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Clinical Protocol IM101566

A Phase II Randomized, Placebo-Controlled, Double-Blind, Parallel Arms, Pilot Study to Evaluate the Efficacy and Safety of Intravenous Abatacept in Treatment Resistant Nephrotic Syndrome (Focal Segmental Glomerulosclerosis/ Minimal Change Disease)

Revised Protocol Number: 02

Incorporates amendment(s): 02

Study Director/Medical Monitor

Michael Maldonado, MD

[redacted]

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	18-Apr-2018	Incorporates Amendment 02.
Amendment 02	18-Apr-2018	Updated protocol title to delete "with Switchover." Changed Period 1 to Double-Blind Period. Added an option for early escape at Day 85 for pediatric subjects depending on investigator discretion (Day 57 UPCR >3 and assessment of clinical response). Deleted Period 2. Replaced schematic with a new version reflecting the new study design. Updated [redacted] efficacy assessments based on modification of the study design. Deleted information on relapse. Added adjustment of background treatment in the OLE. Added treatment with systemic corticosteroids for adverse events limited to ± 2 weeks. Added inhaled corticosteroids are permitted for the treatment of asthma, COPD, etc. Updated definition of serious breach. [redacted]
Revised Protocol 01	17-Apr-2017	Incorporates Amendment 01
Amendment 01	17-Apr-2017	Added EUDRACT number since the study is enrolling pediatric subjects. Changed address and telephone for the Medical Monitor. Changed address for Bristol Myers Squibb. Decreased minimum eGFR at screening to ≤ 45 for subjects <18 years using the new Schwarz equation. Amended the Post Study Drug Access to indicate the post study drug will be available for subjects who demonstrate clinical benefit at the conclusion of the study. Clarified description for treatment resistance and treatment intolerance. Clarified language regarding treatment with an ACE or ARB. Deleted detailed description on method of contraception from the body of the protocol and added Appendix 2. Updated numbering of other appendices. Added exclusion for subjects who are post-renal transplantation, including relapsing post-transplant FSGS. Clarified Restricted Treatment and Other Restrictions and Precautions. Added the dose windows for Period 2. Added sample collection for DNA and Additional Research. Corrected to add CBC collection at Day 197 and Total Cholesterol and Triglycerides at Days 169 and 197. Added pregnancy testing in open label. Clarified exclusion criteria for BMI.
Original Protocol	05-Oct-2015	Not applicable

SYNOPSIS

Clinical Protocol IM101566

Protocol Title: A Phase II Randomized, Placebo-Controlled, Double-Blind, Parallel Arms, Pilot Study to Evaluate the Efficacy and Safety of Intravenous Abatacept in Treatment Resistant Nephrotic Syndrome (Focal Segmental Glomerulosclerosis/ Minimal Change Disease).

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): The study will utilize the IV abatacept formulation. Subjects randomized to abatacept treatment in the Double-Blind Period will be dosed as follows. Adults will use the weight-tiered dose: < 60 kg: 500 mg, 60 to 100 kg: 750 mg, > 100 kg: 1000 mg; pediatric patients 6 to 17 years who weigh < 75 kg will receive:10 mg/kg and those who weigh ≥ 75 kg will follow adult dosing.

Dosing is on Day 1, 15, 29 and then every 28 days for 113 days. Subject in the placebo arm will receive normal Saline or D5W following the same dosing schedule. In the open-label extension, subjects who enter will all receive age and weight-based IV abatacept every 28 days for 169 days.

Study Phase: II

Research Hypothesis: Subjects with treatment resistant nephrotic syndrome (TRNS) due to either focal segmental glomerulosclerosis (FSGS) or Minimal Change Disease (MCD) [TRNS (FSGS/MCD)] will demonstrate improvement in proteinuria when treated with abatacept.

Objectives:

Primary Objective: Demonstrate improvement in nephrotic range proteinuria to sub-nephrotic range while maintaining renal function following treatment with abatacept compared to placebo.

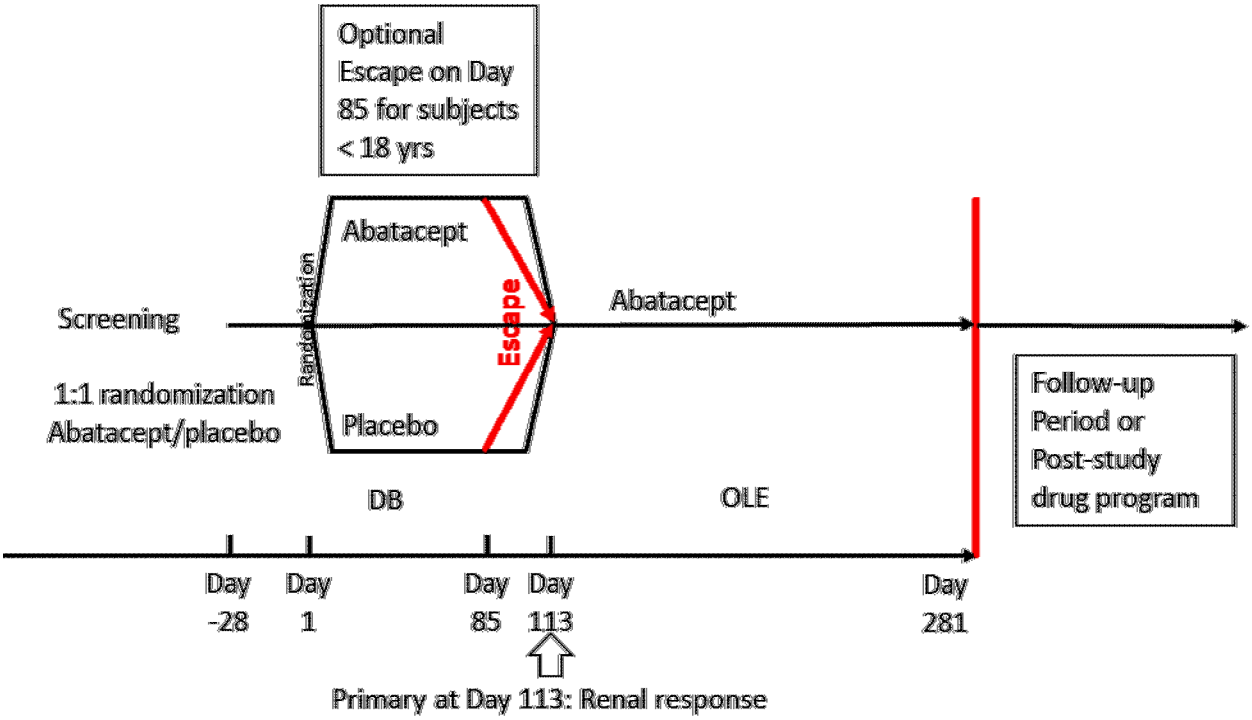
- Demonstrate difference in percent of renal responders defined by composite renal index at Day 113.

Secondary Objectives:

1) Assess improvement in change from baseline in the level of proteinuria following treatment with abatacept compared to placebo.
   - Assess difference in mean change from baseline in UPCR at Day 113.
2) Assess improvement in serum albumin levels following treatment with abatacept compared to placebo.
   - Assess difference in mean change from baseline in serum albumin at Day 113.
3) Assess improvement in complete remission while maintaining renal function following treatment with abatacept compared to placebo.
   - Assess difference in percent of subjects achieving complete remission (UPCR ≤ 0.3) with preservation of eGFR at Day 113.
4) Assess improvement in patient reported outcomes related to nephrotic syndrome.
   - Assess changes using the Patient Reported Outcomes Measurement Information System (PROMIS) at Day 113.
5) Assess the safety and immunogenicity of abatacept in subjects with TRNS.
   - Describe rates of AEs and SAEs and immunogenicity testing.
6) Assess the pharmacokinetics of abatacept in subjects with TRNS
   - Describe the pharmacokinetics of abatacept.

Study Design: This pilot study will randomize approximately 90 subjects 1:1 to intravenous (IV) abatacept or placebo in a double-blind (DB) fashion into a parallel arms. The trial will consist of 4 periods totaling ~17 months: the Screening Period will be 28 days (can be extended an additional 14 days to complete testing by repeating screening labs), a 16 week Double-Blind Treatment Period (parallel arms: IV abatacept vs placebo) with a possible

early escape at Day 85 for pediatric age subjects, a 168 day abatacept Open Label Extension Period (OLE), and a 6 month Follow-up Period (see schematic).



Subjects will be recruited from approximately 25 sites in North America. Written informed consent will be provided by the subjects prior to undergoing any procedures during the screening phase. Randomization will be stratified by results of genotyping of *APOL1* gene and age (< 18 and ≥ 18).

The primary efficacy assessment, renal response, will be on Day 113 (end of the double-blind period). The rationale for allowing non-responders to enter the OLE and receive abatacept is to allow these non-responders who wish to determine if a longer exposure to abatacept with or without adjustment of background therapy could lead to a response, to do so. During the OLE the durability (ie, continuous response) and stability (ie, variability in the improvement in UPCR) of response will be determined by continuing to capture and describe the same study outcomes among responders. Adjustment of background therapy will also be allowed during the OLE at the discretion of the investigators and subjects to determine the relative contribution (or need) of these agents for renal responses.

Study Population: Subjects who enroll must meet the criteria for TRNS (FSGS/MCD). This includes the pathological findings of either FSGS (excluding collapsing FSGS, a sub-set of FSGS seen in both HIV and non-HIV infected subjects with a more severe presentation and poor prognosis) or MCD on the most recent renal biopsy. NS will be defined by a UPCR ≥ 3 (g/g or unitless). Subjects will need to have a minimal preserved renal function as measured by eGFR (≥ 45 for children and adults (mL/min/1.73m^2) based on the CKD-EPI for adults and the new Schwartz equation for children). Treatment resistance will be defined as persistence of NS in spite of therapy with either corticosteroids (CS) or other accepted agents for the required period of time (listed in the inclusion criteria) or intolerance to any two of these agents. Subjects age 6 and older will be enrolled. Subjects receiving permitted background therapy at the time of enrollment may continue these as long as the dose has been stable for 4 weeks prior to randomization. Subjects will be required to use either an angiotensin-converting-enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) at stable doses during the course of the double-blind (DB) period unless intolerant. Management of hypertension and volume will follow standard of care. Subjects will be tested at screening for the SNPs associated with the high-risk *APOL1* variants. Subjects will be allowed to opt-out of genotyping and still enroll. This will be used for stratification during randomization.

Key Inclusion Criteria:

- Male and female subjects ages ≥ 6 years
- Subjects diagnosed with TRNS (FSGS/MCD)
  - Pathological findings of either FSGS (excluding collapsing FSGS) or MCD on the most recent renal biopsy (renal biopsies will not be part of this study). This will be confirmed by review of the pathology report (not slides) by a central pathologist
  - UPCR ≥ 3 at screening
  - Treatment resistant defined as:
    - Persistence of UPCR ≥ 3 in spite of therapy with any one of the following agents: corticosteroids (CS), calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus, mycophenolate mofetil (MMF), mycophenolic acid (MPA) or cyclophosphamide
    - Duration of therapy: The duration of CS therapy required to determine treatment resistance will be 6 weeks in subjects < 18 year of age and 12 weeks for subjects ≥ 18 years. For all other agents, the minimum duration of therapy will be 16 weeks, regardless of age
    - Intolerance to any two of these agents, regardless of duration of treatment or age
- Subjects must be receiving either an angiotensin-converting-enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) at stable doses for at least 2 weeks prior to randomization unless intolerance is documented. Combined use of renin angiotensin system (RAS) inhibitors will not be allowed. If aldosterone inhibitors (spirolactone or eplerenone) or aliskiren (direct renin inhibitor) are used, they must also be at stable doses.
- A minimal level of renal function at screening based on estimated glomerular filtration rate (eGFR) will be required (≥ 45 for both children and adults)
- *APOL1* Genotyping. Subjects will be genotyped for the *APOL1* renal risk variants SNPs [Risk allele G1 (rs73885319 and rs60910145) and risk allele G2 (rs71785313)]. Subjects with 2 copies of the high-risk *APOL1* variants are in the *APOL1* high-risk group which will be used for stratification at randomization. Genotyping during screening will not be necessary if results of previous testing are available. Subjects will be allowed to opt-out of genotyping for *APOL1*. Subjects who refuse genotyping will still be eligible to be randomized.
- Concomitant medication. Subjects may enroll with or without the following background agents used to treat TRNS (FSGS/MCD): CS (low dose, prednisone or equivalent at doses ≤ 10 mg/day), calcineurin inhibitors (cyclosporine and tacrolimus), MMF or mycophenolic acid. Agents must be used at standard doses, must not have been started within 8 weeks of enrollment and must be stable for at least 4 weeks prior to randomization. No adjustment in doses of concomitant medications will be allowed during the double-blind period. Dose decrease or holds to address drug-related toxicity are allowed.

Key Exclusion Criteria:

- Subjects with other causes of TRNS other than FSGS or MCD (eg, IgA nephropathy, obesity related glomerulopathy or membranous nephropathy)
- Subjects with collapsing FSGS, also known as collapsing glomerulopathy
- Subjects with systemic lupus erythematosus (SLE)
- Subjects with diabetes mellitus, both type 1 and type 2
- Subjects with clinically significant congestive heart failure (CHF; New York Heart Association [NYHA] Class III or Class IV)
- Body mass index (BMI) > 40 for adults

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for IM101566		
Medication	**Potency**	**IP/Non-IP**
Intravenous Abatacept	10 mg/kg	IP

Study Assessments: The primary outcome used will be a composite renal index which will be used to determine the rate of renal responders. Secondary endpoints will be determined by assessing complete remission (defined as UPCR ≤ 0.3 with preservation of eGFR), the change in patient reported outcomes (using PROMIS measures), change in height as determined by standard deviation score (HSDS; z-scores) for subjects < 18 years and laboratory assessments (serum albumin, serum total cholesterol and triglycerides).

Statistical Considerations:

Sample Size: The study is planned to randomize 90 subjects to assess the primary endpoint of proportion subjects in Renal Response at Day 113 between the IV Abatacept and placebo arms. The randomization will be stratified by Genotype (*APOL1* high risk group vs Others) and Age (< 18 and ≥ 18).

Endpoints:

Primary Endpoint: The primary efficacy endpoint is the proportion of subjects in Renal Response at Day 113.

Secondary Efficacy Endpoint(s):

- Mean change from baseline in UPCR at Day 113
- Mean change from baseline in serum albumin at Day 113
- Proportion of subjects achieving complete remission (UPCR ≤ 0.3 with eGFR: normal or ≥ 75% baseline if below normal at baseline) at Day 113
- Mean change from baseline in PROMIS measures at Day 113

Safety Endpoints:

- All adverse events (AEs, SAEs, AE leading to discontinuation, deaths)
- AEs of interest (infections, malignancies, autoimmune disorders, infusional related reactions, renal-related events)
- Laboratory test abnormalities

Immunogenicity Endpoint: Proportion of subjects with positive antibody response relative to baseline over time.

[redacted]

Analyses:

Summary of Planned Efficacy Analyses	
Measure of Interest	**Analysis Method**
Renal Response	Primary Analysis: Using a logistic regression model that includes treatment arm, randomization stratification factor (Genotype, Age) and baseline UPCR as continuous variable and point estimate of adjusted ORs, corresponding 95% CI and p-value will be provided.
Differences in proportions: proportion of subjects achieving complete remission at Day 113	Secondary Efficacy Analysis: Using a logistic regression model that includes treatment arm, stratification variables (Genotype and Age) and baseline UPCR as continuous variable and point estimate of adjusted ORs, corresponding 95% CI will be provided.
Difference in mean change from baseline in continuous endpoints (UPCR, Serum Albumin, [redacted]	Longitudinal (repeated measure) mixed model [including treatment group, baseline value of variable and randomization stratification factors (genotype and Age), time, and time by treatment interaction as fixed effects and subject as a random effect], adjusted mean, SE, 95% CI for adjusted mean difference between treatment groups will be provided.

Safety Analyses

Significant physical examination findings, and clinical and laboratory test results will be listed. Summary statistics will be tabulated. Frequency distributions and individual listings of all adverse events will be generated. Changes from baseline in clinical laboratory test results will be summarized and listed. Frequencies of marked abnormal laboratory measures will also be provided. Safety analyses will be presented by treatment arms in the double-blind period.

Pharmacokinetic Analyses

Summary statistics will be tabulated by treatment for the pharmacokinetic parameters (Cmax, Tmax, and AUC) and by study days for Cmin. Geometric means and coefficients of variation will be presented for Cmin, Cmax, and AUC. Medians and ranges will be presented for Tmax.

[redacted]

[redacted].

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1.2 Research Hypothesis

Subjects with treatment resistant nephrotic syndrome (FSGS/MCD) will demonstrate improvement in proteinuria when treated with abatacept.

1.3 Objectives(s)

1.3.1 Primary Objectives

Demonstrate improvement in nephrotic range proteinuria to sub-nephrotic range while maintaining renal function following treatment with abatacept compared to placebo.

- Demonstrate difference in percent of renal responders defined by composite renal index at Day 113.

1.3.2 Secondary Objectives

1) Assess improvement in change from baseline in the level of proteinuria following treatment with abatacept compared to placebo.
   - Assess difference in mean change from baseline in UPCR at Day 113.
2) Assess improvement in serum albumin levels following treatment with abatacept compared to placebo.
   - Assess difference in mean change from baseline in serum albumin at Day 113.
3) Assess improvement in complete remission while maintaining renal function following treatment with abatacept compared to placebo.
   - Assess difference in percent of subjects achieving complete remission (UPCR $\leq$ 0.3) with preservation of eGFR at Day 113.
4) Assess improvement in patient reported outcomes related to nephrotic syndrome at Day 113.
   - Assess changes using the Patient Reported Outcomes Measurement Information System (PROMIS) at Day 113.

5) Assess the safety and immunogenicity of abatacept in subjects with TRNS.
   - Describe rates of AEs and SAEs and immunogenicity testing.
6) Assess the pharmacokinetics of abatacept in subjects with TRNS.
   - Describe the pharmacokinetics of abatacept.

1.5 Overall Risk/Benefit Assessment

Subjects with TRNS (FSGS/MCD) with nephrotic syndrome are at significant risk of multiple complications, including increased susceptibility to infection, end-stage renal disease (ESRD) and increased mortality. TRNS (FSGS/MCD) impacts both children and adults. Clinical care depends on both immunomodulatory and nonimmunologic therapy aimed at reducing proteinuria, although there is no clear standard of care.[8]

IV abatacept has been studied primarily in autoimmune or immune-mediated diseases including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, including lupus nephritis, Crohn's disease, ulcerative colitis, acute graft-versus-host disease prevention (aGVHD) and ANCA-associated vasculitis.[22,33,34] The major identified risk of abatacept is an increased incidence of infections. Consistent with its mechanism of action, the abatacept RA program identified both non-serious and serious infections, mainly bacterial [upper respiratory infections (URI's), pneumonias] and viral (herpes simplex), as occurring more frequently in abatacept-treated subjects. Despite this identified risk, the majority of infections presented typically, responded appropriately to treatment, and there did not appear to be a major difference in outcome between abatacept and placebo. The risk for serious infections did not

increase in the open-label periods with increasing exposure. Opportunistic infections and tuberculosis (TB) were uncommon, although all subjects were screened for latent TB. The overall risk of malignancy for abatacept-treated subjects was comparable with placebo-treated subjects during the double-blind periods. The incidence of malignancy did not appear to be greater with increased exposure. An important caution is that the clinical studies contain neither sufficient numbers of subjects nor follow up of sufficient duration to assess long term treatment or to rule out increases in the risk of AEs with long latency, such as malignancy. Treatment with abatacept was associated with an excellent peri-infusional safety profile, no increased risk of autoimmunity, and was associated with a low level of immunogenicity which is not dependent on use of concomitant therapy.

A significant co-factor in assessing the risk of therapy with IV abatacept is the use of concomitant therapies that also have immunomodulatory properties as they can contribute significantly to the risk of infections. Abatacept has been studied across multiple disease states with a wide variety of these agents including MMF, methotrexate and corticosteroids, both high and low doses, but rarely with calcineurin inhibitors (cyclosporine and tacrolimus).[22,35,33,36,37] The potential risk of combining these agents can by mitigated by limiting which agents can be used concurrently, discontinuation prior to study entry or minimizing dosages.

There is more extensive experience in the use of IV abatacept in subjects age 18 and older. Most experience in the use of IV abatacept in younger subjects comes from subjects with JIA.[22] Additional experience has been reported from both controlled studies and case series in other disease states including Type 1 diabetes, systemic onset JIA (soJIA), lupus nephritis, aGVHD and uveitis (refractory JIA-related and idiopathic).[38,35,33,24,39,40] Most of this reported experience has been with the use of IV abatacept at the dose of 10 mg/kg every 28 days. One case series used higher doses of abatacept of up to 18 mg/kg in subjects with active soJIA with no associated safety signal.[35] Clinical development of IV abatacept has been limited to age 6 and older due to immune system abnormalities seen in studies in juvenile rats exposed to abatacept and the unknown impact it may have on the developing human immune systems.[22]

The pharmacokinetic (PK) profile of IV abatacept in subjects with lupus nephritis with and without nephrotic syndrome has been studied.[22] The presence of nephrotic range proteinuria can impact multiple PK parameters including decreasing the area under the concentration-time curve for a dosing interval [AUC(TAU)] and trough concentration (Cmin). These impacts were seen at both IV abatacept doses studied (30 mg/kg and ~10 mg/kg). More robust improvements in proteinuria were seen in abatacept dose groups, including the ~10 mg/kg dose, compared to placebo for subjects with baseline nephrotic range proteinuria (UPCR ≥ 3). Based on case reports and the more robust available clinical experience, especially in subjects age 17 and younger, the ~10 mg/kg dose of abatacept seems the most appropriate initial dose to examine the safety and efficacy of IV abatacept in this mixed age population of subjects with TRNS (FSGS/MCD).

Abatacept is classified as a Pregnancy Category C with no adequate and well-controlled studies of ORENCIA use in pregnant women. There have been over 200 reports of abatacept exposure during pregnancy, both maternal and paternal.[22] Impact on nursing mothers and infants is very

limited but there is theoretic concern with maternal-infant transmission which could impact live vaccination adversely. Women of childbearing potential will be required to practice effective contraception and undergo pregnancy testing throughout the study.

It is not known if all or even some of the subjects with TRNS (FSGS/MCD) who may respond to abatacept will require ongoing therapy to maintain the clinical response.

As an initial controlled study in a new disease state, a Data Monitoring Committee (DMC) will be created to provide oversight of safety and efficacy considerations in this study. The DMC will provide advice to BMS regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for abatacept. The creation of a DMC will help mitigate the risk associated with this pilot study.

Preclinical work and case reports suggest that a subset of patients with TRNS (FSGS/MCD) may benefit from treatment with IV abatacept. This subset includes both pediatric and adult age subjects. A greater safety experience in subjects age 17 and younger and the observed benefits on nephrotic range proteinuria in subjects with either active lupus nephritis or TRNS (FSGS/MCD) justifies the initial study of the approximately 10 mg/kg dose of IV abatacept in this pilot study in subjects with TRNS (FSGS/MCD). The risk associated with the use of abatacept, with or without concomitant immunomodulatory therapy, is acceptable for this group of subjects with high morbidity and risk of ESRD.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of 1 or more subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the

subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The study will randomize approximately 90 subjects 1:1 to intravenous (IV) abatacept or placebo in a double-blind (DB) fashion into parallel arms. The trial will consist of 4 periods totaling ~17 months: the Screening Period will be 28 days (can be extended an additional 14 days to complete testing by repeating screening labs), a 16 week Double-Blind Treatment Period (parallel arms: IV abatacept *vs* placebo), a 168 day abatacept Open Label Extension Period (OLE), and a 6 month Follow-up Period (see schematic). The primary efficacy assessment, renal response, will be on Day 113. This treatment time is based on case reports which suggest that subjects that respond to abatacept will do so in this time frame.[11,12] On Day 113, all subjects who choose to receive open label therapy with abatacept will enter the OLE. The rationale for allowing non-responders to enter the OLE and receive abatacept is to allow these non-responders who wish to determine if a longer exposure to abatacept with or without adjustment of background therapy could lead to a response, to do so. During the OLE the durability (ie, continuous response) and stability (ie, variability in the improvement in UPCR) of response will be determined by continuing to capture and describe the same study outcomes among responders. Adjustment of background therapy will also be allowed during the OLE at the discretion of the investigators and subjects to determine the relative contribution (or need) of these agents for renal responses.

The main purpose of the study is to decrease the level of proteinuria from a nephrotic range to a sub-nephrotic range in subjects with TRNS (FSGS/MCD). The endpoint used will capture a change in proteinuria that is clinically relevant without an associated negative impact on renal function [ie, change in estimated glomerular filtration rate (eGFR)] and which accounts for

varying degrees of baseline proteinuria.[41,42] The primary outcome used will be a composite renal index which will be used to determine the rate of renal responders. Renal responders are defined as subjects who achieve a reduction of their baseline UPCR of ≥ 50% and to less than 3 with no worsening of baseline estimated glomerular filtration rate (eGFR: normal or ≥ 75% baseline if below normal at baseline). Secondary and exploratory endpoints will assess associated features of nephrotic syndrome and demonstrate improvements that support the primary endpoint. These will include complete remission (UPCR ≤ 0.3 with preservation of eGFR: normal or ≥ 75% baseline if below normal at baseline), patient reported outcomes (PROMIS measures), change in height as determined by standard deviation score (HSDS; z-scores) for subjects < 18 years and laboratory assessments (UPCR, serum albumin, serum total cholesterol and triglycerides).[43,44,45,46]

Subjects who enroll must meet the criteria for TRNS (FSGS/MCD). This includes the pathological findings of either FSGS (excluding collapsing FSGS, a sub-set of FSGS seen in both HIV and non-HIV infected subjects with a more severe presentation and poor prognosis) or MCD on the most recent renal biopsy (renal biopsies will not be performed as part of this study). This will be confirmed by review of the pathology report (not renal biopsy slides) by a central pathologist.

NS will be defined by a UPCR ≥ 3 (g/g or unitless). Subjects will need to have a minimal preserved renal function as measured by eGFR (≥ 45 for children and adults (mL/min/1.73 m2) based on the CKD-EPI for adults and the new Schwartz equation for children).[47,48]

Treatment resistance will be defined as persistence of NS in spite of therapy with either CS or other accepted agents for the required period of time (listed in the inclusion criteria) or intolerance to any 2 of these agents.

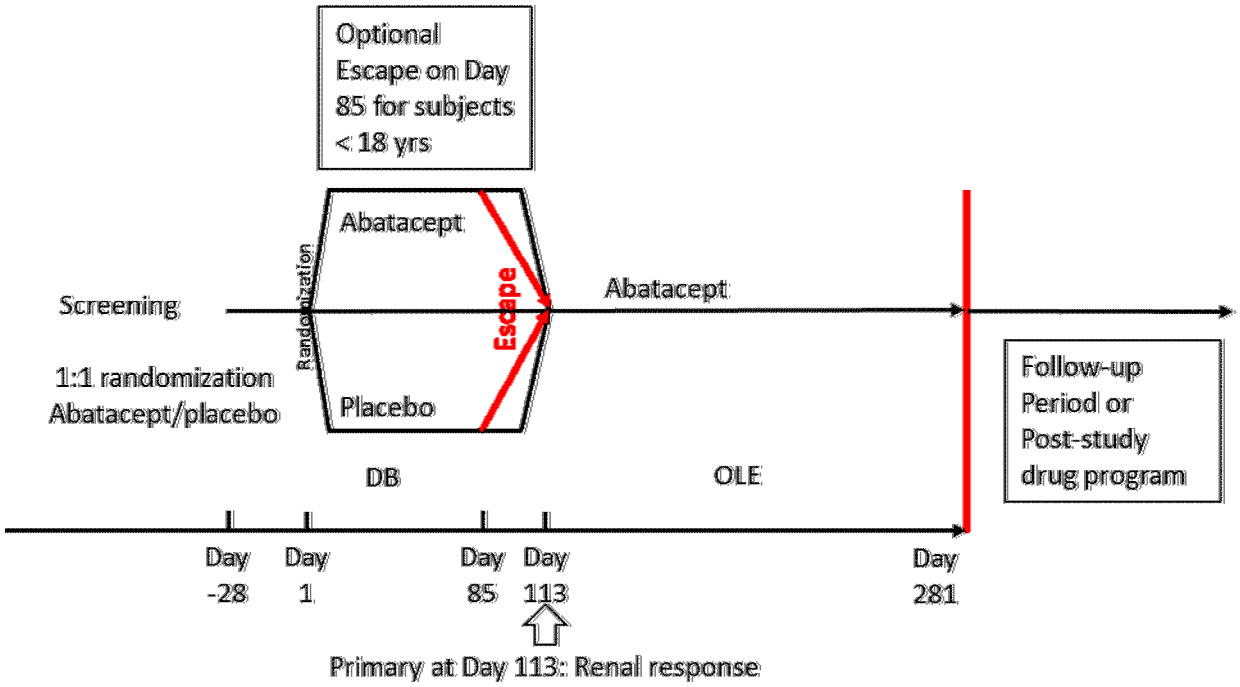
Subjects age 6 and older will be enrolled. While there are some differences in clinical characteristics and disease course between children and adults with TRNS (FSGS/MCD), the overall disease course and response to therapy is sufficiently similar so as to justify their inclusion in the same study that will test the same intervention (use of abatacept) with the same primary outcome (Renal Response).[42,46] There is the option for an early escape on Day 85 only for pediatric age (≤ 18 years) as described below. Subjects receiving permitted background therapy at the time of enrollment may continue these as long as the dose has been stable for 4 weeks prior to randomization. Subjects will be required to use either an angiotensin-converting-enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) at stable doses during the course of the Double Blind period unless intolerant. Management of hypertension and volume will follow standard of care. All subjects will be asked, but not required, to be tested at screening for the SNPs associated with the high-risk *APOL1* variants.[7] The results will be used for stratification at randomization.

The study will utilize the IV abatacept formulation with doses previously established in studies with adults with RA and in pediatric patients with juvenile idiopathic arthritis and included in the current US Prescribing Information.[2] Abatacept serum trough levels in subjects with nephrotic

syndrome due to lupus nephritis are lower than in non-nephrotic subjects receiving either the ~10 mg/kg or ~30 mg/kg dose.[24] Clinical efficacy was still seen in subjects with lupus nephritis at the ~10 mg/kg dosing level.[13] Case reports demonstrating benefit in patients with TRNS (FSGS/MCD) was also reported at this dosing level.[11,12] There is no clinical trial experience with IV abatacept doses of ~30 mg/kg in subjects less than 18 years of age. Therefore, a risk-benefit assessment suggests that the initial study including both pediatric and adult age subjects should be conducted at this dose level for which there is the most clinical experience, including safety data, in both age groups.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



3.1.1 Screening Period:

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity and safety assessments. Randomization should occur within 28 days of signing the informed consent. This may be extended to 42 days to allow for screening results (eg, TB, *APOL1* SNP, UPCR and eGFR).

3.1.2 Double-Blind Period (Day 1 - Day 113):

On Day 1, subjects will be randomized to one of two blinded parallel treatment arms in a 1:1 ratio:

Abatacept IV

adults use weight-tiered dose:

< 60 kg:	500 mg
60 to 100 kg:	750 mg
> 100 kg:	1000 mg

pediatric patients 6 to 17 years:

< 75 kg: 10 mg/kg
≥ 75 kg follow adult dosing.

Placebo (Normal Saline or D5W following the same dosing schedule).

Dosing is on Day 1, 15, 29, and then every 28 days.

The duration of the Double-Blind Period is 113 days.

There is an option to Early Escape into the OLE on Day 85 for pediatric age subjects only (< 18 years of age at randomization). The decision to Early Escape will be based on the Day 57 UPCR (> 3) and the assessment of clinical status on Day 85. If at the discretion of the investigator, in consultation with the subject (and their guardians), it is decided that the subject's clinical status has worsened or not improved sufficiently based on both of these criteria, the Day 85 visit may be skipped. The subject would complete the Double-Blind Period Early Termination visit (Table 5.1-2). The decision will then be made to either proceed to the OLE Day 1 visit (Table 5.1-3) or the Follow-up Visits (Table 5.1-4).

3.1.3 Open Label Extension (Day 1 - Day 169):

At the end of the Double Blind, there will be a 169 day open label extension (OLE). Subjects may enter this extension in 2 different manners. Subjects who reach the end of Double Blind will be able to volunteer to enter the OLE at the discretion of the investigators. Pediatric age subjects (6 to 17 years) who choose to Early Escape may then choose to enter the OLE. This includes both responder and non-responders who wish to determine if a longer exposure to abatacept could lead to a response. Abatacept will be administered every 28 days starting on Day 1 of the OLE (Day 1 of the OLE will be Day 113 of the Double Blind Treatment Period), without a loading dose. Adjustment in background therapy is allowed but limited. This includes increases or decreases in doses, including discontinuation, or change from one permitted agent to another (3.4.1.2, Restricted Treatments During Double-Blind).

Subjects who do not wish to enter the OLE should receive appropriate standard of care following discontinuation of study drug.

3.1.4 Post-Treatment Follow-up Period

Subjects who discontinue treatment of study drug or complete the study and do not transition to commercial abatacept will have three follow-up visits over the 168 day Follow-up Period, to perform safety and laboratory assessments.

Treatment codes will be provided to the investigators after completion of the study.

The start of the trial is defined as the date the first subject signs the informed consent. End of trial is defined as the last visit or scheduled procedure shown in the Time & Events schedule for the last subject. The study will continue beyond primary endpoint collection until the End of Trial.

3.2 Post Study Access to Therapy

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of abatacept for this indication is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulation.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Prior to study participation, written informed consent from subjects, or in the case of minors (< 18 years), written permission (informed consent) from parents, guardians, or legally acceptable representatives must be obtained according to local laws and regulations.

b) Assent from minor subjects should be obtained per local requirements.

2. Target Population

a) Subjects diagnosed with TRNS (FSGS/MCD).

i) Pathological findings of either FSGS (excluding collapsing FSGS) or MCD on the most recent renal biopsy (renal biopsies will not be part of this study). This will be confirmed by review of the pathology report (not slides) by a central pathologist. The criteria for pathology review are in Appendix 1.

ii) UPCR ≥ 3 at screening.

iii) Treatment Resistant or Treatment Intolerant

(1) Treatment resistant is defined as persistence of UPCR ≥ 3 in spite of therapy with any one of the following agents: corticosteroids (CS), calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus, mycophenolate mofetil (MMF), mycophenolic acid (MPA), or cyclophosphamide.

(a) Duration of therapy: The duration of CS therapy required to determine treatment resistance will be 6 weeks in subjects < 18 year of age and 12 weeks for subjects ≥ 18 years. For all other agents, the minimum duration of therapy will be 16 weeks, regardless of age.

(2) Intolerance to any 2 of these agents, regardless of duration of treatment or age.

b) Subjects must be receiving either an angiotensin-converting-enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) or have intolerance documented in the source documents maintained at the site. If a subject is currently receiving an ACEi or ARB, the dose must be stable for at least 2 weeks, prior to randomization. Combined use of renin-angiotensin system (RAS) inhibitors will not be allowed. If aldosterone inhibitors (spirolactone or eplerenone) or aliskiren (direct renin inhibitor) are used, they must also be at stable doses.

c) A minimal level of renal function at screening based on estimated glomerular filtration rate (eGFR) will be required.

i) ≥ 45 for subjects < 18 years (new Schwartz equation).[48]

ii) ≥ 45 for subjects ≥ 18 years (CKD-EPI equation).[47]

d) ***APOL1* genotyping**: Subjects will be genotyped for the *APOL1* renal risk variants SNPs [Risk allele G1 (rs73885319 and rs60910145) and risk allele G2 (rs71785313)]. Subjects with 2 copies of the high-risk *APOL1* variants are in the *APOL1* high-risk group which will be used for stratification at randomization. Genotyping during screening will not be necessary if results of previous testing are available. Subjects will be allowed to opt-out of genotyping for *APOL1*. Subjects who refuse genotyping will still be eligible to be randomized.

e) **Concomitant Medication**:

i) Subjects may enroll with or without the following background agents used to treat TRNS (FSGS/MCD):

(1) CS (low dose, prednisone or equivalent at doses ≤ 10 mg/day)

(2) calcineurin inhibitors (cyclosporine and tacrolimus)

(3) MMF

(4) MPA

ii) Agents must be used at standard doses, must not have been started within 8 weeks of enrollment

iii) Agents must be **stable for at least 4 weeks prior to randomization**.

iv) No adjustment in doses of concomitant medications will be allowed during the double-blind period other than for dose reductions or holds to address drug-related toxicity.

f) Subjects who had previously been treated with rituximab are allowed in the study if use had occurred more than 6 months prior to randomization and there are laboratory results indicating the presence of circulating B cells (CD19+).

g) Hypertension must be controlled and stable. Hypertension control is defined as a blood pressure (BP) ≤ 140/90 for subjects ≥ 18 years of age and < 95th percentile for subjects < 18 year of age by gender, age and height percentile.[49]

h) Changes in diuretic use should be avoided prior to the Day 113 assessment unless necessary to manage an adverse event.

i) Treatment to manage dyslipidemia is allowed. HMG CoA reductase (hydroxymethylglutaryl CoA reductase) inhibitors or statins use must be stable 2 weeks prior to randomization and throughout the treatment periods.

j) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Males and Females, ages ≥6 years.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (abatacept/placebo) plus 5 half-lives (70 days) plus 30 days (duration of ovulatory cycle) for a total of 100 days post-treatment completion.

e) Females who are not of childbearing potential must have documented proof that they are not of childbearing potential (eg, not experienced menarche, surgically sterile).

f) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (abatacept/placebo) plus 5 half-lives of the study drug (70 days) plus 90 days (duration of sperm turnover) for a total of 160 days post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time.

g) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

Investigators shall advise on the use of highly effective methods of contraception (Appendix 2) which have a failure rate of < 1% when used consistently and correctly.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with other causes of TRNS other than FSGS or MCD (eg, IgA nephropathy, obesity related glomerulopathy or membranous nephropathy).

b) Subjects with collapsing FSGS, also known as collapsing glomerulopathy.

c) Subjects with systemic lupus erythematosus (SLE).

d) Subjects with diabetes mellitus, both type 1 and type 2.

e) Subjects with clinically significant congestive heart failure (CHF; New York Heart Association [NYHA] Class III or Class IV).

f) Subjects post renal transplantation, including relapsing post-transplant FSGS.

2. Medical History and Concurrent Diseases

a) Subjects at risk for tuberculosis (TB) defined as follows:

i) Current clinical, radiographic or laboratory evidence of active TB.

ii) Chest x-rays [PA (posterioranterior) and lateral] obtained within the 6 months prior to randomization will be permitted but the images must be available and reviewed by the investigator. TB testing (IFN-γ release assay or PPD) performed in the past month prior to randomization will be accepted; however, a copy of the report must be placed in the subject binder.

iii) A history of active TB

iv) Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless they have no evidence of current TB on chest x-ray at screening and they are actively being treated for TB with isoniazid (INH) or other therapy for latent TB given according to local health authority guidelines (eg, Center for Disease Control). Treatment regimens should be dictated by local guidelines as long as the treatment dose and duration meet or exceed local health authority guidelines. If permitted by local guidelines regarding treatment with biologic medications, subjects may be randomized prior to completion of treatment as long as they have completed at least 4 weeks of treatment and they have no evidence of current TB on chest x-ray at screening.

b) Subjects with recent acute infection defined as:

i) Any acute infection within 60 days prior to randomization that required hospitalization or treatment with parenteral antibiotics.

ii) Any acute infection within 30 days prior to randomization that required oral antimicrobial or antiviral therapy.

c) Subjects with history of chronic or recurrent bacterial infection (such as chronic pyelonephritis, osteomyelitis, and bronchiectasis etc.) or evidence (as assessed by the Investigator) of active or latent bacterial or viral infections at the time of enrollment, including subjects with evidence of Human Immunodeficiency Virus (HIV) infection.

d) Subjects with history of recurrent herpes zoster (more than 1 episode) or disseminated (more than 1 dermatome) herpes zoster or disseminated herpes simplex, or ophthalmic zoster will be excluded. Symptoms of herpes zoster or herpes simplex must have resolved more than 60 days prior to screening.

e) Subjects with history of primary immunodeficiency.

f) Subjects who have present or previous malignancies, except documented history of cured non-metastatic squamous or basal skin cell carcinoma, or cervical carcinoma in situ, with no recurrence in the 5 years prior to screening. Subjects who had screening procedure that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations.

g) Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, neurological, or cerebral disease including severe and uncontrolled infections, such as sepsis and opportunistic infections. Concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.

h) Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines during the study. Study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication. Subjects who are in close contact with others who have received a live vaccine may be enrolled at the investigator's discretion.

i) Subjects who have undergone a major surgical procedure within the 60 days prior to randomization.

j) Subjects with a known current problem with drug or alcohol abuse history or known cirrhosis including alcoholic cirrhosis.

k) Subjects who have received prior treatment with abatacept or CTLA4Ig or other CTLA4 therapies.

3. Physical and Laboratory Test Findings

a) Body mass index (BMI): > 40 in subjects $\geq$18 years of age and $\geq$99% percentile for subjects < 18 years of age.

b) Hepatitis B surface antigen (HBsAg)-positive, or Hepatitis B core antibody (HBcAb)-positive subjects with detectable hepatitis B viral DNA

c) Hepatitis C antibody (HCAb)-positive subjects with detectable hepatitis C viral RNA

d) Hemoglobin (Hgb) < 8.5 g/dl

e) White Blood Count (WBC) < 3,000/mm^3 (3 x 10^9/L)

f) Platelets < 100,000/mm^3 (100 x 10^9/L)

g) Serum ALT or AST > 2 times upper limit of normal.

h) Evidence of active cardiac or pulmonary disease on chest X-Ray (CXR).

i) Any test results that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

4. Allergies and Adverse Drug Reaction

a) Hypersensitivity to abatacept and/or its excipients.

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required.)

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

c) Subjects with a history or suspicion of unreliability, poor cooperation, or non-compliance with medical treatment.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding a subject for any reason (emergency or non-emergency)
- Use of prohibited medication
- Missed two or more doses of investigational product for any reason during the Double Blind Period

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female becomes pregnant during a clinical trial, the study drug must be discontinued immediately. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of

study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

Subjects who discontinue study drug may continue to be followed.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all

attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Abatacept for Injection

Normal Saline or 5% Dextrose in Water (provided by the investigational site)

Table 4-1: Study Drugs for IM101566

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Abatacept for injection	250 mg per vial	IP	Open label	White to off-white, whole or fragmented cake in a vial. Vials will be assembled into boxes for shipping.	STORE REFRIGERATED, 2-8 DEGREES C (36-46 DEGREES F); PROTECT FROM LIGHT.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

Further information with regard to preparation of abatacept for intravenous use will be provided separately in the IM101566 dosing procedure manual. For this study, placebo shall be considered an equal volume of diluent as used for active infusion admixture in either Dextrose 5% in Water or Normal Saline.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

4.4 Method of Assigning Subject Identification

At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, each subject at a site will be assigned a unique sequential subject number beginning with 001, 002, 003, etc. for identification throughout the study. This subject number must not be reused for any other participant at the site. The physician/coordinator must contact the Central Randomization System to enroll each subject into a centralized database at the beginning of the study (Screening).

4.5 Selection and Timing of Dose for Each Subject

Subjects will be randomized to 1 of 2 treatment groups:

- Abatacept intravenous infusions.
- Placebo (D5W or Normal Saline) intravenous infusions.

Dosing for subjects 18 years and older will follow adult dosing rules. Dosing for subjects younger than 18 years will follow pediatric dosing rules.

4.5.1 Abatacept Dosing

4.5.1.1 Pediatric Subjects

Pediatric subjects receiving active abatacept will be dosed based on their weight at each visit following these rules:

- Pediatric subjects weighing < 75 kg: 10 mg/kg intravenously.
- Pediatric subjects weighing ≥ 75 kg: or more should be administered abatacept following the adult intravenous dosing regimen, not to exceed a maximum dose of 1000 mg
  - ≥ 75 to 100 kg: 750 mg
  - > 100 kg: 1000 mg

4.5.1.2 Adult Subjects

Adult subjects receiving active abatacept will be dosed based on their screening visit weight following these rules:

- Subjects weighing < 60 kg will receive 500 mg
- Subjects weighing 60 to 100 kg will receive 750 mg
- Subjects weighing > 100 kg will receive 1000 mg.

4.5.2 Administration of Abatacept or Placebo

The Central Randomization System will confirm the subject's body weight and age and assign the number of vials of abatacept to allocate for the visit. Subjects will receive doses of study medication at every treatment period visit (Days 1, 15, 29, 57 and 85 during Double Blind Period).

Subjects who are randomized to receive placebo will be given either Dextrose 5% in Water (D5W) or Normal Saline (NS) at the discretion of the investigator. Placebo (NS or D5W) will be supplied by the investigative site.

A ± 3 day window is allowed for the dose on Day 15, a -3 and +7 day window is allowed for the dose on Day 29 and a ± 7 day window is allowed for doses thereafter. Infusions should occur at approximately the same time of day throughout the duration of the study.

All doses of study medication will be administered intravenously in a fixed volume of 100 ml at a constant rate of flow over approximately 30 minutes. Please flush with D5W or NS at the end of the infusion to ensure that the administration line used to deliver the drug solution is adequately cleared; please refer to the infusion set's manufacturer's materials to determine the appropriate flush volume needed to assure delivery of the entire dosage. The infusion solution must be prepared by a qualified staff member and supplied to personnel administering the dose in a container not identifying the contents so as to maintain the blind. The infusion of the fully diluted abatacept/placebo must be completed within 24 hours of reconstitution of the vials. The fully diluted abatacept/placebo may be stored at room temperature or refrigerated at 2°C to 8°C (36°F to 46°F) before use. The fully diluted solution should be discarded if not administered within 24 hours.

All intravenous infusions will be with the subject in the seated position. No adjustments will be made in treatment dose level or schedule. Subjects will be observed for adverse events and vital signs (seated blood pressure, heart rate, and temperature) from the start of each infusion (pre-dose and 60 minutes). There is a ± 5-minute window for vital sign collection. Subjects will be observed for a minimum of 1 hour from the start of the infusion. The observation period should be extended if clinically indicated.

4.5.3 Dosing During the Open Label Extension

Adult subjects who enter the Open Label Extension (OLE) following completion of the Double Blind will receive doses of study medication at every OLE period visit (OLE Days 1, 29, 57, 85, 113, and 141) **based on their OLE Day 1 visit weight**.

Pediatric subjects who enter the Open Label Extension (OLE) following completion of the Double Blind Period will receive doses of study medication at every OLE period visit (OLE Days 1, 29, 57, 85, 113, and 141) **based on their weight at each visit**.

They will follow the same pediatric and adult dosing rules in Sections 4.5.1.1 and 4.5.1.2.

4.5.4 Dose Modifications

4.5.4.1 Dose Modifications in the Absence of Adverse Events

In the absence of adverse events deemed at least possibly related to study medication treatment, subjects should complete their scheduled IV infusions as prescribed by protocol. Dosing windows to adjust for the subject's and/or the site personnel's convenience are as follows. A ± 3 day window beyond the target date is allowed for the Double Blind Period at Day 15, and a -3 and +7 day window is allowed for Day 29. A ± 7 day window is allowed for all subsequent IV infusions.

4.5.4.2 Dose Modifications Due to an Adverse Event

If there is evidence of toxicity in abnormal laboratory tests or clinical adverse events that, in the judgment of the Investigator, could place the subject at increased risk, study drug administration should be interrupted and the investigator should notify BMS. Subjects may be considered eligible to receive further study medication treatment only if full resolution of the adverse event is documented. Under no circumstances should the dose of study drug be altered due to an adverse event.

The IV infusion dosing window may be extended if the delay is due to an adverse event and if the adverse event has completely resolved. For Day 15, the dose may be delayed up to 7 days. For all subsequent IV infusions, the dose may be delayed up to 14 days. If the adverse event has not resolved within these windows, the IV infusion scheduled for that visit should be skipped (missed one IV dose). For example, if the Day 57 dose could not be administered until the 73rd day, the Day 57 dose should be skipped and the subject's next dose would occur at the Day 85 visit. Only two missed doses are allowed in the Double Blind Period.

4.6 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is the Central Randomization System.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

The BMS Bioanalytical Science Department or its designee will be unblinded to the randomized treatment assignments in order to accurately perform sample analysis for the PK and immunogenicity samples.

4.7 Treatment Compliance

All subjects are expected to receive study therapy as outlined in the protocol. Permitted dose modifications are described in Section 4.5.4. Conditions under which therapy must be discontinued due to non-compliance are outlined in Section 3.5. Randomized subjects failing to receive any infusion of study medication will be deemed pre-treatment drop-outs and will not be followed for further evaluation. Subjects receiving at least one dose of study medication will be followed for safety, efficacy, pharmacodynamics, pharmacokinetics and immunogenicity testing. Subjects who will be discontinued from the study will be evaluated as outlined in Section 5.1 (Flow Chart/Time and Event Schedule).

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Retained Samples for Bioavailability/Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening

Procedure	Visit 1 (all subjects)	Optional Visit 2 (if Visit 1 occurred > 28 days prior)	Notes
Eligibility Assessments			
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Medical History	X		
Renal Biopsy History	X		Review of the report by a central pathologist is required.
Prior Medication Review. Stabilize/Withdraw Prohibited Medication (if necessary)	X	X	
Enroll Subject (contact Central Randomization System)	X		
Safety Assessments			
Physical Examination	X		
Vital Signs	X	X	Seated BP, heart rate, temperature
Height, Standing	X	X	
Weight	X	X	
Body Mass Index	X		
Chest X-ray	X		Not required if performed within 6 months of obtaining written informed consent and if documentation is on file.
Serious Adverse Events Assessment		X	

Table 5.1-1: Screening

Procedure	Visit 1 (all subjects)	Optional Visit 2 (if Visit 1 occurred > 28 days prior)	Notes
Laboratory Tests			
TB Screening	X		PPD or interferon gamma release assay. Testing performed locally.
CBC	X	X	
Chemistry Panel	X	X	
eGFR	X	X	
[redacted]	X		
Urine sample for protein/creatinine ratio (UPCR)	X	X	To be taken from a 24-hour urine collection. If not possible, then from a single voided specimen, preferably in the morning.
Urinalysis	X		Testing performed locally
Hepatitis B surface antigen	X		If positive, obtain HBV DNA
Hepatitis B core antibody	X		If positive, obtain HBV DNA
Hepatitis C antibody	X		If positive, obtain HCV RNA
HIV Testing	X		Testing performed locally if required.
Urine Pregnancy Test	X	X	Testing performed locally on WOCBP subjects only.
APOL1 Genotyping	X		This is not necessary if results of previous testing are available. Subjects will be able to opt-out of genotyping for *APOL1*.

Table 5.1-2: Double Blind Period

Visit Day	Day 1	Day 15	Day 29	Day 57	Day 85[a]	Day 92 (PK Visit)	Day 99 (PK Visit)	Day 106 (PK Visit)	Day 113 or Early Termination	Notes
Contact Central Randomization System	X	X	X	X	X				X	
Outcomes Research Assessments										
PROMIS Questionnaires	X				X				X	
Safety Assessments										
Adverse Event Monitoring	X	X	X	X	X				X	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]	
Targeted Physical Exam	X	X	X	X	X				X	
Weight	X	X	X	X	X				X	
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]				[redacted]	[redacted]
Vital Signs	X	X	X	X	X				X	Seated BP, heart rate, temperature should be taken pre-dose and 60 minutes post-dose.
Emergency Room/ Hospitalization CRF	X	X	X	X	X				X	
Laboratory Assessments										
CBC	X		X		X				X	
Chemistry panel	X	X	X	X	X				X	
eGFR	X								X	

Table 5.1-2: Double Blind Period

Visit Day	Day 1	Day 15	Day 29	Day 57	Day 85[a]	Day 92 (PK Visit)	Day 99 (PK Visit)	Day 106 (PK Visit)	Day 113 or Early Termination	Notes
[redacted]	X			X					X	
Urine sample for protein/creatinine ratio	X	X	X	X	X				X	Taken from a 24-hour urine collection on Day 1 and 113; if not possible, then from a single voided specimen. Taken from a single voided specimen at all other time points. A single voided specimen is also required at Day 1 and Day 113. For single voids, morning collections are preferred.
Urinalysis	X								X	Testing performed locally.
Urine pregnancy test	X	X	X	X	X				X	Testing performed locally on WOCBP subjects only
[redacted]										
[redacted]	[redacted]	[redacted]			[redacted]				[redacted]	
[redacted]	[redacted]									[redacted]
[redacted]	[redacted]	[redacted]			[redacted]				[redacted]	
[redacted]	[redacted]	[redacted]			[redacted]				[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]	

Table 5.1-2: Double Blind Period

Visit Day	Day 1	Day 15	Day 29	Day 57	Day 85[a]	Day 92 (PK Visit)	Day 99 (PK Visit)	Day 106 (PK Visit)	Day 113 or Early Termination	Notes
Pharmacokinetics and Immunogenicity										
Pharmacokinetic Sampling in Blood	X*	X*	X*	X*	X*	X**	X**	X**	X	* The samples will be collected both prior to dosing and at the end of infusion. ** The samples will be collected during the PK visit. All the PK assessments are specified in Section 5.4.1.
Pharmacokinetic Sampling in Urine	X	X	X	X	X				X	To be taken from a 24-hour urine collection on Day 1 and 113; if not possible, then from a single voided specimen. From a single voided specimen at all other time points. A single voided specimen is also required at Day 1 and Day 113. For single voids, morning collections are preferred. The samples will be collected prior to dosing.
Immunogenicity anti-Abatacept Ab testing	X								X	
Clinical Supplies										
Drug preparation by a pharmacist	X	X	X	X	X					
Abatacept/placebo dosing	X	X	X	X	X					

[a] Pediatric subjects may early escape at Day 85 at the discretion of investigator (and consultation with the subject's guardian) based on criteria specified in Section 3.1.2. In such situations, the Day 85 will be the Early Termination visit.

[b] If a subject does not consent to the use of their samples for additional research, their samples will be discarded after all protocol-specified testing has been completed (not to exceed 15 years).

Table 5.1-3: Open Label Extension								
Visit Day (± 7 days)	**Day 1 (Same day as last visit of the Double Blind Period)**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169 or Early Termination**	**Notes**
Contact Central Randomization System	X	X	X	X	X	X	X	
Safety Assessments								
Adverse Event Monitoring		X	X	X	X	X	X	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Targeted Physical Exam		X	X	X	X	X	X	
Weight		X	X	X	X	X	X	
Vital Signs		X	X	X	X	X	X	Seated BP, heart rate, temperature should be taken pre-dose and 60 minutes post-dose.
[redacted]		X	X	X	X	X	X	[redacted]
Emergency Room/Hospitalization CRF		X	X	X	X	X	X	
Laboratory Assessments								
CBC							X	
Chemistry panel			X		X		X	
Total Cholesterol and Triglycerides, fasting							X	
Urine sample for protein/creatinine ratio		X	X	X	X	X	X	To be taken from a single voided specimen. Morning collections are preferred.
eGFR							X	
Urine pregnancy test		X	X	X	X	X	X	Testing performed locally on WOCBP subjects only

Table 5.1-3: Open Label Extension								
Visit Day (± 7 days)	**Day 1 (Same day as last visit of the Double Blind Period)**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169 or Early Termination**	**Notes**
Clinical Supplies								
Drug preparation by a pharmacist	X	X	X	X	X	X		
Abatacept dosing	X	X	X	X	X	X		

Table 5.1-4: Follow-Up Visits (after last dose)[a]				
Visit (± 14 days)	**56 Days after Last Dose**	**84 Days after Last Dose**	**168 Days after Last Dose**	**Notes**
Adverse Event Monitoring	X	X	X	
[redacted]	[redacted]	[redacted]	[redacted]	
Targeted Physical Exam	X	X	X	
Vital Signs	X	X	X	Seated BP, heart rate, temperature
Emergency Room/Hospitalization CRF	X	X	X	
Laboratory Assessments				
Urine pregnancy test	X	X	X	Testing performed locally on WOCBP subjects only
Immunogenicity anti-abatacept Ab testing	X	X	X	
Pharmacokinetic Sampling in Blood	X	X	X	The sample will be stored until a decision is made that the testing will be needed.

[a] Testing will be required only if the subject is off abatacept treatment and does not transition to commercially available treatment with abatacept.

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.1.2 Study Materials

- Instructions for completion of the eCRF pages
- Pregnancy Prevention Information Sheet
- Pregnancy Surveillance Forms
- Source documents for outcomes research instruments
- Drug Inventory Binder
- Pharmacy Manual
- Central Randomization System Worksheets
- Laboratory test kits for all required testing

5.2 Safety Assessments

On Day 1, the results of all assessments must be reviewed to assure that eligibility requirements are met before contacting the Central Randomization System for the subject's randomization assignment.

Subjects who terminate treatment early should complete the appropriate Early Termination Visit. The Early Termination Visit should be as soon as possible after the last dose of study medication. If a subject does not transition to treatment with commercial abatacept, the subject will be required to complete the Post Drug Follow-up Visits.

All assessments should be performed or administered prior to study drug administration unless otherwise indicated.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from BMS.

5.2.1 Imaging Assessment for the Study

Not Applicable.

5.2.2 Adverse Events of Special Interest

As part of the safety evaluation, AEs that may be associated with the use of immunomodulatory drugs will be identified. Specific events within the categories of infection, autoimmune disorders, malignancies, infusion reactions, and renal-related events will be prospectively identified and classified as "AE of special interest." These AE are a subset of all AEs and include serious and non-serious events.

5.2.3 Physical Examination

Physical examinations must be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician Assistant (PA), or Nurse Practitioner (NP).

The physical examination should include examination of the heart, lungs, abdomen, the lymph nodes, liver, spleen and skin. A physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any other body systems as clinically indicated.

5.2.4 Chest X-ray

A posterior-anterior and lateral chest x-ray, performed during screening, is required for all subjects unless performed within 6 months prior to obtaining written informed consent and documentation of the earlier x-ray is on file. Investigators must ensure that the results of the chest x-ray satisfy criteria for eligibility. The chest x-ray result will be recorded on the appropriate page of the eCRF.

5.2.5 Physical Measurements

Weight is to be recorded at all visits noted in Section 5.1, Flow Chart/Time and Events Schedule.

Standing height is required for subjects $\geq$18 years only at the Screening Visit.

5.2.6 Vital Signs

Vital signs (seated blood pressure, heart rate, and temperature) will be recorded during every office visit and prior to and after dose administration is complete, when applicable. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.

5.2.7 Body Mass Index (BMI)

Body mass index (BMI) will be used to exclude subjects who have obesity related glomerulopathy as the primary cause of the subject's refractory proteinuria. (Exclusion Criteria Section 3.3.2, 3,a) Since BMI may fluctuate due to accumulated edema secondary to severe proteinuria and not be indicative of the role an elevated BMI may have played in the underlying disease process, subjects with an elevated BMI at screening may enroll, at the discretion of the investigator, if the high BMI is due to accumulated edema and the BMI was not known to be elevated at onset of disease. These factors must be documented in the study source documents at randomization.

BMI will be calculated at screening for purposes of checking for the exclusion criteria. For BMI determination in children, follow the 2000 CDC Growth Charts (www.cdc.gov/growthcharts) by age and gender.

For adults, BMI is calculated from the weight and standing height as follows:

BMI = body weight (kg) ÷ height (meters) squared

5.2.8 TB Screening

A chest x-ray and physical examination are considered part of the process to assess a subject's eligibility. In addition to a chest x-ray that does not show any evidence or suspicion of latent TB, a tuberculin test will be performed and interpreted according to local country Health Authorities and/or Medical Society guidelines. Some guidelines have specific recommendations for subjects who are to receive biologics[51,52,53] or immunosuppressant therapies (eg, RA experience with biologic agents), or who are immunocompromised and who have had prior BCG vaccination(s).[54,55] Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG. An interferon gamma release assay (eg, QuantiFERON® Gold or Tspot/ELISpot) is an acceptable alternative when skin testing for tuberculosis (ie, PPD) is not appropriate.

5.2.9 Renal Biopsy History

All subjects must have a biopsy report confirming the diagnosis of FSGS/MCD prior to enrollment in the study. The report will be reviewed by a central pathologist to confirm the diagnosis prior to the subject qualifying for randomization. Light microscopy, immunofluorescence/immunohistochemistry and electron microscopy are required to fulfill pathologic enrollment criteria. The criteria for path review are found in Appendix 1.

5.2.10 Hospitalizations and Emergency Room (ER) Visits

Hospitalizations and ER visits will be recorded on the eCRF.

5.2.11 Laboratory Assessments

All laboratory assessments will be analyzed centrally except where noted.

Blood and/or urine samples will be obtained at all visits noted in Section 5.1, Flow Chart/Time and Events Schedule. Any laboratory test result that the investigator considers clinically relevant should be recorded on the appropriate Adverse Event page of the CRF (see Appendix 3).

5.2.11.1 Hematology

Hemoglobin

Hematocrit

Total WBC, including differential

Platelet count

5.2.11.2 Blood Chemistry

Sodium	Creatinine
Potassium	Blood urea nitrogen (BUN)
Chloride	Total bilirubin
Total Protein	Alanine aminotransferase (ALT)
Albumin	Aspartate aminotransferase (AST)
Calcium	Gamma-glutamyltransferase (GGT)
Phosphorus	Alkaline phosphatase
Glucose	hsCRP
Uric Acid	Cystatin C

5.2.11.4 Urinalysis

The urinalysis testing is performed locally.

- pH
- Protein
- Glucose
- Blood

5.2.11.5 Urine Testing

Urine Protein Creatinine Ratio (UPCR) will be determined from spot urine collections except for baseline and Day 113 in which 24-hour urine collections will be performed. If 24-hour collections are not possible, these samples will be determined from spot urine specimens. 24-hour collections are preferable although they can be inconvenient for patients and are subject to incorrect collection. While spot urines have inherent biological variation, they are still suitable for study endpoint determination.[56]

5.2.11.6 Estimated Glomerular Filtration Rate (eGFR)

eGFR will be calculated by the new Schwartz equation for subjects < 18 years and the CKD-EPI equation for subjects ≥ 18 years.

5.2.11.7 Hepatitis Screening

The results must be available on Day 1 prior to dosing.

- Hepatitis B surface antigen, hepatitis B core antibody -- If positive, reflex HBV DNA testing must be performed.
- Hepatitis C antibody. If positive, reflex HCV RNA testing must be performed

5.2.11.8 Pregnancy Testing

Urine pregnancy tests (minimum sensitivity 25 IU/L of β-HCG) must be performed for all WOCBP within 24 hours prior to dosing for visits specified in Section 5.1, Flow Chart/Time and Events Schedule. Urine tests are the preferred method and must be performed unless serum is required by local requirements. A serum test must be performed centrally for confirmation of any positive urine test result. Urine tests can be processed locally. If any female subject becomes pregnant, she will stop receiving study treatment immediately and enter the Post Treatment Follow-up Period. A pregnancy surveillance form will be completed and submitted to Bristol-Myers Squibb.

5.2.11.9 HIV Testing

HIV testing will be performed locally if required based on the judgment of the investigator.

5.2.11.10 FSH Testing

FSH testing must be performed to confirm menopause for female subjects under the age of 55. The female subject must have a serum FSH level > 40 mIU/ml in screening.

FSH testing will be performed for female subjects who become menopausal after entry into the study.

5.2.11.11 Genetic Testing

Genotyping for the *APOL1* renal risk variants SNPs [Risk allele G1 (rs73885319 and rs60910145) and risk allele G2 (rs71785313)] will be requested for all subjects. Genotyping during screening will not be necessary if results of previous testing are available. Subjects may opt out of testing.

[redacted]

[redacted]

5.3 Efficacy Assessments

5.3.1 Primary Efficacy Assessment

Primary efficacy will be the renal response rate which will be determined using a composite renal index.

5.3.1.1 Renal Response

The renal response will be present if all the following criteria are met at Day 113:

PROTEINURIA:	Reduction of baseline UPCR of ≥ 50% and to less than 3.
RENAL FUNCTION:	No worsening of baseline (Study Day 1) estimated glomerular filtration rate (eGFR) defined as normal or ≥ 75% baseline value if below normal at baseline. eGFR determination will be based on the CKD-EPI for adults and the new Schwartz equation for children.

Proteinuria assessment for primary and secondary endpoints will be obtained from 24 hour urine collections performed at baseline and Day 113. When a 24 hour collection is not possible, a single voided specimen (ie, spot urine) will be utilized, preferably in the morning.

5.3.2 Secondary Efficacy Assessments

5.3.2.1 Improvement in Proteinuria

Improvement in proteinuria will be determined by the change from baseline in the level of proteinuria as assessed by UPCR at Day 113.

5.3.2.2 Improvement in Serum Albumin

Improvement in serum albumin will be determined by the change from baseline in the level of serum albumin as assessed by UPCR at Day 113.

5.3.2.3 Complete Remission

Complete remission will be present if all the following criteria are met at Day 113:

PROTEINURIA:	UPCR ≤ 0.3

RENAL FUNCTION: No worsening of baseline (Study Day 1) estimated glomerular filtration rate (eGFR) defined as normal or ≥ 75% baseline value if below normal at baseline.

eGFR determination will be based on the CKD-EPI for adults and the new Schwartz equation for children.

5.3.2.4 Patient Reported Outcomes Measurement Information System (PROMIS)

Improvement in patient reported outcomes related to nephrotic syndrome will be captured using age-appropriate PROMIS. For subjects below the age of 18, both the subjects and the parents/guardians will complete PROMIS.

[redacted]

5.4 Pharmacokinetic Assessments

5.4.1 Pharmacokinetic: Blood and Urine Sample Collection

Table 5.4.1-1 lists the sampling schedule to be followed for the assessment of pharmacokinetics (blood and urine) as well as the immunogenicity.

The actual date and time of sample collection must be recorded. The volume of urine collection must be recoded. Every effort should be made to collect PK samples as close to the protocol-specified times as possible.

Table 5.4.1-1: Sampling Schedule

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	PK Blood Sample	PK Urine Sample[a]	Immunogenicity Sample
Double Blind					
1	0 (predose)	00:00	X	X	X
1	0.5 (postdose)	0.5:00	X		X
15	0 (predose)	00:00	X	X	
15	0.5 (postdose)	0.5:00	X		
29	0 (predose)	00:00	X	X	
29	0.5 (postdose)	0.5:00	X		
57	0 (predose)	00:00	X	X	
57	0.5 (postdose)	0.5:00	X		
85	0 (predose)	00:00	X	X	
85	0.5 (postdose)	0.5:00	X		
92	168	168:00	X		
99	336	336:00	X		
106	504	504:00	X		
113 (or Early Termination	0 (predose)	00:00	X	X	X
Follow-Up Visits[b]					
56 Days after Last Dose	1344	1344:00	X		X
84 Days after Last Dose	2016	2016:00	X		X
168 Days after Last Dose	4032	4032:00	X		X

[a] To be taken from a 24-hour urine collection on Day 1and Day 113. If not possible, the sample will be taken from a single voided specimen. Single voided specimens are to be taken at all other time points including Day 1 and Day 113. For single voids, morning collections are preferred.

[b] Only for subjects discontinuing use of abatacept (off study and not on commercial abatacept).

5.4.2 Pharmacokinetic Sample Processing, Labeling and Shipping

Detailed instructions on processing, labeling, handling, storage, and shipping of PK specimens for analysis will be supplied to Investigators in a separate laboratory manual at or before the time of study initiation.

5.4.3 Pharmacokinetic Sample Analysis

A sensitive validated enzyme immunoassay (EIA) method will be used to measure concentrations of abatacept in serum and urine. Samples collected in Period 2 from the previous protocol will still be analyzed.

5.4.4 Pharmacokinetic Evaluation

The pharmacokinetics of abatacept will be derived from serum concentration versus time data. Individual subject pharmacokinetic parameter values will be derived by non-compartmental methods and summarized. Urinary abatacept determinations will be obtained primarily for the purpose of determining whether abatacept is excreted in urine in the setting of proteinuria and whether the amount of abatacept found in urine is related to the level of ongoing proteinuria. Volume of urine collection from single voids and the total volume of urine collection from 24-hr collections will be recorded so that amount of abatacept present in urine can be determined. The pharmacokinetic evaluations will be comprised of the following parameters:

Serum PK:

- **C_{min}** (μg/mL): Trough level serum concentration of abatacept on Days 1, 15, 29, 57, 85, and 113)
- **C_{max}** (μg/mL): Peak serum concentration of abatacept on Day 85
- **T_{max} (**hr**)**: Time to reach peak serum concentration of abatacept on Day 85
- **AUC (TAU)** (μg.h/mL): Area under the serum concentration time curve in a dosing interval between Days 85 and 113 (TAU) = 28 days) where TAU = 28 days

Urine PK:

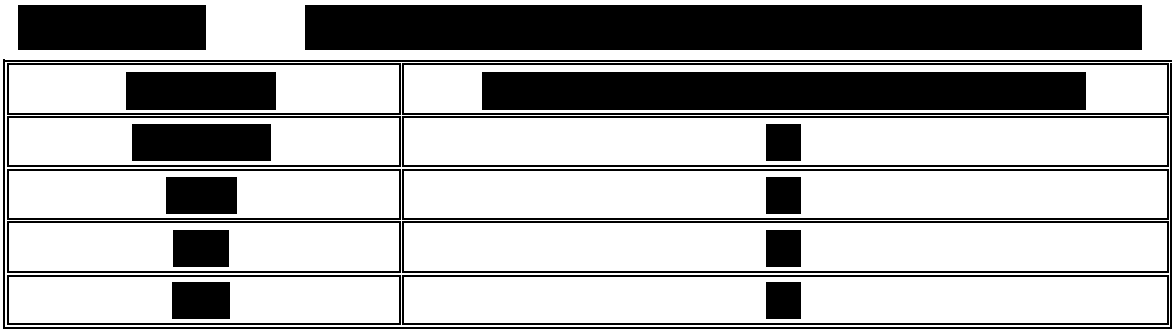
- **Xu (**μg**)**: Amount of abatacept excreted in urine

[redacted]

[redacted]

[redacted]

[redacted]



5.6 Outcomes Research Assessments

The Patient Reported Outcomes Measurement Information System (PROMIS) will be used to capture patient reported outcomes relevant to subjects with nephrotic syndrome. The PROMIS project was established as part of the National Institutes of Health Roadmap Initiative to create item banks for both adults and children, which are publically available, efficient, precise, and valid across a variety of diseases to assess PROs (www.nihpromis.org).[60]

In this study, the static short forms (ie, containing a fixed set of items) will be used, eg, in pencil-and-paper format. This will bypass the need to use the computerized adaptive testing approach. The item banks chosen are based on prior experience with these items in nephrotic syndrome as well as on the characteristics of the disease condition.[46,61] For subjects 17 and younger, both the subjects and their parent proxy will complete the appropriate static short forms.

The following static short forms will be utilized from the following PROMIS items banks (see Appendix 4).

- For subjects 18 and older:
  - SF Physical Function v1.2 Form 8b
  - SF Fatigue v1.0 Adult Form 8a
  - SF Pain Interference v1.0 Adult Form 8a
- For subjects 8-17 and younger and their parent proxy:
  - SF Physical Function - Mobility v1.0 Peds Form 8a
  - SF Fatigue v1.0 Peds Form 10a
  - SF Pain Interference v1.0 Peds Form 8a
- For subjects 6-7 and their parent proxy
  - SF Physical Function Mobility v1.0 Parent Proxy Form 8
  - SF Fatigue v1.0 Parent Proxy Form 10
  - SF Pain Interference v1.0 Parent Proxy Form 8

5.7 Other Assessments

5.7.1 Immunogenicity Assessments

The immunogenic potential of the study medication will be assessed based on levels of antiabatacept antibodies.

5.7.2 Immunogenicity: Blood Sample Collection and Processing

The blood sampling schedule to be followed for the assessment of immunogenicity is shown in Table 5.4.1-1. Detailed instructions of immunogenicity specimens will be supplied to Investigators in a separate laboratory manual.

5.7.3 Immunogenicity: Sample Analysis

A validated, sensitive, electrochemiluminescence assay (ECL) method will be used to analyze for the presence of anti-abatacept and anti-CTLA4-T antibodies in serum. Samples that are confirmed positive for anti-CTLA4 antibodies with the ECL immunogenicity assay and has abatacept serum concentrations below 1 µg/mL will be further analyzed with a validated, in vitro, cell-based bioassay to determine whether the sera contained abatacept neutralizing activity.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease

temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Section 5.5.1 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 6 months of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will be instituted to perform safety monitoring oversight. Details will be contained in the DMC Charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This pilot study is planned to randomize approximately 90 subjects to assess the primary endpoint of proportion subjects in Renal Response at Day 113 between the IV Abatacept and placebo arms. The randomization will be stratified by Genotype for whom test results, obtained either prior to enrollment or at screening, are available (*APOL1* high risk group vs Others) and Age (< 18 and ≥ 18).

A total of 90 subjects randomized in a 1:1 ratio to Abatacept vs placebo will yield approximately 80% power to detect a treatment difference (delta) of 28% between the two treatment arms. This power estimate assumes a 2-sided alpha level of 5%, Renal Response rate of 40% and 12% in the IV Abatacept and Placebo arms respectively. The 12% estimate of Renal Response in the placebo arm was based on observed rate of Renal Response in the FONT II study[42] which has a similar population that is proposed for the present study and expert opinion.

8.2 Populations for Analyses

Efficacy endpoints will be summarized according to the **Intent-to-Treat (ITT)** population and safety endpoints will be summarized according to the **As Treated** population. These populations are described below along with the Per-Protocol population and the Immunogenicity population.

Intent-to-Treat Analysis Population

The Intent-to-Treat (ITT) Analysis Population is defined to include all subjects randomized into the study for whom Case Report Form (CRF) data indicate that at least one dose of study medication (IV Abatacept or placebo) is administered during the Double-Blind Period.

All subjects who are randomized but never received study medication are to be excluded. Given the blinded nature of this study, it is reasonable to assume that subjects who discontinue prior to the receipt of study medication do so for reasons unrelated to study medication.

Subjects are grouped according to the treatments to which they are randomized by the Central Randomization System (IV Abatacept vs placebo).

ITT Analysis Population is also referred to as 'All Randomized and Treated Subjects'.

As-Treated Analysis Population

The As-Treated Analysis Population contain all subjects for whom CRF data indicate that at least one dose of study medication was administered during the Double-Blind Period.

Subjects are grouped according to the treatments to which they are randomized, except in cases where information is available, which indicate that a subject receives a different treatment for the entire course of the 16 week Double-Blind Period. In this case, the subject will be presented by the treatment they actually received.

The As Treated Analysis Population will also be referred as 'All Treated Subjects'.

Per-Protocol Analysis Population

The Per-protocol Analysis Population is defined as a subset of the ITT Analysis Population which excludes subjects who have relevant protocol deviations during the 16 week double-blind period. A programmable list of relevant protocol deviations will be included in the Statistical Analysis Plan and approved prior to the database lock for the 16 week Double-Blind period.

The Per-protocol Analysis Population will only be used if more than 10% of the subjects in either treatment group have relevant protocol deviations. In such a case, the analysis of the primary efficacy endpoints will be repeated in the Per-protocol Analysis Population.

Immunogenicity Analysis Population

The immunogenicity analysis population includes subjects who received at least 1 dose of abatacept and had an immunogenicity result available during the Double-Blind Period.

PK Analysis Population

The PK analysis population includes subjects who received at least 1 dose of abatacept and had a measurable concentration result available during the Double-Blind Period.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary efficacy endpoint is the proportion of subjects in Renal Response at Day 113.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Secondary Efficacy Endpoints

- Mean change from baseline in UPRC at Day 113.
- Mean change from baseline in serum albumin at Day 113
- Proportion of subjects achieving complete remission (UPCR ≤ 0.3 with eGFR: normal or ≥ 75% baseline if below normal at baseline) at Day 113.
- Mean change from baseline in PROMIS measures at Day 113.

8.3.2.2 Safety Endpoints

- All adverse events (AEs, SAEs, AEs leading to discontinuation, deaths, etc.)
- AEs of interest (infections, malignancies, autoimmune disorders, infusional related reactions, renal-related events)

- Laboratory test abnormalities

8.3.2.3 Immunogenicity Endpoint

- Proportion of subjects with positive antibody response relative to baseline over time.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions and summary statistics of all demographic variables and baseline characteristics will be presented by treatment arm using the ITT population.

8.4.2 Efficacy Analyses

The analysis for the double-blind period will be performed once all subjects complete the Double Blind Period Day 113 visit assessment or discontinue prematurely. The double-blind analysis will include the analysis of the primary efficacy endpoint and all other efficacy endpoints on subjects who were treated in the Double-Blind Period.

8.4.2.1 Primary Efficacy Analysis:

The primary comparison of proportion of subjects in renal response at Day 113 at the end of the Double Blind period between IV Abatacept and Placebo arm will be assessed using a logistic regression model. To account for randomization stratification, the logistic regression model will adjust for baseline UPCR and the randomization stratification variables of Genotype (*APOL1* high risk group vs Others) and Age (< 18 vs ≥ 18). Point estimate of the adjusted Odds Ratios (OR) of the odds of achieving Renal Response in the IV Abatacept arm compared to the Placebo arm, corresponding 95% CI and p-value will be provided. Unadjusted point estimate of the proportion of renal response in each treatment arm and corresponding 95% CI will also be provided. All subjects who discontinue prematurely prior to reaching the primary endpoint, Day 113, assessment visit will be considered as not achieving response in the primary analysis. A sensitivity analysis of the primary endpoint will be performed using a logistic regression model that does not adjust for the 2 stratification factors. Analysis of the renal response by APOL1 and Age subgroups will also be performed to assess differences in renal response within each category of stratification variables by treatment arm; details of any additional analyses to assess these differences will be provided in the Statistical Analysis Plan. The efficacy analysis will be performed based on the ITT population.

8.4.2.2 Secondary Efficacy Analyses

In addition to the primary efficacy endpoint, analyses related to the secondary efficacy objectives will also be included in the double-blind analysis. The secondary efficacy assessment of change from baseline in UPRC at Day 113 will be assessed using a longitudinal (repeated measure) mixed model including treatment arm, baseline value UPRC and randomization stratification factors (genotype and Age), time (study days in which UPRC is measured), and time by treatment interaction as fixed effects and subject as a random effect. Adjusted mean, SE, 95% CI for adjusted mean difference between treatment arms will be provided. A similar mixed model will also be used to assess the change from baseline in serum albumin at Day 113. The model will include treatment group, baseline value serum albumin value and randomization stratification factors (genotype and age), time (study days in which serum albumin is measured), and time by treatment interaction as fixed effects and subject as a random effect. Adjusted mean, SE, 95% CI for adjusted mean difference between treatment arms will also be provided.

The secondary efficacy endpoint of proportion of subjects achieving complete remission (UPCR ≤ 0.3 with eGFR: normal or $\geq 75\%$ baseline if below normal at baseline) at Day 113 will be assessed using a logistic regression model similar to the one used for the primary efficacy endpoint. The logistic regression model will include treatment arm, stratification variables (Genotype and Age) and baseline UPCR as continuous variable and point estimate of adjusted ORs, corresponding 95% CI will be provided.

A summary of the analysis methods to be used for the analysis of the primary, secondary and exploratory efficacy endpoints are presented in Table 8.4.3-1 below. Further details on the primary and secondary analyses along with exploratory evaluations, any additional sensitivity analyses and data handling details regarding issues such as missing data are provided in the Statistical Analysis Plan.

8.4.3 Efficacy Analyses

Table 8.4.3-1: Summary of Planned Efficacy Analyses

Measure of Interest	Analysis Method
Renal Response	Primary Analysis: Using a logistic regression model that includes treatment arm, randomization stratification factor (Genotype, Age) and baseline UPCR as continuous variable and point estimate of adjusted ORs, corresponding 95% CI and p-value will be provided.
Differences in proportions: proportion of subjects achieving complete remission at Day 113	Secondary Efficacy Analysis: Using a logistic regression model that includes treatment arm, stratification variables (Genotype and Age) and baseline UPCR as continuous variable and point estimate of adjusted ORs, corresponding 95% CI will be provided.
Difference in mean change from baseline in continuous endpoints (UPCR, Serum Albumin, [redacted]	Longitudinal (repeated measure) mixed model [including treatment group, baseline value of variable and randomization stratification factors (genotype and age), time, and time by treatment interaction as fixed effects and subject as a random effect], adjusted mean, SE, 95% CI for adjusted mean difference between treatment groups will be provided.

8.4.4 Safety Analyses

Significant physical examination findings, and clinical and laboratory test results will be listed. Summary statistics will be tabulated. Frequency distributions and individual listings of all adverse events will be generated. Changes from baseline in clinical laboratory test results will be summarized and listed. Frequencies of marked abnormal laboratory measures will also be provided. Safety analyses will be presented by treatment arms in the Double Blind Period.

8.4.5 Pharmacokinetic Analyses

Summary statistics will be tabulated by age group (<18 years and ≥18 years) for the pharmacokinetic parameters (C_{max}, T_{max}, and AUC) and by age group and study day for Cmin. Geometric means and coefficients of variation will be presented for Cmin, Cmax and AUC. Medians and ranges will be presented for T_{max}. The amount of abatacept excreted in urine (Xu) will be summarized by collection time.

[redacted]

8.4.7 Outcomes Research Analyses

Descriptive summary statistics for changes in patient reported outcomes of physical function, fatigue and pain interference from baseline over time during the Double-Blind Period for the

PROMIS static short forms will be provided by age group (for subjects 18 and older: SF Physical Function v1.2 8b, SF Fatigue v1.0 Adult 8a and SF Pain Interference v1.0 Adult 8a; for subjects 17 and younger and their parent proxy: SF Physical Function - Mobility v1.0 Peds 8a, SF Fatigue v1.0 Peds 10a and SF Pain Interference v1.0 Peds 8a). Results for adults and pediatric subjects will be reported separately. The results for subjects 17 and younger will also be reported separately from their parent proxy form results. The mean change from baseline in these measures will be presented based on an analysis of covariance (ANCOVA) model.

8.5 Interim Analyses

No formal interim analysis is planned for this study. Analyses for the DMC reporting will be detailed in the DMC analysis plan for the study.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records.

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period

specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.
Renal Responder	Renal responders are defined as subjects who achieve a reduction of their baseline UPCR of ≥ 50% and to less than 3 with no worsening of baseline estimated glomerular filtration rate (eGFR: normal or ≥ 75% baseline if below normal at baseline).

11 LIST OF ABBREVIATIONS

Term	Definition
ACEi	angiotensin-converting-enzyme inhibitor
ACTH	adrenocorticotropic hormone
AE	adverse event
aGVHD	Acute graft-versus-host disease
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-HCG	beta-human chorionic gonadotrophin
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CDC ACIP	The Center for Disease Control Advisory Committee on Immunization Practices
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	confidence interval
CKD-EPI	Chronic Kidney Disease - Epidemiology
C1-	chloride
cm	centimeter
Cmax	Peak serum concentration of abatacept
Cmin	Trough level serum concentration of abatacept
CRF	Case Report Form, paper or electronic
CS	corticoseroids
CTA	Clinical trial agreement
CXR	Chest X-ray

Term	Definition
DB	Double-blind
DILI	Drug induced liver injury
dL	deciliter
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
D5W	5% Dextrose in Water
ECL	electrochemiluminescence
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
eGFR	Estimated glomerular filtration rate
EIA	enzyme immunoassay
ELISA	Enzyme-linked immunoabsorbent assay
EMRs/EHRs	electronic medical/health records
ER	Emergency room
ESRD	End stage renal disease
F	Fahrenheit
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act

Term	Definition
HIV	Human Immunodeficiency Virus
HRT	hormone replacement therapy
hsCRP	High sensitivity C-reactive protein
HSDS	height standard deviation score
IB	Investigator Brochure
ICD	International Classification of Diseases
ICF	Informed consent
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma release assay
Ig	immunoglobulin
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
INH	isoniazid
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine-hormonal releasing system
IV	intravenous
kg	kilogram
JIA	Juvenile idiopathic arthritis
L	liter
LAM	lactation amenorrhea method
ln	natural logarithm
LN	Lupus nephritis
LPLV	Last patient last visit
MCD	Minimal Change Disease

Term	Definition
mg	milligram
min	minute
mL	milliliter
MMF	mycophenolate mofetil
mmHg	millimeters of mercury
MPA	mycophenolic acid
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N/A	not applicable
ng	nanogram
Non-IMP	non-investigational medicinal product
NS	Nephrotic Syndrome
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OLE	Open Label Extension
OR	Odds ratio
PA	posterioranterior
PD	pharmacodynamics
PEF	Peak expiratory flow
pJIA	Polyarticular juvenile idiopathic arthritis
PK	pharmacokinetics
PPD	Purified protein derivative
PROMIS	Patient Reported Outcomes Measurement Information System
RA	Rheumatoid arthritis
RAS	Renin-angiotensin system
RBC	red blood cell
RNA	Ribonucleic acid
SAE	serious adverse event
SD	standard deviation

Term	Definition
SLE	Systemic lupus erythematosus
SNPs	single nucleotide polymorphisms
SOP	Standard Operating Procedures
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TB	tuberculosis
Tmax	Time to reach peak serum concentration of abatacept
TRNS	Treatment Resistant Nephrotic Syndrome
ULN	Upper limit normal
UPCR	Urine Protein to Creatinine Ratio
UR	urinary recovery
URI	Upper respiratory infections
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
Xu	Amount of abatacept excreted in urine

APPENDIX 1 CENTRAL PATHOLOGY REVIEW

CENTRAL PATHOLOGY REVIEW SOURCE DOCUMENT

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Page 1 of 2

Site #	*Subject #*	*Date of Kidney Biopsy Report (DD-MMM-YYYY)*	*Date Sent to Central Reader (DD-MMM-YYYY)*

Instructions: LM, IF/IHC, and EM are required to fulfill pathologic enrollment criteria for FSGS.

Check Response	*Inclusion Criteria*
__ **Yes** __ **No**	• **LM:** Minimum sample requirement is 5 or more glomeruli for LM in the LM/IF/IHC/EM sections combined. At least one glomerulus in combined tissue for LM/IF/IHC/EM with segmental sclerosis (with or without hyalinosis) or consolidation described in the Columbia FSGS Classification System (excluding collapsing variant) or as described for infantile/childhood "diffuse mesangial sclerosis". If yes, classify as:
__	**NOS variant**
__	**Tip variant**
__	**Perihilar variant**
__	**Cellular variant**
__	**"Diffuse mesangial sclerosis" using CureGN criteria**
__	**Indeterminate (insufficient for confident classification)**
__ **Yes** __ **No**	• **IF/IHC**: <1+ glomerular staining for IgG and IgA; and ≤ 1+ glomerular IgM, C3 and C1q (on a scale of 0-3 or 0-4) (except in areas of hyalinosis or sclerosis). **Note**: >1+ staining for C1q reflexes case to C1qN enrollment.
__ **Yes** __ **No**	• **EM:** Absence of immune complex-type electron dense deposits other than small segmental mesangial dense deposits (except in cases reflexed to C1qN).

CENTRAL PATHOLOGY REVIEW SOURCE DOCUMENT

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Page 2 of 2

Check Response	*Exclusion Criteria:*
__ **Yes** __ **No**	• **LM/IF/IHC/EM** findings indicative of other glomerular disease [including collapsing FSGS (collapsing glomerulopathy)]
__ **Yes** __ **No**	• **IF/IHC:** ≥1+ glomerular staining for IgG and IgA, and >1+ glomerular IgM, C3 and C1q (on a scale of 0-3 or 0-4) (except in areas of hyalinosis or sclerosis). **Note**: >1+ staining for C1q reflexes case to C1qN enrollment.
__ **Yes** __ **No**	• **EM**: Widespread well-defined immune complex-type electron dense deposits (except in cases reflexed to C1qN).
	Non-Excluding Pathology Findings:
__	• **LM:** Mild mesangial hypercellularity or concurrent features of arterionephrosclerosis.
Check Response	***Assessment of Central Pathology Reader***
__ **Yes** __ **No**	• **Pathology entry criteria for FSGS fulfilled** **Date of Assessment (DD-MMM-YYYY) _____** **Assessor Initials: _____**
__	• **Reflexed to C1q nephropathy**

CENTRAL PATHOLOGY REVIEW SOURCE DOCUMENT

MINIMAL CHANGE DISEASE

Page 1 of 2

Site #	*Subject #*	*Date of Kidney Biopsy Report (DD-MMM-YYYY)*	*Date Sent to Central Reader (DD-MMM-YYYY)*

Instructions: LM, IF/IHC and EM are required to fulfill pathologic enrollment criteria for MCD.

Check Response	*Inclusion Criteria*
__ **Yes** __ **No**	• **LM:** Ten or more nonsclerotic glomeruli must be available for examination in LM/IF/IHC/EM. Histologically unremarkable glomeruli except for mesangial hypercellularity and globally sclerotic obsolescent glomeruli. **Note:** Any amount of mesangial hypercellularity will be allowed and scored later
__ **Yes** __ **No**	• **IF/IHC**: <1+ glomerular staining for IgG and IgA and ≤ 1+ glomerular C3 and C1q (on a scale of 0-3 or 0-4). Any intensity of IgM staining is allowed and the intensity scored later. **Note**: >1+ staining for C1q reflexes case to C1qN enrollment.
__ **Yes** __ **No**	• **EM:** Absence of immune complex-type electron dense deposits (except in cases reflexed to C1qN). Any degree of foot process effacement is allowed, however, if there is minimal or no foot process effacement, clinical/laboratory features must strongly support a diagnosis of MCD in the patient (e.g. substantial proteinuria at some point in the course of disease).
Check Response	*Exclusion Criteria:*
__ **Yes** __ **No**	• **LM/IF/IHC/EM** findings indicative of other glomerular disease.
__ **Yes** __ **No**	• **IF/IHC:** ≥1+ glomerular staining for IgG, and IgA, and >1+ glomerular C3 or C1q (on a scale of 0-3 or 0-4). **Note**: >1+ staining for C1q reflexes case to C1qN enrollment.

CENTRAL PATHOLOGY REVIEW SOURCE DOCUMENT

MINIMAL CHANGE DISEASE

Page 2 of 2

Check Response	***Exclusion Criteria***
__ Yes **__ No**	• **EM**: Immune complex-type electron dense deposits (except in cases reflexed to C1qN).
Check Response	***Non-Excluding Pathology Findings:***
—	• **LM:** Globally sclerotic glomeruli, mild mesangial hypercellularity, or concurrent features of arterionephrosclerosis
Check Response	***Assessment of Central Pathology Reader***
__ Yes **__ No**	• **Pathology entry criteria for MCD fulfilled** **Date of Assessment (DD-MMM-YYYY) _____** **Assessor Initials: _____**
—	• **Reflexed to C1q nephropathy**

CENTRAL PATHOLOGY REVIEW SOURCE DOCUMENT

C1q Nephropathy

Site #	*Subject #*	*Date of Kidney Biopsy Report (DD-MMM-YYYY)*	*Date Sent to Central Reader (DD-MMM-YYYY)*

Check Response	*Inclusion Criteria:*
__ **MCD** __ **FSGS**	• **LM:** Light microscopic findings fulfilling CureGN criteria for minimal change disease or focal segmental glomerulosclerosis (excluding collapsing variant). If yes for FSGS, classify as follows:
__	**NOS variant**
__	**Tip variant**
__	**Perihilar variant**
__	**Cellular variant**
__	**Indeterminate (insufficient for confident classification)**
__ **Yes** __ **No**	• **IF/IHC**: >1+ staining for C1q with any amount of staining for IgG, IgA, IgM and C3 (on a scale of 0-3 or 0-4).
__ **Yes** __ **No**	• **EM:** Mesangial immune complex-type electron dense deposits with or without scattered subendothelial and subepithelial deposits.
Check Response	*Exclusion Criteria:*
__ **Yes** __ **No**	• **LM/IF/IHC/**EM findings indicative of glomerular disease other than MCD or FSGS, especially lupus GN.

Check Response	*Non-Excluding Pathology Findings:*
—	• **LM:** Globally sclerotic glomeruli, mild mesangial hypercellularity or concurrent features of arterionephrosclerosis
Check Response	***Assessment of Central Pathology Reader***
__ Yes **__ No**	• **Pathology entry criteria for C1qN fulfilled** **Date of Assessment (DD-MMM-YYYY) _____** **Assessor Initials: _____**

APPENDIX 2 METHODS OF CONTRACEPTION

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1) Progestogen only hormonal contraception associated with inhibition of ovulation.
2) Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3) Nonhormonal IUDs, such as ParaGard®
4) Bilateral tubal occlusion
5) Vasectomised partner with documented azoospermia 90 days after procedure
   a) Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
6) Intrauterine hormone-releasing system (IUS).
7) Complete abstinence
   a) Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
   b) Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
   c) It is not necessary to use any other method of contraception when complete abstinence is elected.
   d) Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 6.4.
   e) Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
   f) The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Local laws and regulations may require use of alternative and/or additional contraception methods.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method (LAM)

[redacted]

APPENDIX 3 LABORATORY GUIDELINES: PATIENT STUDIES

Laboratory test results, which meet these criteria, and the Investigator feels is clinically relevant should be described on the Adverse Event Form. Those which are judged to be SERIOUS events require the completion of a Serious Adverse Event Form (see Sections 6.1.1 and 6.3).

[NOTE: LLN = lower limit of normal; ULN = upper limit of normal.]

albumin - < 0.9xLLN or if pretreatment value is < LLN, < 0.75x pretreatment

alkaline phosphatase - >2 x ULN; or if pretreatment > ULN, 3x pretreatment value

basophils (%) - > 3% if 0-1% pretreatment, > 3x pretreatment value if pretreatment > 1%

bilirubin

a. direct - > 1.5x ULN, or if pretreatment above ULN, > 2x pretreatment
b. total - > 2x upper limit of normal, or if pretreatment above ULN, > 4 x pretreatment value

blasts - > 0

blood urea nitrogen (BUN) - > 2x pretreatment

calcium - < 0.8x LLN or > 1.2x ULN; < 0.75x pretreatment if pretreatment below LLN, or > 1.25x pretreatment if pretreatment above ULN; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

chloride - < 0.9x LLN or > 1.1x ULN; or < 0.9x pretreatment if pretreatment below LLN, or > 1.1x pretreatment if pretreatment above ULN; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

creatinine - >1.5x pretreatment value

eosinophils (%) - > 3x pretreatment and > 8% if pretreatment normal; if pretreatment > ULN, > 3 x pretreatment

erythrocytes - < 0.75x pretreatment value

estimated glomerular filtration rate (eGFR): 0.5x pre-treatment

glucose - < 0.8x LLN or >1.5x ULN; if pretreatment < LLN then < 0.8x pretreatment; if pretreatment > ULN then >2x pretreatment; < LLN if > ULN pretreatment, or > ULN if < LLN pretreatment

hematocrit - < 0.75x pretreatment

hemoglobin - > 3 g/dL decrease from pretreatment value

lactic dehydrogenase (LDH) - > 1.5x ULN; if pretreatment value is above ULN, > 3x pretreatment value

leukocyte (WBC) count - < 0.75 x LLN or >1.25x ULN; <0.8x pretreatment if pretreatment < LLN or > 1.2x pretreatment if pretreatment > ULN; > ULN if pretreatment < LLN or < LLN if > ULN pretreatment

lymphocytes (%) - < 0.5x LLN or > 2.0 x ULN, or < 0.5x pretreatment if below LLN pretreatment; > 2.0x pretreatment if above ULN pretreatment. > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

monocytes (%) - > 2x ULN; >2x pretreatment if pretreatment above ULN

neutrophil count (neutrophils+bands) - < 0.67x pretreatment if pretreatment < 1000/mm^3; otherwise, < 1000/mm^3.

phosphate - < 0.75 x LLN or > 1.25x ULN; < 0.67x pretreatment value if below LLN pretreatment, or > 1.33x pretreatment if above ULN pretreatment; > ULN if < LLN pretreatment, or < LLN if >ULN pretreatment

platelet count - < 0.67x LLN or > 1.5 x ULN; if below normal pretreatment, < 0.5x pretreatment value and < 100,000/mm^3

potassium - < 0.9x LLN or > 1.1x ULN; < 0.9x pretreatment if pretreatment below LLN, or > 1.1x pretreatment if pretreatment above ULN; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

protein, total - < 0.9x LLN or > 1.1x ULN; < 0.9 x pretreatment if below LLN pretreatment, or > 1.1x ULN if above ULN pretreatment; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

SGOT and SGPT (ASAT and ALAT) - > 3 x upper limit of normal; if pretreatment above ULN, > 4x pretreatment value

sodium - < 0.95x LLN or > 1.05x ULN; < 0.95x pretreatment if below LLN pretreatment, > 1.05x pretreatment if above ULN pretreatment; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

uric acid - > 1.5x ULN; if pretreatment above ULN, > 2x pretreatment value

urinalysis

a) urinary protein - > 1 gram/24 hours and 2x pretreatment value

b) urinary RBC - > 5/HPF or, > 4x pretreatment if pretreatment value 5/HPF

c) urinary WBC - > 5/HPF or, > 4x pretreatment if 5/HPF pretreatment

d) creatinine clearance (glomerular filtration rate) - < 0.67x pretreatment value

e) urine dipstick measurements: Protein, blood, sugar, and acetone- 2+, or if 1+ pretreatment, 2x pretreatment. Do not evaluate protein if quantitative protein determination done

stool hemoccult - positive if negative pretreatment

APPENDIX 4 PROMIS QUESTIONNAIRES (ADULT, PARENT PROXY, AND PEDIATRIC)

PROMIS Item Bank v1.0 – Pain Interference – Short Form 8a

Pain Interference – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9 1	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22 2	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31 3	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34 4	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ12 5	How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ36 6	How much did pain interfere with your enjoyment of social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ3 7	How much did pain interfere with your enjoyment of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ13 8	How much did pain interfere with your family life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

 Page 1 of 1

PROMIS Item Bank v1.0 – Fatigue – Short Form 8a

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

		Not at all	A little bit	Somewhat	Quite a bit	Very much
	During the past 7 days…					
HI7 1	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3 2	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41 3	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40 4	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35 5	How much were you bothered by your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49 6	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		Never	**Rarely**	**Sometimes**	**Often**	**Always**
	In the past 7 days…					
FATIMP3 7	How often did you have to push yourself to get things done because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16 8	How often did you have trouble finishing things because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS SF v1.2 – Physical Function 8b

Physical Function – Short Form 8b

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11 1	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21 2	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23 3	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53 4	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFC12 5	Does your health now limit you in doing two hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB1 6	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5 7	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4 8	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

 Page 1 of 1

PROMIS Parent Proxy Item Bank v1.0 – Fatigue 10

Fatigue – Short Form 10

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
[illegible]	Being tired made it hard for my child to play or go out with friends as much as he/she would like	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	My child felt weak	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	My child got tired easily	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	Being tired made it hard for my child to keep up with schoolwork	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	My child had trouble finishing things because he/she was too tired	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	My child had trouble starting things because he/she was too tired	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	My child was so tired it was hard for him/her to pay attention	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	My child was too tired to do sports or exercise	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	My child was too tired to do things outside	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
[illegible]	My child was too tired to enjoy the things he/she likes to do	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

 Page 1 of 1

PROMIS Parent Proxy Item Bank v1.0 – Physical Function Mobility 8

Physical Function Mobility – Short Form 8

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able do
Pf1mobil3	My child could do sports and exercise that other kids his/her age could do.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil9	My child could get up from the floor.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf4mobil4	My child could keep up when he/she played with other kids.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil8	My child could move his/her legs.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil3	My child could stand up without help	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf2mobil7	My child could stand up on his/her tiptoes.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf2mobil4	My child could walk up stairs without holding on to anything.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf1mobil1	My child has been physically able to do the activities he/she enjoys most.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

 Page 1 of 1

PROMIS Parent Proxy Item Bank v1.0 – Pain Interference 8

Pain Interference – Short Form 8

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
PIDpain8	My child had trouble sleeping when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
PIDpain7	My child felt angry when he/she had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
PIDpain2	My child had trouble doing schoolwork when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
PIDpain2	It was hard for my child to pay attention when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
PIDpain4	It was hard for my child to run when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
PIDpain4	It was hard for my child to walk one block when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
PIDpain4	It was hard for my child to have fun when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
PIDpain8	It was hard for my child to stay standing when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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PROMIS® Pediatric Item Bank v.1.0 - Physical Function - Mobility - Short Form 8a

Pediatric Physical Function - Mobility - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…..

		With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
235R1	I could do sports and exercise that other kids my age could do.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4124R1	I could get up from the floor.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
236R1	I could keep up when I played with other kids.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3892R1	I could move my legs.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2646R1	I could stand up by myself.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4185R1	I could stand up on my tiptoes.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2707R2	I could walk up stairs without holding on to anything.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5023R1	I have been physically able to do the activities I enjoy most.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

PROMIS® Pediatric Item Bank v.1.0 - Pain Interference - Short Form 8a

Pediatric Pain Interference - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…..

		Never	Almost Never	Sometimes	Often	Almost Always
1698bR1	I felt angry when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2035R1	I had trouble doing schoolwork when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3793R1	I had trouble sleeping when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9004	It was hard for me to pay attention when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2045R1	It was hard for me to run when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2049R1	It was hard for me to walk one block when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
1703R1	It was hard to have fun when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2180R1	It was hard to stay standing when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMISPA02

PROMIS® Pediatric Item Bank v.1.0 - Fatigue - Short Form 10a

Pediatric Fatigue - Short Form

Please respond to each item by marking one box per row.

In the past 7 days.....

		Never	Almost Never	Sometimes	Often	Almost Always
4212R1	Being tired made it hard for me to play or go out with my friends as much as I'd like.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4213R1	I felt weak.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2876R1	I got tired easily.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4239aR2	Being tired made it hard for me to keep up with my schoolwork.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4221R1	I had trouble finishing things because I was too tired.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4220R1	I had trouble starting things because I was too tired.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4210R2	I was so tired it was hard for me to pay attention.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4241R2	I was too tired to do sports or exercise.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4208bR2	I was too tired to do things outside.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4196R1	I was too tired to enjoy the things I like to do.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4