X
LABORATORY-Urine					
Urinalysis	X			X	X
24 hour urine: total protein, creatinine, kappa, and lambda	X			X	X
UPEP / UIFE / TV	X			X	X
PATHOLOGY					
BM biopsy	X[2]				
Fat aspirate (if not previously done)	X				
X-RAYS AND SCANS					
ECG / CXR	X				
Echocardiogram	X			Every 6 months	
PFTs (required for chronic smokers or known COPD)	X				

1 For women of childbearing potential only.
2 Bone marrow biopsy and aspiration must have been repeated following any previous therapy > 1 cycle.
3 CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); Equation parameters such as Sex have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (1), represent the values that will be used. The default unit of measure for weight is kilograms. Please verify that the correct unit of measure has been selected. http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault
4 While on study drug or until disease progression or start of another therapy.
5 30 days following last dose (+/-) 7 days.

6 Order type and screen and blood bank phenotype on patients prior to starting daratumumab and document in the order that the patient will be receiving daratumumab as notification to Blood Bank due to its interference with serological testing. See Section 7.3.
7 Full history and physical exam with liver measurements required monthly while on protocol. Limited physical examination at other visits only if clinically indicated.
8 If FLCs have normalized, full HAM1-5 panels to be completed at next visit.
9 Screening tests should be performed within 28 days of initiating study drug with the exception of Echocardiogram, CXR, PFTs and EKG, which could occur within 60 days.
10 HBV serology testing: HBsAg, antibody to antiHBs, and antibody to antiHBc assessments should be obtained for those on study treatment for less than 6 months at the time of amendment 11. Subjects who have serologic evidence of HBV exposure, but are HBsAg negative and do not have active HBV infection will have testing monitored every 3 months while on study treatment.
11. HBV DNA testing: Q12W during treatment, at the End of treatment visit, and Q12W for up to 6 months after last dose of study treatment. For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. See section 7.3

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Patients will not be required to have a delta FLC of 40 mg/L for study entry as primary endpoint of the study is to evaluate safety and tolerability of the study drug. Hematologic responses will be assessed by other hematologic measures of disease including M-spike and presence of clonal plasma cells in the bone marrow. Organ responses will be assessed by changes in 24 hour protein excretion for patients with renal involvement; by changes in NT-proBNP for patients with cardiac involvement; and by changes in alkaline phosphatase levels and liver span for patients with hepatic involvement.

10.1 Toxicities:

Safety of the study drug will be assessed by using vital sign information in addition to data pertaining to the duration of therapy, interruption of therapy, routine laboratory assessments, and frequency and severity of AEs

10.2 Responses:

It is important to note that daratumumab is an IgGk monoclonal antibody that can be detected as an individual monoclonal band on SPEP and serum immunofixation electrophoresis (IFE). It can be confused with the endogenous IgG-k M-protein of the patient during IFE interpretation. Co-migration can introduce a bias in M-protein quantification and can also mask clearance of the patient's M-protein by IFE. For optimal M-spike monitoring, our laboratory specialist will be informed if a patient is receiving daratumumab.

10.2.1 Hematologic Response Criteria

CR: Negative serum and urine immunofixation electrophoresis, normal serum free light chain ratio

VGPR: Reduction in the dFLC to <40 mg/L, dFLC = difference in involved and uninvolved serum free light-chain levels

PR: dFLC reduction by >50%, dFLC = difference in involved and uninvolved serum free light-chain levels

SD: Meets neither criteria for CR, VGPR, PR or PD

PD: An increase in FLC of 50% to > 100mg/L. From CR, any detectable M protein or abnormal FLC ratio (light chain must double). From VGPR, PR or SD, an increase in the serum M-protein from the lowest level by > 50%, as long as the absolute magnitude of this increase is > 0.5 g/dL; or an increase in the urine M-protein from the lowest level by 50%, as long as the absolute magnitude of this increase is > 200 mg/day; or an increase in the serum or urine monoclonal free light chain by > 50% from the lowest level, as long as the absolute magnitude is > 10 mg/dL (100 mg/L).

10.2.2 Organ Response Criteria

Cardiac:

Cardiac response:
- NT-proBNP response (>30% and >300 ng/L decrease in patients with a baseline NT-proBNP >650 ng/L
- NYHA class response (> two-class decrease if baseline NYHA class 3 or 4)

Cardiac progression:
- NT-proBNP progression (>30% and >300 ng/L increase)
- cTn progression (> 33%)
- EF progression (≥ 10% decrease)

Renal:

Renal response:
- Decrease in proteinuria by > 30% or below 0.5 g/24 h without renal progression. Serum creatinine and creatinine clearance (or calculated estimated GFR) must not worsen by 25% over baseline

Renal progression:
- 50% increase (at least 1 g/day) of 24-hour urine protein to >1g/day or 25% worsening of serum creatinine or creatinine clearance

10.4 Performance Status: Patients will be graded according to the ECOG performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
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.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 New York Heart Association (NYHA) Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size Estimation

Estimated patient accrual and trial duration: The study will be designed as a single armed phase II trial, in which the response in 20 evaluable patients will be determined, with 25 patients enrolled to ensure that 20 are evaluable

Completion of accrual will be expected in ~2 years, with an additional year of monitoring and follow up after the last patient is enrolled.

11.2 Interim Analysis

The study will be temporary closed for an interim analysis after the first 5 patients have completed at least 3 doses. At this time the Medical Monitor will review the safety results of the study. The recommendation is to consider stopping the study for safety concerns if during this time (3 doses for the first 5 patients) 3 or more grade 4 or 5 adverse events clearly related to study drug are recorded. If 3 or more out of the first 5 patients experience a Grade 3 infusion reaction clearly related to study drug in either of the first 3 doses, the protocol will be re-evaluated to consider modifying the schedule of daratumumab (for example, split the first dose of daratumumab over two days or adding mandatory concomitant medications). If fewer than 3 out of the first 5 patients experience a Grade 3 infusion reaction in either of the first 3 doses, the study will re-open and enrollment will be expanded to an additional cohort of subjects.

11.3 Statistical Methods

The primary endpoints for the study are related to safety and tolerability of infusion of daratumumab in AL amyloidosis with respect to infusion reactions.

Secondary endpoints include hematologic response rate of single agent daratumumab, organ responses with respect to cardiac biomarkers and proteinuria, and time to next treatment.

The Health Related Quality of Life, as reported in SF-36, will be an exploratory endpoint.

Statistical analysis will be based on all eligible subjects. Safety analysis population includes all enrolled subjects who received at least one dose of study drug. The safety analysis population will be used for evaluating subject characteristics, treatment administration, safety endpoints, and efficacy analyses.

There will be no formal statistical hypothesis testing applied in this study. Descriptive summary statistics will be used throughout. Data will be summarized primarily by administration time and aggregated across the first 8 weeks and 2 weeks after.
Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum.
Categorical variables will be summarized by the number of non-missing observations, frequencies and percentages.
All analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, U.S.) version 9.4 or higher.

11.3 Handling of Missing Data

Data will be analyzed as recorded in the database. No imputation of missing values will be performed unless indicated otherwise.

12.0 DATA AND SAFETY MONITORING PLAN

Toxicity and accrual monitoring will be performed on a routine basis by the study investigators as well as the multidisciplinary members of the Amyloid Center at Boston University, which has over 40 years' experience in the treatment of AL amyloidosis. Subjects will undergo toxicity assessment, performance status assessment and laboratory tests before each dose. Response assessment will be conducted every three months. The clinical status and laboratory reports of the study participants will be reviewed routinely by treating physicians. Dose modifications/interruptions or discontinuation will be implemented according to Section 8.

In addition, a Medical Monitor will be assigned to the study. The Medical Monitor must be a qualified clinician with relevant expertise, but no direct connection with the research, whose primary responsibility is to provide independent safety monitoring in a timely fashion. The PI will submit a

report to the Medical Monitor, at a minimum of once every 6 months, including a list of all adverse events and serious adverse events (regardless of relatedness). In addition, any unanticipated problems involving risks to participants or others and participant deaths within 30 days of study intervention will be reported to the Medical Monitor within 48 hours. The Medical Monitor is expected to provide a formal, unbiased written report evaluating individual and cumulative participant safety data when making recommendations regarding continuation of the study. Although the PI is responsible for assigning causality, the medical monitor will comment on whether or not (s)he is in agreement. Medical Monitor reports will must be submitted to the PI following each review (at a minimum of once every 6 months), which the PI will, in turn, submit to the IRB. Although there is no pre-determined criteria for early termination due to toxicity, the Medical Monitor and investigators will evaluate toxicities on a continuing basis, and will terminate the study early if toxicities exceed acceptable parameters. Each individual situation will be reviewed, and response data will be considered. The study will be stopped early if it appears that the benefit no longer outweighs the risks.

12.1 Interventional IIS Janssen Scientific Affairs Requirements for Safety Data Collection and Reporting

12.1.1 OVERVIEW

As the sponsor of the Study, the principal investigator shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The principal investigator will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

12.1.2 Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this section will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: DARZALEX™ (daratumumab)

12.1.3 Definitions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be

any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Adverse Events of Special Interest
Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- Tumor lysis syndrome
- Other malignancies
- Intravascular hemolysis – all grades

Any Adverse Event of Special Interest that is to be reported to the COMPANY should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY within 24 hours of knowledge of the event.

Individual Case Safety Report (ICSR)
A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

- **Hospitalization**
  For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious

adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]
- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

- **Life-Threatening Conditions**
  Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

12.1.4 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.
http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

For DARZALEX™ (daratumumab),the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure

12.1.5 Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:
- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

12.1.6 Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by the principal investigator **within 24 hours of becoming aware of the event** using the Serious

Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the principal investigator **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.1.7 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The principal investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

12.1.8 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs, LLC

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

12.1.8.1 SAEs, Adverse Events of special Interest and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The principal investigator will transmit all SAEs, Adverse Events of special interest and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 12.1.10,Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the principal investigator, **within 24 hours becoming aware**, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, serious ADR or special situation is required.

- The principal investigator is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 12.1.10 within **24 hours of such report or correspondence being sent to applicable health authorities.**

12.1.8.2 Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

12.1.8.3 PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture. All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the principal investigator **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed. If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the principal investigator must report the PQC to Janssen Scientific Affairs, LLC according to

the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

12.1.9 Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the principal investigator should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

12.1.10 Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

12.2 INVESTIGATOR REPORTING TO THE FDA

This protocol is conducted under IND #131818, held by the PI. The conduct of the study will comply with all FDA reporting requirements.

Adverse drug reactions that are **Serious, Unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related. Each SAE report will include an SAE Assessment Form (Appendix 14.2) documenting the PI's assessment reporting requirements.

The investigator/physician shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug. As soon as possible but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

Serious Adverse Events That Are Not Study Endpoints and are not "expected" (e.g., not in the IB), can be anticipated to occur with some frequency during the course of the trial, regardless of drug exposure, depending on the patient population and disease under study. Examples of such "anticipated" events include known consequences of the underlying

disease or condition under investigation, events anticipated from any background regimen, events common in the study population, or re-emergence or worsening of a condition relative to pretreatment baseline. In general, a limited number of occurrences of such an adverse event in a study population in which occurrences of the event are anticipated is not an adequate basis to conclude that the event is a suspected adverse reaction (i.e., that there is a reasonable possibility that the drug caused the event). Such events should not be reported individually as they occur because they are uninformative as single cases. Such anticipated adverse events should nonetheless be monitored at appropriate intervals, and the numbers of events in each arm of a controlled study should be compared. The adverse event must be reported to FDA expeditiously as an IND safety report if there is an imbalance between arms suggesting there is a reasonable possibility that the drug caused the adverse event (21 CFR 312.32(c)(1)(i)(C)). It is important to consider the entire clinical trial database in such analyses.

13.0 REFERENCES

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Appendix 14.1

SAE Assessment Form

Date: _____
Study #: **BMC IRB #H-35360; Janssen Protocol #54767414AMY2002**
Sponsor/Investigator: **Vaishali Sanchorawala, MD**

A PHASE I-II TRIAL OF DARATUMUMAB FOR THE TREATMENT OF PATIENTS WITH AL AMYLOIDOSIS

PATIENT #_____ EVENT(s): _____ DATE: _____

In accordance with the CCTO Standard Operating Procedures, documentation from the PI is required to document the outcome of his/her review of the events outlined in the SAE Report referenced above. **Please check the boxes, as appropriate, below…**

The OHRP and the FDA regulations require that *unanticipated problems* be promptly reported to the IRB. So what exactly is an *unanticipated problem*? The guidances state that in order for any **incident, experience, or outcome** to be an *unanticipated problem*, it must meet **all three** of the following criteria (unless the event is considered to be "anticipated"):

1	YES ___ NO ____	Is the event unexpected? It is unexpected if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application;
2	YES ___ NO ____	Is the event related or possibly related to participation in the research (in this guidance document *possibly related* means there is a **reasonable** possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3	YES ___ NO ____	Does the safety report suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Anticipated Events: Serious Adverse Events That Are Not Study Endpoints and are not "expected" (e.g., not in the IB), can be anticipated to occur with some frequency during the course of the trial, regardless of drug exposure, depending on the patient population and disease under study. Examples of such "anticipated" events include known consequences of the underlying disease or condition under investigation, events anticipated from any background regimen, events common in the study population, or re-emergence or worsening of a condition relative to pretreatment baseline. In general, a limited number of occurrences of such an adverse event in a study population in which occurrences of the event are anticipated is not an adequate basis to conclude that the event is a suspected adverse reaction (i.e., that there is a reasonable possibility that the drug caused the event). Such events should not be reported individually as they occur because they are uninformative as single cases. Such anticipated adverse events should nonetheless be monitored at appropriate intervals, and the numbers of events in each arm of a controlled study should be compared. The adverse event must be reported to FDA expeditiously as an IND safety report if there is an imbalance between arms suggesting there is a reasonable possibility that the drug caused the adverse event (21 CFR 312.32(c)(1)(i)(C)). It is important to consider the entire clinical trial database in such analyses.

4	YES ___ NO ____	Is the event anticipated? An event is anticipated if it is not a study endpoint, and can be anticipated to occur with some frequency based on the patient population/disease or background regimen or worsening of a pre-study baseline condition.

5	YES ___ NO ____	This event warrants a change in the protocol or consent.

PI Signature: _____ Date: _____

Appendix 14.2

Mayo Cardiac Biomarker Staging
• NT-proBNP value cutoff of <332pg/mL • Troponin I cutoff of 0.1ng/mL
• Stage I: Both under the cutoff • Stage II: One, but not both under the cutoff • Stage III: Both over the cutoff   • Stage IIIb: Both over the cutoff AND NT-proBNP >8500ng/L