A single-center phase 2 open-label trial evaluating the efficacy and safety of daratumumab in treatment of patients with proliferative glomerulonephritis with monoclonal immune deposits and C3 glomerulopathy associated with monoclonal gammopathy

NCT03095118

July 18, 2019

A single-center phase 2 open-label trial evaluating the efficacy and safety of daratumumab in treatment of patients with proliferative glomerulonephritis with monoclonal immune deposits and C3 glomerulopathy associated with monoclonal gammopathy

Principal Investigator: Fernando C. Fervenza, M.D., Ph.D.
Mayo Clinic
Division of Nephrology and Hypertension Research
200 First Street SW, Rochester, MN
507-266-1045

Co-Investigator: Ladan Zand, M.D.

Institutional Sponsor: Mayo Clinic
200 First Street SW, Rochester, MN
507-266-1045

Funding: Janssen Scientific Affairs, LLC
[redacted]

Study Product: Daratumumab (generic), Darzalex (brand)

Protocol Number: (IRB) 16-004805

Initial version:[12/16/2016] Version **(1.0)**
Revised: [1/25/2017] Version (1.1)
Revised: [2/27/2017] Version (1.2)
Revised: [4/27/2017] Version (1.3)
Revised: [11/20/2017] Version (1.4)
Revised: [1/18/2018] Version (1.5)
Revised: [4/19/2018] Version (1.6)
Revised: [9/6/2018] Version (1.7)
Revised: [2/22/2019] Version (1.8)
Revised: [4/5/2019] Version (1.9)
Revised: [7/18/2019] Version (2.0)

Table of Contents

List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
MGRS	Monoclonal gammopathy of renal significance
PGNMID	Proliferative glomerulonephritis with monoclonal immunoglobulin deposition
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	A single-center phase 2 open-label trial evaluating the efficacy and safety of daratumumab in treatment of patients with proliferative glomerulonephritis with monoclonal immune deposits and C3 glomerulopathy associated with monoclonal gammopathy
Running Title	Daratumumab in PGNMID/C3GN
Protocol Number	16-004805
Phase	Phase 2
Methodology	Open-label, Proof of Concept
Overall Study Duration	60 months
Subject Participation Duration	12 months with optional 24 month open label extension
Single or Multi-Site	Single center
Objectives	Is daratumumab effective and safe in treating patients with proliferative glomerulonephritis with monoclonal immune deposits or those with C3 glomerulopathy associated with monoclonal gammopathy
Number of Subjects	12
Diagnosis and Main Inclusion Criteria	Patients with renal biopsy consistent with membranoproliferative glomerulonephritis with monoclonal immune deposits or C3 glomerulonephropathy in addition to positive serum studies for monoclonal gammopathy within 5 years of enrollment
Study Product, Dose, Route, Regimen	For the main study, daratumumab infusions are at a dose of 16 mg/Kg once weekly for 8 doses followed by once every 2 weeks for an additional 8 doses. Patients in open-label extension (OLE) who relapse will receive 12 cadditional doses of daratumumab(16 mg/kg). The first 8 doses will be administered weekly and the last 4 will be given every other week.
Duration of Administration	6 months for main trial and the OLE includes a maximum of 3 courses over 24 months
Reference therapy	No reference therapy
Statistical Methodology	The incidence of treatment emergent major infection, grade 3 or 4 anemia, leukopenia or thrombocytopenia will be summarized. A paired t-test will be performed for changes in HgB, WBC count and platelet count from Baseline (Day 0) to 6 month and 12 month timepoints

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Monoclonal gammopathy (MG) are well known to cause kidney damage. The most common example is light chain deposition disease that occurs commonly in the setting of multiple myeloma.[1] Over the last several years, however, there is more recognition that many kidney lesions are associated with low-grade plasma cell dyscrasia or lymphoproliferative disorders.[2] In fact the term monoclonal gammopathy of renal significance (MGRS) has been introduced to capture kidney lesions associated with monoclonal gammopathy (MG) in the absence of multiple myeloma.[3] One of the lesions commonly encountered in patients with MGRS is proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID) were damage is caused by direct deposition of the monoclonals with associated inflammation.[4-6] Another is C3 glomerulopathy (C3 GN) in the setting of MG where the monoclonals result in activation of complement pathway and indirectly result in renal injury.[7-9] PGNMID and C3 GN associated with MG are diagnosed based on renal biopsy. Majority of patients present with hematuria and proteinuria and many have a progressive course with loss of renal function over time. Up to 70% of patients with PGNMID may have negative serum electrophoresis with immunofixation, normal serum free light chains and no clone may be identified on bone marrow biopsy.[6] Treatment of patients with PGNMID and C3GN associated with MG should be directed towards the pathologic clone. There is currently no standardized treatment for these patients and treatments vary based on clinical practice. We currently use combination of cyclophosphamide, bortezomib and dexamethasone in patients with IgG and IgA monoclonals, and rituximab in patients with IgM monoclonals.[10] The current treatments however, have had limited success rate and are associated with significant side effects. There is a desperate need for additional therapeutic options in this population. The high expression of CD38 on plasma cells and low expression on other myeloid cells makes CD38 an appealing target for monoclonal antibody therapy such as daratumumab. Daratumumab has been efficacious in treatment of patients with refractory multiple myeloma and overall is well-tolerated. [11] We propose use of daratumumab as first or second line agent in patients with PGNMID and C3GN associated with MG.

1.2 Investigational Agent

Daratumumab is an IgG1-kappa human monoclonal antibody that binds to the CD38 transmembrane glycoprotein on the surface of tumor cells and induces apoptosis. This process is mediated through Fc mediated cross linking and immune-mediated cell lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity and antibody dependent cellular phagocytosis. It has an elimination half-time of 18 days and volume of distribution of 4.7L. Daratumumab is FDA approved for use in treatment of multiple myeloma, however is not approved for treatment of the condition under study, PGNMID and C3 GN associated with MG. The study was submitted by the Principal Investigator to the FDA for review and granted an IND Exemption.

1.3 Clinical Data to Date

The safety and efficacy of daratumumab in patients with refractory multiple myeloma has been shown in two open-label studies. The first was a phase 1-2 study published in NEJM which evaluated the efficacy and safety of daratumumab in 42 patients. Overall 36% of patients had complete or partial response. The second study was an open label phase 2 study published in Lancet that evaluated the efficacy and safety of daratumumab in 106 patients with refractory multiple myeloma and 29 percent of patients experienced a complete or partial remission. These were patients that had failed at least 3 previous therapies. Daratumumab was overall well tolerated. Fatigue and anemia of any grade were the most common adverse events but no drug-related adverse events led to treatment discontinuation.

1.4 Dose Rationale and Risk/Benefits

The dose of daratumumab that has proven to be effective in patients with multiple myeloma is 16 mg/kg started once weekly for 8 weeks followed by every other week for 16 weeks, and then once every 4 weeks thereafter. We will be using similar dose (16 mg/kg) and similar dosing interval for a total of 16 doses over a 24 week period. The drug is only available to be administered intravenously and we aim to use the same route of administration.

Daratumumab overall is well-tolerated. The most common side-effect is infusion-related reaction (48%). We aim to use the same pre and post treatment regimen (including corticosteroid, diphenhydramine and acetaminophen) as has been done in the previous trials. Serious adverse effects include anemia, grade 3 or 4 (19%), lymphocytopenia grade 3 or 4 (40%), neutropenia, grade 3 or 4 (20%), thrombocytopenia, Grade 3 or 4 (18%), and increased risk of infection specifically pneumonia (11%). Common adverse effects include nausea (27%), anemia all grades (45%), lymphocytopenia all grades (72%), neutropenia all grades (60%), thrombocytopenia all grades (48%), backache (23%), cough (21%), upper respiratory infection (20%), fatigue (39%), fever (21%).

The treatment options for patients with PGNMID or C3GN associated with monoclonal gammopathy are limited with variable success. If untreated, majority of patients will progress to endstage renal disease. The current therapeutic options include rituximab vs. cyclophosphamide and prednisone with or without bortezomib. Daratumumab has a similar if not better side-effect profile to the above-mentioned treatment options and therefore we believe the risks associated with daratumumab are acceptable.

2 Study Objectives

Primary Objective
To assess the safety of daratumumab in patients with PGNMID or C3GN associated with monoclonal gammopathy.

Secondary Objective

To assess the efficacy of daratumumab in inducing complete or partial remission in patients with PGNMID or C3GN associated with monoclonal gammopathy as measured by change in proteinuria and serum creatinine.

3 Study Design

3.1 General Design

This study is an open-label phase 2 trial of the safety and efficacy of daratumumab, in the treatment of PGNMID and C3GN associated with monoclonal gammopathy. Subjects will be screened at outpatient Nephrology Clinic visit appointments and interested qualified subjects will be consented and offered participation in this trial. Once consent has been obtained baseline values will be established and subjects will begin treatment and follow-up for the next 12 months. Daratumumab will be administered once weekly for 8 weeks and then once every 2 weeks for 8 additional doses. Patients will be followed for a total of 12 months (6 months after the last infusion). A final visit for evaluation and collection of lab samples will be conducted at the end of the study.

3.2 *The clinical course of the patients who have achieved complete or partial remission following daratumumab is unclear, therefore these patients who have consented to the OLE and achieved complete or partial remission, will be followed for 24 months following completion of the main trial. In the OLE, patients will be assessed every 3 to 6 months. Relapse is defined as a 30% increase in proteinuria from the lowest level the patient has achieved and will be documented with two 24 hour urine collections two weeks apart. If there is evidence of relapse, patients will receive 12 additional doses of daratumumab(16 mg/kg). The first 8 doses will be given weekly and the last 4 doses will be administered every other week.* Primary Endpoints

Incidence of major infection (defined as the development of pneumonia, severe urinary tract infection/pyelonephritis, sepsis, meningitis), grade 3 or 4 anemia, leukopenia or thrombocytopenia and changes in HgB, WBC count and platelet count from baseline to 6 month and 12 month timepoints.

3.3 Secondary Endpoints

Proportion of patients achieving complete or partial remission where the responses are defined as below:

a) Complete Response at 12 months
- < 300 mg proteinuria/24 hours
- No greater than a 15% reduction in GFR as determined by creatinine clearance

b) Partial Response at 12 months
- > 50% reduction in 24 hour proteinuria
- No greater than a 30% reduction in baseline GFR as determined by creatinine clearance

c) No Response at 12 months
- ≤ 50% reduction, unchanged or increasing proteinuria over baseline levels

- A greater than a 30% reduction in baseline GFR as determined by creatinine clearance

d) Improvement in hematuria (Categorical: <3 rbc/hpf; 3-10 rbc/hpf; 10 to 50; 50 to 100; >100 rbc/hpf)

e) Improvement in complement 3 level (increase of 25% from baseline)

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- Age ≥ 18 years of age
- Renal biopsy read at Mayo Clinic confirming the diagnosis of PGNMID or C3 GN
- In cases of C3GN serum electrophoresis with immunofixation should confirm presence of monoclonal gammopathy
- Proteinuria ≥ 1000 mg over 24 hours
- eGFR ≥ 20 mL/min/SA
- Subjects able and willing to give informed consent

4.2 Exclusion Criteria

- Pregnancy
- Seropositive for human immunodeficiency virus (HIV)
- Seropositive for hepatitis B (defined as 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 PCRSeropositive 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).
- Multiple myeloma
- Anemia with Hgb < 8.5 g/dL
- Thrombocytopenia with platelet count < 100,000
- Leukopenia with WBC < 3.5
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complication
- Unable to provide consent
- Patients receiving therapy with oral prednisone or glucocorticoid equivalent in the last 6 weeks. Patients treated with low dose oral prednisone or glucocorticoid are allowed to be included if they are taking the medication for conditions unrelated to PGNMID or C3GN (e.g., asthma, gout) at a daily dose of 10mg or less.
- Patients who had received immunosuppressive therapy with cyclophosphamide, in the last 3 months

- Patients treated with MMF, cyclosporine, tacrolimus or azathioprine are allowed to be included if proteinuria has not improved or is worsening despite these medications and/or kidney function is worsening despite treatment with any of these medications. Once treatment with daratumumab is started, these medications will be discontinued.
- Patients who received rituximab previously with CD20 count of zero at the time of enrollment

4.3 Subject Recruitment, Enrollment and Screening

- Patients will be recruited from the principal investigator or co-investigator clinical practices
- Referring nephrologist within the Division of Nephrology and Hypertension at Mayo Rochester
- Review of renal biopsies and lab values conducted as part of clinical care
- Patients will receive $1000 remuneration total for study participation ($40 per completed study visit). Five hundred dollars will be given after completion of the 16th and final infusion, which is study visit Day 162. Five hundred dollar will be given after completion of the final visit on Day 365. If the patients withdraw from the study for any reason, they will receive prorated remuneration at $40 per completed study visit.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

- Subjects decision to withdraw from the study (withdrawal of consent)
- Failure of subject to adhere to protocol requirements (missing more than two infusions within the first 8 weeks or more than three infusions in the following 4 months). If a patients experiences an adverse event and the PI determines the next dose must be delayed, the dose may be delayed for up to 4 weeks and continue on the protocol schedule without being withdrawn.
- Disease progression (> 50% increase in proteinuria and > 30% reduction in GFR as measured by creatinine clearance) at day 77 visit
- Severe infection (defined as the development of pneumonia, severe urinary tract infection/pyelonephritis, sepsis, meningitis)
- If Hgb < 8.0 g/dL or platelet <50,000 , or WBC < 3.0 or absolute neutrophil count (ANC) < 500, the infusion will be held and restarted once blood counts have improved.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

- Subjects that withdraw consent or are withdrawn from the study due to safety issues or not following through with the protocol will be followed clinically by the PI or co-investigators or will be sent back to the referring nephrologist

5 Study Drug

5.1 Description

Daratumumab is an IgG1-kappa human monoclonal antibody that binds to the CD38 transmembrane glycoprotein on the surface of tumor cells and induces apoptosis. It appears in liquid form and is administered intravenously.

5.2 Treatment Regimen

The drug will be given intravenously at a dose of 16 mg/kg once weekly for 8 weeks followed by once every 2 weeks for 8 additional doses

If there is evidence of relapse, patients in OLE will be treated with 12 doses of daratumumab (16 mg/kg). The first 8 doses will be given weekly and the last 4 doses will be administred every other week.

5.3 Method for Assigning Subjects to Treatment Groups

This study is non-randomized trial and all 12patients that are enrolled in this study will receive daratumumab.

5.4 Preparation and Administration of Study Drug

Study drug will be prepared in the research pharmacy.

Pretreatment: Fifteen minutes prior to the first infusion, 100 mg methylprednisolone will be administered via IV along with 1000 mg acetaminophen and 50 mg diphenhydramine given by mouth. Fifteen minutes prior to all subsequent infusions, only 1000 mg acetaminophen and 50 mg diphenhydramine will be administered by mouth.

First Infusion and those part of OLE being retreated due to relapse (16 mg/Kg): IV infusion in 1000 mL 0.9% NaCl via 0.2 or 0.22 micron in-line filter, beginning at 50 mL/hr. Increase by 50 mL/hr every 60 minutes, as tolerated, to a maximum rate of 200 mL/hr. Vital signs will be taken every 15 minutes for first hour, then every hour until end of infusion, and then again after IV flush.

Second Infusion (16mg/Kg): IV infusion in 500 mL 0.9% NaCl via 0.2 or 0.22 micron in-line filter, beginning at 50 mL/hr. Increase by 50 mL/hr every 60 minutes, as tolerated, to maximum rate of 200 mL/hr. If the first infusion was not well tolerated (infusion-related reaction > Grade 1), then instructions for the first infusion should be used. Vital signs will be taken every 15 minutes for first hour, then every hour until end of infusion, and then again after IV flush.

Subsequent Infusions(16 mg/Kg): IV infusion in 500 mL 0.9% NaCl via 0.2 or 0.22 micron in-line filter, beginning at 100 mL/hr. Increase by 50 mL/hr every 60 minutes, as tolerated, to maximum rate of 200 mL/hr. If the previous infusion was not well tolerated (infusion-related reaction > Grade 1), then instructions for the second infusion will be used. Vital signs will be taken every 15 minutes for first hour, then every hour until end of infusion, and then again after IV flush.

Infusion related reactions: Diphenhydramine 25 mg IV can be given every 4 hours as needed and may repeat once if symptoms are not relieved within 15 minutes of initial dose. Methylprednisolone 100 mg IV can be given as needed for infusion related reactions.

Post-infusion: All patients should receive dexamethasone 4 mg by mouth once daily with food for two days beginning the day after daratumumab. In addition, acyclovir 400 mg by mouth twice daily, beginning within one week of starting daratumumab, and continuing for 3 months after the last daratumumab infusion. Beginning the day after their first daratumumab infusion, patients will also start single strength Bactrim once a day (or its equivalent) to prevent opportunistic infections, including pneumocystis pneumonia. Treatment with Bactrim will continue for six months after the last daratumumab infusion.

A worksheet will be created specifically for this study, which would include a dose calculation with a double check by another pharmacist for added safety. The drug will be prepared in the following steps.

1. Prepared in the non-hazardous sterile hood.
2. Drug volume calculated based upon the 16 mg/kg dose.
3. Utilize 0.9% 1000 mL for the first dose, then 0.9% 500 mL for subsequent doses.
4. Remove drug volume from 0.9% IV bag.
5. Infusion rate instructions:
   Continuous Infusion: 1st and 2nd doses: Start infusion at 50 mL/hr. Rate may be increased by 50 mL/hour every hour to a maximum rate of 200 mL/hour.
   Subsequent doses: Start infusion at 100 mL/hr. Rate may be increased by 50 mL/hour every hour to a maximum rate of 200 mL/hour.
6. Light protect IV bag.

5.5 Subject Compliance Monitoring

This drug is administered intravenously in the CRU and we can ensure compliance. If patient misses more than one infusion within the first 8 weeks or more than two infusions in the following 4 months the subject will be withdrawn from the study. We will continue to follow the subject as part of the research study with blood and urine studies and clinic visits to ensure safety.

5.6 Prior and Concomitant Therapy

The patient should be off of all immunosuppressive therapies (cyclophosphamide, MMF, cyclosporine, tacrolimus, azathioprine, ACTH) within three months of enrollment in the study. If patient has received rituximab prior to the study there should be evidence of B-cell reconstitution prior to enrollment (CD 20 count>5). The subject should be off of prednisone or glucocorticoid equivalent in the last 6 weeks prior to enrollment, unless they are being treated with low dose oral prednisone or glucocorticoid for a condition unrelated to PGNMID or C3GN (e.g., asthma, gout) at a daily dose of 10mg or less.
Patients can receive ACE-I or ARB while enrolled in the study but dose adjustment is not allowed unless down titration for safety reasons.

Rescue treatment is not permitted while receiving daratumumab. If patient is failing treatment with evidence of disease progression (> 50% increase in proteinuria and > 30% reduction in GFR based on creatinine clearance) on visit day 77, the subject will be withdrawn from the study and can then receive other immunosuppressive therapy per discretion of the treating physician.

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 see Section 6.

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.

5.7 Packaging

Commercially available supplies of daratumumab will be obtained for use in this study. Daratumumab is supplied in glass vials containing daratumumab at a concentration of 20 mg/mL. These will remain in the commercial packaging until prepared by the research pharmacy. After infusion preparation by the research pharmacy, the final infusion will be labeled as follows: "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

5.8 Masking/Blinding of Study

This is an open-label study and all participants will be receiving the study drugs. There will be no blinding or masking.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Janssen Scientific Affairs, LLC will ship the study medication directly to the Mayo Clinic Research Pharmacy. Mayo Clinic Research Pharmacy will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal of all the study drug in compliance with regulatory and institutional requirements.. Any discrepancies, damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The sponsor-investigator will be notified immediately of any discrepancies, damaged or unusable products that are received.

5.9.2 Storage

Research Pharmacy will store the study medication in a refrigerator specifically delegated for Research use only. The temperature is monitored electronically 24/7, 365 days/year. All study drug vials will be stored in in a refrigerator ranging from 2°C to 8°C (36ºF to 46ºF) and will not be utilized after the expiry date printed on the label. The product must be protected from light so it will be kept in the boxes that it is shipped in until its use. The drug must not be frozen. Daratumumab does not contain preservatives; therefore any unused portion remaining in the vial must be discarded. The Research Pharmacy is a separate area within the Central Pharmacy. To enter the pharmacy, it requires identification badge scanning. Only pharmacy personnel have access to the pharmacy.

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

See chart below

Test and Monitoring Schedule

Tests/ Assessments	Screening	D1, Inf 1	D8, Inf 2	D15, Inf 3	D21	D22, Inf 4	D29, Inf 5	D36, Inf 6	D43, Inf 7	D49	D50, Inf 8	D64, Inf 9	D77	D78, Inf 10	D92, Inf 11	D105	D106, Inf 12	D120, Inf 13	D133	D134, Inf 14	D148, Inf 15	D161	D162, Inf 16	D264	D365	OLE [8]
History/Exam[1]	X									X			X									X		X	X	
Informed Consent	X																								
CBC with 5-part WBC differential	X				X					X			X			X			X			X		X	X	X
Basic Metabolic Panel	X									X			X									X		X	X	X
Albumin, serum	X												X									X		X	X	X
Protein total, serum	X									X			X									X		X	X	X
Protein electrophoresis, serum	X									X			X									X		X	X	X
Immuno subtraction (immunofix), serum	X									X			X									X		X	X	X
Hepatitis B tests[2]	X																							X	X	
Hepatitis C tests	X																									
HIV test[3]	X																									
Pregnancy test, serum[4]	X																									X
Lipid panel	X																								X	
Complement C-3 & C-4, serum	X																								X	
Urinalysis w/microscopic	X									X			X									X		X	X	X
Kappa & Lambda free light chain, serum	X									X			X									X			X	X
Creatinine clearance	X									X			X									X		X	X	X
Protein total, 24 hour urine	X									X			X									X		X	X	X
Immunofixation, 24 hour urine	X									X			X									X		X	X	X

Electrophoresis,24 hour urine	X									X			X									X		X	X	X
Immunoglobulin quantitative IgA, IgG, IgM	X												X									X			X	
Indirect Antiglobulin Test (IAT) [5]	X																									
Pregnancy Test, urine[6]		X	X	X		X	X	X	X		X	X		X	X		X	X		X	X		X			
Pre-infusion medications[7](methylprednisolone, acetaminophen and diphenhydramine		X	X	X		X	X	X	X		X	X		X	X		X	X		X	X		X			X
Daratumumab Infusion		X	X	X		X	X	X	X		X	X		X	X		X	X		X	X		X			X
Adverse Events			X			X		X		X			X		X		X			X		X		X	X	X

1 Exam will include vitals (i.e., height, weight, temperature, blood pressure and pulse)

2 Subjects If hepatitis B results are positive HBV testing by PCR will be performed. 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 Test and Monitoring Schedule Table above. Local law requires positive test results be reported to local health authorities.

3If HIVor Hepatitis C test results are positive a reflex test will be conducted to confirm . Local law requires positive test results be reported to local health authorities.

4 Serum pregnancy test for women with childbearing potential.

5Daratumumab treatment affects pre-transfusion blood testing. Therefore, in the event that a patient may need a blood transfusion Indirect Antiglobulin Testing will be performed at screening, prior to the first daratumumab infusion, and the results given to patients to carry for the duration of the study.

6 Urine pregnancy test prior to infusion for women with childbearing potential.

7Pre-infusion medication methylprednisolone given prior to first infusion and only as needed for subsequent infusions for infusion reactions. Pre-infusion medications acetaminophen and diphenhydramine given prior to all infusions.

8 In the OLE patients will be followed clinically every 3 to 6 months, as determined by the treating nephrologist in consultation with the PI. If there is evidence of relapse defined as a 30% increase in their proteinuria from the lowest proteinuria level that the patient had achieved, patients will be treated with 12 additional doses daratumumab at 16 mg/kg.

7 Statistical Plan

7.1 Sample Size Determination

This is a proof-of-concept study and therefore a power calculation was not performed. The primary endpoint of this study is the safety of this drug in terms of incidence of rate of treatment emergent major infection, grade 3 or 4 anemia, leukopenia or thrombocytopenia in patients with PGNMID and C3 GN associated with monoclonal gammopathy and the secondary endpoint is to the efficacy of daratumumab in this patient population. A paired t-test will be utilized to test the hypotheses described below. Twelve subjects will be enrolled in the study.

7.2 Statistical Methods

Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) in each response category will be tabulated. Time-to-response will be analyzed descriptively with Kaplan-Meier method.

For the primary endpoint, the number and proportion of patients with treatment-emergent major infections, grade 3 or 4 anemia, leukopenia or thrombocytopenia will be summarized. Changes in Hgb, WBC count and platelet count from baseline (Day 0) will be analyzed through a paired t-test by comparing post-baseline to baseline values. The secondary endpoint of the proportion of patients with complete or partial response will be summarized in a similar manner.

It is expected that 9 patients will enter the OLE. The rate of relapse in addition to the time to relapse from the last dose of daratumumab to initiation of retreatment will be evaluated. Paired t-test will be used to evaluate change in the proteinuria from time of relapse to the end of the study. Rate of CR and PR will be evaluated at the end of the OLE.

Handling of Missing Data

This is a study of only 12 patients and expect that majority of patients will have complete data available.

Primary Hypothesis: Daratumumab is safe and well-tolerated in patients with PGNMID and C3GN associated with monoclonal gammopathy

To test this hypothesis, the incidence of major infection will be examined, specifically the development of pneumonia, severe urinary tract infection/pyelonephritis, sepsis, meningitis will be reported. In addition, anemia, leukopenia, thrombocytopenia will be examined by evaluating changes in Hgb, WBC count and platelet count, respectively. Statistical significance will be assessed using paired t-test comparing 6 months and 1 year value compared to baseline. The

number of patients who had to discontinue drug due to side effect (drop in blood counts, infection) will also be reported.

Secondary Hypothesis: Daratumumab is effective in inducing remission (defined as improvement in proteinuria and eGFR) in patients with PGNMID and C3GN associated with monoclonal gammopathy

A paired t-test will be performed to assess change in proteinuria and renal function at 6 months and 12 months compared to baseline (screening visit).

Interim Analysis
Interim analysis will be done every 6 months to assess safety of the drug. The study will be stopped if four patients experience serious adverse events including infection, anemia, thrombocytopenia or leucopenia resulting in discontinuation of study drug.
A four person Data Safety Monitoring Board (DSMB) comprised of clinical researchers not affiliated with the study will be established and responsible for evaluating the ongoing progress of the study. The DSMB will communicate by meeting every 6 months to review interim analysis. The Chairperson of the DSMB will be notified of SAEs within 48 hours of them being reported and the Chair will have an additional 48 hours in which to respond and determine whether an emergency of the DSMB is required. The DSMB will act in an advisory capacity to the PI's to monitor participant safety, data quality and evaluate the progress of the study.

7.2 Subject Population(s) for Analysis

All-treated population: Any subject that received at least one dose of study drug.

8 Safety and Adverse Events

The primary side effects associated with daratumumab include anemia, neutropenia and thrombocytopenia and these will be evaluated initially by monthly CBC done on Day 21, 49, 77, 105, 133, 161 and then every 3 months done on Day 264, 365. Further, these will be evaluated during OLE laboratory assessments.

Other side effects include risk of infection specifically pneumonia and patients will be asked about any sings of symptoms suggestive of infection (e.g fever, cough) or any hospitalization, emergency department visits or other doctor visits at the clinical visits on Day 49, 77, 133, 161, 264, 365 and during OLE when laboratory assessments are completed or an infusion is administeredOther side effects include symptoms of nausea and fatigue and similarly patients will be asked regarding these symptoms at the time of clinic visits and during OLE when laboratory assessments are completed or an infusion is administered.

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is

"unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

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.

Serious Adverse Event

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*

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

*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.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period
For this study, the study treatment follow-up period is defined as 365 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if:

- Monthly CBC shows that Hgb is < 8.0 g/dL
- Monthly CBC shows that WBC is < 3.0
- Monthly CBC shows ANC < 500
- Monthly CBC shows that platelet count is < 50,000

Hospitalization, Prolonged Hospitalization or Surgery
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.]

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report all serious, unanticipated and possibly drug related events to the FDA utilizing the Voluntary Reporting Form 3500. See FDA information on Reporting for NON IND Events:

http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm

8.3.3 Sponsor-Investigator reporting: Notifying the Manufacturer

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

8.3.3.1 Overview

As the sponsor of the Study, Mayo Clinic and 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 Mayo Clinic and 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.

8.3.3.2 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 Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after 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)

8.3.3.3 Definitions

Adverse Event (AE)
See Adverse Event Definition in Section 8.1 above

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)
See Serious Adverse Event Definition in Section 8.1 above

Hospitalization
See Hospitalization Definition in Section 8.1 above

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.

8.3.3.4 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.

8.3.3.5 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
- Any failure of expected pharmacological action (i.e., lack of effect) 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.**

8.3.3.6 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.

8.3.3.7 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The Mayo Clinic and 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.

8.3.3.8 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.

8.3.3.8.1 SAEs 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 Mayo Clinic and 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 10, Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC.

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, Adverse Event of Special Interest, serious ADR or special situation is required.

- The Mayo Clinic and 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 extraordinary 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 10 from this Exhibit within **24 hours of such report or correspondence being sent to applicable health authorities.**

8.3.3.8.2 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.

8.3.3.8.3 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 for any reports of 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.

8.3.3.9 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.

8.3.3.10 Transmission Methods

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

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

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

8.4 Stopping Rules

The study will be stopped if four patients experience serious adverse events including infection, anemia, thrombocytopenia or leucopenia resulting in discontinuation of study drug..

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.5.1 Internal Data and Safety Monitoring Board

A four person DSMB (clinical researchers) not affiliated with the study will be responsible for evaluating the progress of the study and will be provided data on a regular basis to monitor patient safety. This committee will communicate by meeting at 3 months, 6 months and then 12 months. They will be responsible for determining if and when the study must be discontinued as a result of excessive adverse events. Study data will be provided to the DSMB by the data coordinating center (including all adverse event reports and the GFR data). The Committee will make its recommendations by periodically monitoring progress, data, outcomes, toxicity, safety and other confidential data, and may recommend stopping the clinical trial if an excessive number of serious adverse events are observed.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The investigator will review, approve and sign/date each completed CRF; the investigator signature serving as attestation of the investigator responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management
Investigators will enter the information required by the protocol into electronic Case Report Forms (eCRFs). This study will use REDCap which allows web-based data entry, has edit checks, audit trails, controlled access, and undergoes frequent back-up.

Data Security and Confidentiality
All clinical data will be processed in a secure electronic environment that includes virus protection, and restricted access. Electronically stored data are subject to extensive security measures including virus detection, and restricted access. Security measures in place for the database management system proposed for this study include: browser security, firewall protection, user name/password protection, user re-authentication, and inactivity time-out.

Data Quality Assurance
Quality control will take place at time of data entry (range, consistency checks) and will be ensured by oversight by the P.I. Before the enrollment of any subject in this study, designated study personnel will review with the investigator and personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs. Information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered, safety information will be reviewed for completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators.

By signing the protocol, the Mayo Clinic agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol and accepted standards of Good Clinical Practice.

Data Clarification Process
Data queries generated by identification of incomplete or inconsistent data will be raised directly within the electronic eCRF and should be resolved by the study coordinator or PI in a timely manner. Corrections or changes in the data management system are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

Whichever is longer

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Data and safety monitoring provides a clinical investigation with a system for appropriate oversight and attention to the protection of human subjects by the investigator, research team, or an independent reviewer. A Data and Safety Monitoring Plan is a quality assurance plan for a research study. A written Data and Safety Monitoring Plan (DSMP) prospectively identifies and documents monitoring activities intended to protect the safety of the subjects, the validity of the data and the integrity of the research study. The DSMP may also identify when to terminate a subject's participation (i.e. individual stopping rules) and/or the appropriate termination of a study (i.e. study stopping rules).

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

Janssen Scientific Affairs is providing drug and funding support for this study. This study is funded by Janssen.

13 Publication Plan

A policy similar to the NIH policy on publication of study results will apply to this study. Details regarding policy statements may be found on the website at http://www1.od.nih.gov/oma/manualchapters.

The PI will hold the primary responsibility for publication of the results of the study. The study will be registered at ClinicalTrials.gov and results will be posted within 12 months of final data collection for the primary and secondary outcomes.

14 References

1. Ivanyi, B: Frequency of light chain deposition nephropathy relative to renal amyloidosis and Bence Jones cast nephropathy in a necropsy study of patients with myeloma. *Arch Pathol Lab Med,* 114**:** 986-987, 1990.
2. Merlini, G, Stone, MJ: Dangerous small B-cell clones. *Blood,* 108**:** 2520-2530, 2006.
3. Leung, N, Bridoux, F, Hutchison, CA, Nasr, SH, Cockwell, P, Fermand, JP, Dispenzieri, A, Song, KW, Kyle, RA: Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. *Blood,* 120**:** 4292-4295, 2012.
4. Nasr, SH, Satoskar, A, Markowitz, GS, Valeri, AM, Appel, GB, Stokes, MB, Nadasdy, T, D'Agati, VD: Proliferative glomerulonephritis with monoclonal IgG deposits. *J Am Soc Nephrol,* 20**:** 2055-2064, 2009.
5. Sethi, S, Zand, L, Leung, N, Smith, RJ, Jevremonic, D, Herrmann, SS, Fervenza, FC: Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. *Clin J Am Soc Nephrol,* 5**:** 770-782, 2010.
6. Bhutani, G, Nasr, SH, Said, SM, Sethi, S, Fervenza, FC, Morice, WG, Kurtin, PJ, Buadi, FK, Dingli, D, Dispenzieri, A, Gertz, MA, Lacy, MQ, Kapoor, P, Kumar, S, Kyle, RA, Rajkumar, SV, Leung, N: Hematologic characteristics of proliferative glomerulonephritides with nonorganized monoclonal immunoglobulin deposits. *Mayo Clin Proc,* 90**:** 587-596, 2015.
7. Bridoux, F, Desport, E, Fremeaux-Bacchi, V, Chong, CF, Gombert, JM, Lacombe, C, Quellard, N, Touchard, G: Glomerulonephritis with isolated C3 deposits and monoclonal gammopathy: a fortuitous association? *Clin J Am Soc Nephrol,* 6**:** 2165-2174, 2011.
8. Zand, L, Kattah, A, Fervenza, FC, Smith, RJ, Nasr, SH, Zhang, Y, Vrana, JA, Leung, N, Cornell, LD, Sethi, S: C3 glomerulonephritis associated with monoclonal gammopathy: a case series. *Am J Kidney Dis,* 62**:** 506-514, 2013.
9. Sethi, S, Sukov, WR, Zhang, Y, Fervenza, FC, Lager, DJ, Miller, DV, Cornell, LD, Krishnan, SG, Smith, RJ: Dense deposit disease associated with monoclonal gammopathy of undetermined significance. *Am J Kidney Dis,* 56**:** 977-982, 2010.
10. Sethi, S, Fervenza, FC, Rajkumar, SV: Spectrum of manifestations of monoclonal gammopathy-associated renal lesions. *Curr Opin Nephrol Hypertens,* 25**:** 127-137, 2016.
11. Lonial, S, Weiss, BM, Usmani, SZ, Singhal, S, Chari, A, Bahlis, NJ, Belch, A, Krishnan, A, Vescio, RA, Mateos, MV, Mazumder, A, Orlowski, RZ, Sutherland, HJ, Blade, J, Scott, EC, Oriol, A, Berdeja, J, Gharibo, M, Stevens, DA, LeBlanc, R, Sebag, M, Callander, N, Jakubowiak, A, White, D, de la Rubia, J, Richardson, PG, Lisby, S, Feng, H, Uhlar, CM, Khan, I, Ahmadi, T, Voorhees, PM: Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet*, 2016.