Official Title of Study:

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)

NCT Number: NCT02592798

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STATISTICAL ANALYSIS PLAN
FOR TREATMENT RESISTANT NEPHROTIC SYNDROME

A PHASE II RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL ARMS, PILOT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRAVENOUS ABATACEPT INTREATMENT RESISTANT NEPHROTIC SYNDROME (FOCAL SEGMENTAL GLOMERULOSCLEROSIS/ MINIMAL CHANGE)

PROTOCOL(S) IM101566

VERSION # 2.0

TABLE OF CONTENTS

Approved v2.0 930132602 2.0

Approved v2.0 930132602 2.0

LIST OF TABLES

Approved v2.0 930132602 2.0

Approved v2.0 930132602 2.0

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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.

Schedule of Analyses:

There are two planned analysis in this study; one at the end of double-blind treatment period and the other at the end of study

Approved v2.0 930132602 2.0

- Double-blind period analysis: This analysis will be performed for the double-blind period when all subjects complete their Day 113 visit assessment or discontinue prematurely prior to Day 113. At the time of the first analysis the data will be unblinded. This analysis will include primary endpoint and secondary endpoints.
- End of study analysis: A second analysis will be performed at the end of the study when all subjects complete their open label extension (OLE) and follow-up period or discontinue prematurely.

This statistical analysis plan will describe the analysis to be performed at the end of the double-blind period and at the end of the study.

Prior to Protocol Amendment 2, the study design had a blinded-study drug period that was twice as long as the current double-blind period and was divided into 2 periods of equal length, known as Period 1 and Period 2, so that randomized subjects could switch blinded therapy. The current design eliminates Period 2 and renames the previous Period 1 as the double-blind period.

This modification does not impact the primary nor secondary study objectives. It does impact the exploratory objectives which addressed persistence of response and onset of response during Period 2, these are now eliminated.

For subjects who completed Period 1 and entered Period 2 prior to the protocol revision, the Period 1 data will be analyzed as part of the double-blind period since study execution during this timeframe is unchanged, the Period 2 data will only be listed. Period 2 data won't be part of any summaries except for safety summaries at the end of the study on the cumulative abatacept safety period.

2 STUDY DESCRIPTION

2.1 Study Design

This is a phase II randomized, placebo-controlled, double-blind, parallel arm design study to evaluate the efficacy and safety of intravenous abatacept in treatment resistant nephrotic syndrome (Focal Segmental Glomerulosclerosis / Minimal Change) in adult and pediatric subjects.

This pilot study will randomize approximately 90 subjects 1:1 to intravenous (IV) abatacept or placebo in a double-blind (DB) fashion. 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 y and ≥ 18 y).

The trial will consist of 4 periods: 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. IV placebo), a 168 day abatacept open label extension period (OLE), and a 6 month follow-up period.

Subjects randomized to abatacept treatment in the double-blind period will be dosed as follows. Adults will use the weight-tiered dose: < 60kg: 500mg, 60 to 100kg: 750mg, > 100kg: 1000mg;

Approved v2.0 930132602 2.0

pediatric patients 6 to 17 years who weigh < 75kg will receive:10mg/kg and those who weigh ≥ 75kg will follow adult dosing. Dosing is on Day 1, 15, 29, 57, 85. Subject in the placebo arm will receive normal Saline or D5W following the same dosing schedule. In the OLE, subjects who enter will all receive age and weight-based IV abatacept every 28 days for 169 days.

The primary efficacy assessment, renal response (defined in Section 8.1.1), will be on Day 113. On Day 113, all subjects who choose to receive open label therapy with abatacept will enter the OLE. During the OLE, the durability (i.e., continuity of response) and stability (i.e., the change in urine protein/creatinine ratio (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.

2.2 Treatment Assignment

Subjects are randomized in a 1:1 ratio within each of the strata to the abatacept or placebo treatment arms across all sites in the double-blind period. 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 y and ≥ 18 y). Subjects who refuse genotyping will be considered as in the "Others" Genotype group.

2.3 Blinding and Unblinding

The subjects and clinical assessor(s) are not aware of which treatment is being administered to the subjects enrolled in the study. The pharmacist (or qualified drug preparation person) will be unblinded to study medication (abatacept or placebo).

The pharmacist (or qualified drug preparation person) will know the scheduled assignments and prepare the appropriate dose of active - abatacept or placebo accordingly. The prepared drug must be supplied to study personnel in a manner such that neither study personnel nor subjects will be aware of whether they receive active drug or placebo.

Blinding is critical to the integrity of this clinical drug trial. 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 treating physician.

Before breaking the blind of an individual subject's blinded treatment, the Investigator should determine that the information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

BMS personnel will be blinded to treatment assignment until all subjects have completed Day 113 and the database is locked for primary analysis.

Approved v2.0 930132602 2.0

The following individuals will have access to the treatment code during the study:

- As described in the DMC Charter, the members of the independent data monitoring committee (DMC) and the external reporting statistician will be partially unblinded with a right to fully unblind treatment codes if necessary to enable review of the emerging data.
- Personnel charged with generating and maintaining randomization files, packaging study medication, and operating the IVRS will also have access to treatment codes.
- Bioanalytical Scientist or its designate will be unblinded to the randomized treatment assignments in order to minimize unnecessary PK analysis of samples from control group subjects. A single pharmacokinetist in Discovery Medicine and Clinical Pharmacology may be unblinded in order to prepare preliminary summaries of pharmacokinetic, pharmacodynamics, and safety data, as needed (for example by the Data Monitoring Committee) before randomization codes will be broken after final database lock. These summaries will not reveal individual subjects' treatment assignments.

2.4 Protocol Amendments

The protocol currently has two amendments. The table below summarizes the main purpose of the amendments.

Table 2.4-1: Protocol Amendment

Amendment No.	Amendment Date	Main Purpose of Amendment
1	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 [redacted]. Added pregnancy testing in open label. Clarified exclusion criteria for BMI.

Approved v2.0 930132602 2.0

Table 2.4-1: Protocol Amendment

Amendment No.	Amendment Date	Main Purpose of Amendment
2	13-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.

2.5 Safety Monitoring

An external independent DMC was formed and charged with periodic monitoring of key safety data. The DMC makes any necessary recommendations regarding the conduct of the study. The contents and methods of safety data reports to the DMC are outlined in the Charter of that Committee.

3 OBJECTIVES

3.1 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 Response (defined in Section 8.1.1) at Day 113.

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 Urine Protein/Creatinine Ratio (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.

Approved v2.0 930132602 2.0

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.

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint

- The primary efficacy endpoint is the proportion of subjects in Renal Response (defined in Section 8.1.1) at Day 113.

4.2 Secondary Efficacy Endpoints

- 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% of baseline value if below normal at baseline) at Day 113.
- Mean change from baseline in PROMIS measures at Day 113.

4.3 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).

Approved v2.0 930132602 2.0

4.4 Laboratory test abnormalities.Immunogenicity Endpoints

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

[redacted]

5 SAMPLE SIZE AND POWER

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 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 y and ≥ 18 y).

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%, and Renal Response rate of 40% and 12% in the 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[3] which has a similar population that is proposed for the present study and expert opinion.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

In this study, there are four study periods: screening period, double-blind period (DB), open label extension period (OLE), and follow-up period.

The following analysis periods defined below are for analysis purposes. The definitions below indicate the data to be included in the analysis of each specified period. Subjects discontinued during a specified period (DB or OLE) will be considered on-treatment for 56 and 42 days after the last dosing in that period for safety and efficacy analysis respectively. Follow-up period data will be included in one of the analysis periods depending on the time of completing the study.

Screening Period: Starts with the day of enrolment and ends prior or on the day of first dose of study medication (abatacept or placebo).

Double-Blind Period: Starts with the first dosing of double-blind study medication and ends 56/42 days (for safety/efficacy analysis) after the last dose of the double-blind period or the first dosing of OLE, whichever is earlier.

Approved v2.0 930132602 2.0

For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, includes data from first dose date in Period 1 up to the first dose in Period 2.

Open Label Extension Period (OLE): Starts with the first dosing in the OLE and ends 56/42 (for safety/efficacy analysis) days after the last dose in the OLE.

Cumulative Abatacept Safety Period: Starts at the time of the first dose of abatacept (either in the double-blind period for the subjects randomized to abatacept or in the OLE for the subjects randomized to placebo) and continues up to 56 days post last dose of abatacept for safety (AE and laboratory summaries). The last abatacept dose can be last dose in double-blind period for subjects not treated in the OLE.

For subjects who completed Period 1 and entered Period 2 prior to the protocol revision:

- For subjects on abatacept during Period 1:
  - For subjects who do not enter OLE period: starts with the first dosing of Period 1 and ends 56 days after the last dosing of Period 1.
  - For subjects who enter OLE period: starts with the first dosing of Period 1 and ends 56 days after the last dosing of Period 1 combined with OLE period that starts with the first dosing in the OLE period and ends 56 days after the last dosing in the OLE period.
- For subjects on placebo during Period 1:
  - For subjects who do not enter OLE period: starts with the first dosing of Period 2 and ends 56 days after the last dosing of Period 2.
  - For subjects who enter OLE period: starts with the first dosing of Period 2 and ends 56 days after the last dosing of OLE period. If a subject's first dosing in OLE period is more than 56 days from last dosing in Period 2, the duration after 56 days from last dosing in Period 2 to the first dosing in OLE will be excluded.

6.2 Treatment Regimens

There are two treatment groups: abatacept IV or placebo IV. Abatacept IV will be dosed based on age group and weight as follows:

- Adults (≥ 18 years):
  - < 60kg: 500mg
  - 60 - 100kg: 750mg
  - > 100kg: 1000mg
- Pediatric (6-17 years):
  - < 75kg: 10mg/kg
  - ≥ 75kg follow adult dosing

Approved v2.0 930132602 2.0

6.3 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, Immunogenicity population and the Pharmacokinetic population

6.3.1 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 (abatacept or placebo) was administered during the double-blind period.

All subjects who were 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 Interactive Response System (IxRS).

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

6.3.2 As-Treated Analysis Population

The As-Treated Analysis Population contains all subjects for whom CRF data indicate that at least one dose of study medication was administered during 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 received 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'.

6.3.3 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 is provided in APPENDIX 1.

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.

Approved v2.0 930132602 2.0

6.3.4 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.

6.3.5 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.

7 STATISTICAL ANALYSES

The randomization is stratified by Genotype (APOL1 high risk group vs. Others) and Age (< 18 y and ≥ 18 y). Therefore genotype and age, which will obtained from IxRS data, will be included as stratification factors in some of the efficacy analyses described below. The analyses to be performed at the end of study on OLE period is outlined in Section 9.

7.1 General Methods

All construction of CIs for differences in response rates between treatment groups will be based on minimum risk weights[4] to account for randomization stratification factors, unless otherwise noted. All construction of CIs for response rates within treatment group will be based on normal approximation, unless otherwise noted.

All construction of CIs for continuous measures will be based on a mixed effects model which includes treatment group, baseline value of variable, randomization stratification factors, time, time by treatment interaction, and baseline value by time interaction as fixed effects and subject as a random effect. An unstructured covariance matrix will be used to model the correlation of the repeated measures within each subject. The SAS procedure PROC MIXED will be used with the restricted maximum likelihood (REML) method for estimation and the denominator degrees of freedom will be calculated according to the Kenward Roger method. In case of non-convergence of the preferred longitudinal model, memory space issues or other computational issues the following back-up models are defined:

- In the first backup model, the repeated statement will specify a spatial power covariance matrix and intercept and slope will be specified as random effects on a subject level.
- In the second backup model, the model will not include terms for the interaction between the baseline variable and time.

Unless otherwise specified, summary statistics will include the following:

- Summary statistics for continuous variables will include means, standard deviations, median, quartiles, minima and maxima.
- Summary statistics for qualitative or discrete variables will include the count and percentage.

Approved v2.0 930132602 2.0

7.2 Study Conduct

Relevant protocol deviations, which could have major impact on the interpretation of the primary efficacy endpoint of the study results, will be identified prior to the unblinding the database for all subjects who are randomized and receive double-blind medication. Relevant protocol deviation criteria are listed in APPENDIX 1.

All relevant protocol deviations, pre-randomization and during double-blind period, will be listed and summarized by treatment arm. The per-protocol analysis population will exclude subjects with at least 1 relevant protocol deviation. Relevant protocol deviations will not be assessed for the OLE analysis.

7.3 Study Population

Summary statistics of data pertaining to subject disposition, demographics, baseline characteristics, and medical history will be tabulated and displayed by randomized treatment arm. No statistical test will be carried out for comparison of any baseline measurement among treatment groups.

7.3.1 Subject Disposition

The number of subjects enrolled into the study, and the number of subjects enrolled but not randomized together with the reasons for not being randomized will be summarized. The reasons for not being randomized will be taken from the CRF pre-randomization status page.

Enrollment at each site and by age group (adult and pediatric) will be summarized as specified in EudraCT requirements.

The disposition of subjects during the double-blind period will include the number of subjects randomized, the number of subjects who are randomized and treated, the number of subjects who are randomized but not treated, the number of subjects who complete the double-blind period and the number of subjects who discontinue the double-blind period together with the reasons for discontinuation.

For subjects who completed Period 1 and entered Period 2 prior to the protocol revision, the number of subjects who complete Period 2 and the number of subjects who discontinue the Period 2 together with the reasons for discontinuation will be summarized.

The number of subjects who enter the OLE, the number of subjects who complete the OLE and the number of subjects who discontinue the OLE together with the reasons for discontinuation will be summarized.

Approved v2.0 930132602 2.0

7.3.2 Demographic and Baseline Disease Characteristics

Demographic and baseline disease characteristics will be summarized using the ITT Analysis Population for pediatric patients (< 18 y), adult patients (≥ 18 y) and overall in separate summaries. Continuous variables will be summarized using means and standard deviations, and categorical variables will be summarized using frequency distributions. Summaries will be presented by randomized treatment group.

The following demographic and baseline characteristics will be summarized:

- Age
- Age group (18 - 64 y, ≥ 65 years for adults and 6 -< 18 y for pediatric subjects)
- Gender
- Race
- Ethnicity
- Weight by age group (pediatric and adult)
- Weight group (< 60, 60 - 100, > 100kg for adult and < 75, 75 - 100, > 100kg for pediatric)
- Height (pediatric only)
- BMI
- Randomization Strata (APOL1 high risk group vs. Others)
- Serum albumin at baseline (g/dL)
- Estimated Glomerular Filtration Rate at baseline (mL/min/1.73m^2)
- Urine protein/creatinine ratio at baseline (mg/mg)
- Diagnosis (FSGS versus MCD)

7.3.3 Medical History and Prior Medication

General medical history will be summarized by each body system for the ITT Analysis Population.

Prior medications are defined as medications a subject started to take prior to the first infusion of double-blind study medication. Prior medications will be summarized for each treatment arm by drug class and generic name for the ITT Analysis Population.

Medications of special interest to TRNS (FSGS/MCD) include corticosteroids (CS) (prednisone or equivalent), calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus, mycophenolate mofetil (MMF), mycophenolic acid (MPA), or cyclophosphamide. A summary of prior medications of special interest will be provided for each treatment group.

Approved v2.0 930132602 2.0

7.4 Extent of Exposure

7.4.1 Study Therapy

Extent of exposure to double-blind study drug will be summarized using the As Treated Analysis Population in two ways:

- Number of infusions.
- Number of days a subject is known to be on study drug ignoring dosing interruptions.

The number of infusions subjects received will be based on the study medication page of the CRF when an infusion date is present.

The number of days the subject is known to be on study drug (exposure to study drug) during each period is calculated as:

Double-blind period:

- Discontinued subjects during double-blind period and subjects completed double-blind period but do not continue into the OLE:

Exposure in days = (date of last study medication in the double-blind period - date of first study medication in the double-blind period + 1) + 56.

- Subjects continuing in the OLE:

Exposure in days = (date of first study medication in OLE - date of first study medication in double-blind period) - adjustment.

Adjustment is the period after 56 days from last study medication from double-blind period to the first study medication in OLE.

- Subjects who completed Period 1 and entered Period 2 prior to the protocol revision:

Exposure = (date of first study medication in Period 2 - date of first study medication in Period 1) - adjustment.

Adjustment is the period after 56 days from last study medication from Period 1 to the first study medication in Period 2.

OLE period:

Exposure = (date of last study medication in OLE - date of first study medication in OLE + 1) + 56.

Cumulative abatacept safety period:

- Subjects treated with abatacept and discontinuing before entering the OLE:

Exposure in double-blind period = (date of last study medication in double-blind period - date of first study medication in double-blind period + 1) + 56.

- Subjects treated with abatacept and continuing in the OLE, it is the sum of the following:

Approved v2.0 930132602 2.0

Exposure in double-blind period = (date of first study medication in OLE - date of first study medication in double-blind period) - adjustment.

Exposure in OLE = (date of last study medication in OLE - date of first study medication in OLE + 1) + 56.

For subjects randomized to placebo, the date of first abatacept study medication is the date of first study medication in OLE. For subjects randomized to abatacept, the date of first abatacept study medication is the date of first double-blind period.

- Subjects who completed Period 1 and entered Period 2 prior to the protocol revision:
  - For subjects on abatacept during Period 1 and entering OLE period, it is the sum of the following:
    - Exposure in Period 1 = (date of first study medication in Period 2- date of first study medication in Period 1 + 1) +56.
    - Exposure in OLE = (date of last study medication in OLE - date of first study medication in OLE + 1) + 56.
  - For subjects on abatacept during Period 2, it is the sum of the following:
    - Exposure in Period 2 = (date of first study medication in OLE period - date of first study medication in Period 2) - adjustment. Adjustment is the period after 56 days from last study medication from Period 2 to the first study medication in OLE.
    - Exposure in OLE = (date of last study medication in OLE - date of first study medication in OLE + 1) + 56.
  - For subjects on abatacept during Period 2 and not entering OLE:
    - Exposure in Period 2 = (date of last study medication in Period 2 - date of first study medication in Period 2 + 1) + 56.

The offset of 56 days is the length of 2 regular dosing cycles and represents approximately 4 times the half-life of abatacept in humans.

Summaries of exposure to study drug will show the distribution of the number of infusions and days on drug, together with the means, standard deviations, medians, minima and maxima, by treatment group.

7.4.2 Discontinuations from Study Medication

Discontinuation from study medication is defined as subject's termination of the study medication (abatacept or placebo) without resumption prior to study completion. A subject will be considered as discontinued from study period if and only if the subject status CRF page indicates he/she did not complete that specific study period. The summary of discontinuations is provided in Section 7.3.1.

Approved v2.0 930132602 2.0

7.4.3 Treatment Compliance

The number of subjects with missed infusions in the double-blind period (excluding missed infusions due to premature discontinuation from study) will be summarized by treatment group and number of missed infusions. An interruption of infusion on a particular day will not be counted as a 'missed' infusion. This summary will be performed with the ITT Analysis Population. A listing of all missed infusions indicating the period will be also provided.

[redacted]

7.5 Efficacy

The primary and secondary efficacy analyses (defined in section 7.5.2 and 7.5.4) will be performed using the ITT Analysis Population by treatment group assigned at randomization during the double-blind period. The primary analysis will be repeated using the PP analysis population if more than 10% of subjects in any treatment group meet the criteria for a relevant protocol deviation. All other efficacy analyses will be performed using the ITT Analysis Population, unless otherwise specified.

The efficacy analysis in this analysis plan is mainly focused on the double-blind period.

Approved v2.0 930132602 2.0

7.5.1 Analysis of Primary Efficacy Endpoint

The primary objective of the study is the comparison of renal response, defined by composite renal index, at Day 113 at the end of double-blind period between abatacept and placebo arms. The definition and computation method for renal response is provided in Section 8.1.1.

The primary comparison of proportion of subjects in renal response at Day 113 at the end of double-blind period between abatacept and placebo arms will be assessed using a logistic regression model. The logistic regression model will adjust for baseline UPCR, baseline eGFR and the randomization stratification variables of Genotype (APOL1 high risk group vs. Others) and Age (< 18 y vs. ≥ 18 y). Point estimate of the adjusted Odds Ratios (OR) of the odds of achieving renal response in the 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, and subjects with missing data for response at Day 113 assessment visit, will be considered as not achieving response in the primary analysis. The primary analysis will be based on the ITT Analysis Population.

7.5.2 Sensitivity Analysis

Since the balance intended in the stratification by Genotype (APOL1 high risk group vs. Others) may be impacted by the number of subjects who choose to refuse genotyping and consequently considered in the "Others" Genotype group, sensitivity analysis of the primary endpoint will be performed. The sensitivity analysis will use a logistic regression model that does not adjust for the stratification factor of Genotype based on the ITT Analysis Population. The comparison between the proportion of subjects in renal response at Day 113 at the end of double-blind period in abatacept and placebo arm will be assessed using a logistic regression model adjusting only for Age (< 18 y vs. ≥ 18 y), baseline UPCR and baseline eGFR. Point estimate of the adjusted Odds Ratios (OR) of the odds of achieving renal response in the abatacept arm compared to the placebo arm, corresponding 95% will be provided. As in the primary analysis, all subjects who discontinue prematurely prior to reaching the primary endpoint, Day 113 assessment visit and subjects with missing data for response at Day 113 assessment visit, will be considered as not achieving response in the primary analysis.

7.5.3 Analysis of Secondary Efficacy Endpoints

- Mean change from baseline in UPCR at Day 113: Longitudinal (repeated measure) mixed model will be used to assess this endpoint. The model will include treatment group, UPCR baseline value and randomization stratification factors (genotype and age), time, baseline value by time interaction, time by treatment interaction as fixed effects and subject as a random effect. An unstructured covariance matrix will be used to model the correlation of the repeated measures within each subject. The SAS procedure PROC MIXED will be used with the restricted maximum likelihood (REML) method for estimation and the denominator degrees of freedom will be calculated according to the Kenward Roger method. Adjusted mean change

Approved v2.0 930132602 2.0

from baseline by treatment groups and associated standard errors (SE) will be presented as well as treatment differences versus placebo with 95% confidence intervals. A summary will be provided, presenting the mean change from baseline in UPCR at each time point in double-blind period as described above. In addition:

  - Summary of mean change from baseline in UPCR at each time point during double-blind period and OLE will be provided. This summary will be descriptive without adjusting for stratification or baseline factors.
  - Graphs of median percent change from baseline in UPCR during all periods will be presented.

- Protein excretion determinations from 24 hour urine collections are considered to be more reliable than those obtained from spot urine collections. This is due primarily to the variability in the protein loss over the course of the day in chronic kidney diseases (CKD). This variability may not be similar between different forms of CKD. To help determine the degree of variability that may exist in subjects with TRNS (FSGS/MCD), UPCR are to be taken from a 24-hour urine collection on Day 1 and 113; if not possible, then from a single voided specimen. To assess the relationship between the two measurements a correlation analysis will be performed between the two measurements as an exploratory analysis. The analysis will be performed if more than 50% of subjects have both 24-hour collection and single voided specimen paired. The correlation between the 24-hour UPCR and single-void UPCR will be examined using the Pearson correlation coefficient or Kendall's Tau if either measure is not normally distributed; the estimate of the correlation coefficient and corresponding 95% CI will be provided; all subjects will be combined into one group for this analysis.
- Mean change from baseline in serum albumin at Day 113. A similar mixed model used in the above secondary endpoint will be applied for this endpoint. Adjusted mean change from baseline by treatment group and associated standard errors (SE) will be presented as well as treatment differences versus placebo with 95% confidence intervals will be provided. A summary will be provided, presenting the mean change from baseline in serum albumin at each time point in double-blind period as described above.
  - Additional summary of mean change from baseline in serum albumin at each time point during OLE will be provided. This summary will be descriptive without adjusting to stratification or baseline factors and will be presented by treatment arm.
- The proportion of subjects achieving complete remission (defined in Section 8.1.2: UPCR ≤ 0.3 with eGFR normal or $\geq 75\%$ baseline if below normal at baseline) at Day 113: the comparison in proportion of subjects achieving complete remission between the abatacept and placebo arms will be assessed using a logistic regression model. To account for randomization stratification, the logistic regression model will adjust for the randomization stratification variables of genotype and age in addition to adjusting for baseline UPCR and baseline eGFR. Point estimate of the adjusted Odds Ratios (OR) of the odds of achieving complete remission in the IV abatacept arm compared to the placebo arm, corresponding 95% CI, will be provided.
- Mean change from baseline in PROMIS measures at Day 113. Descriptive summary statistics for changes in patient reported outcomes of physical function, fatigue and pain improvement from baseline over time during double-blind period for the PROMIS static short forms will be provided by age group.

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- For subjects 18 years and older: SF Physical Function v1.2 8b, SF Fatigue v1.0 Adult 8a and SF Pain Interference v1.0 Adult 8a.
- For younger than 18 years 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 younger than 18 years will also be reported separately from their parent proxy form results. The mean change from baseline in these measures will be presented, for each age group (< 18 y, ≥ 18 y), by treatment group based on Longitudinal (repeated measure) mixed model. The treatment differences in adjusted mean changes from baseline, along with the corresponding 95% two-sided CI, will be based on Longitudinal (repeated measure) mixed model and will be presented at each scheduled visit in double-blind period. The model will include baseline value of variable, genotype, time, time by treatment interaction, and baseline value by time interaction as fixed effects and subject as a random effect.

[redacted]

Approved v2.0 930132602 2.0

[redacted]

7.5.5 Subgroup Analysis

All analyses described in this section will be performed on the ITT Analysis Population. Table 7.5.5-1 shows the subgroups of interest for analyses of the primary efficacy endpoint of renal response. If the value of the grouping variable cannot be determined for a subject, the subject will be excluded from the corresponding subgroup analysis. Only subgroups consisting of 10% or more of the total study population will be considered.

Table 7.5.5-1: Subgroup of Interest of the Primary Efficacy Assessment of Renal Response

Subgroup Factor	Categories
APOL1	High Risk
	Other
Age	Pediatric (< 18 years)
	Adult (≥ 18 years)
Gender	Male
	Female
Race	Caucasian
	Black
	Asian
	Others
Baseline UPCR	Baseline UPCR < 6mg/mg
	6mg/mg ≤ Baseline UPCR < 9mg/mg
	Baseline UPCR ≥ 9mg/mg
Diagnosis	FSGS
	MCD

The proportion of subjects who achieve renal response, defined by composite renal index, at Day 113 at the end of double-blind period in abatacept and placebo arm will be summarized using point estimates and 95% confidence interval for each treatment group by subgroup. The difference in proportions between treatment groups for each subgroup will be provided by point estimate and 2-

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sided 95% confidence interval using normal approximation, without any adjustments for strata, if the number of events in each individual treatment group is at least 5. Otherwise, confidence intervals using an exact method will be provided.

7.6 Safety

Analysis of all safety data will follow the BMS standard safety data conventions and supplements to the standard conventions for the abatacept programs[5].

The evaluation of drug safety is based primarily on clinical AEs, vital signs and laboratory abnormalities reported during the study. All safety presentation will be based on the As Treated Analysis Population by treatment group. Unless otherwise specified adverse events and laboratory abnormalities will be summarized for double-blind period, cumulative abatacept safety period and OLE period as described in APPENDIX 2. The definition of each period is provided in Section 6.1.

Frequency and individual listings of all AEs will be generated. Changes in clinical laboratory test results from baseline will be summarized. Laboratory marked abnormality using pre-defined abnormality criteria will also be descriptively summarized. There will be no statistical testing of group difference with respect to frequencies of AEs or laboratory marked abnormalities.

7.6.1 Adverse Events

Adverse events are recorded by the investigators on the Serious and Non-Serious Adverse Event page(s) of the CRF. All investigators are required to report the nature, the onset and resolution date, intensity, action taken, treatment required for event, and to express their opinion regarding the relationship between the AE and the study medication.

All AEs are coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the Medical Dictionary for Regulatory Activities (MedDRA). Listings and summaries will be based on the resulting SOCs and PTs.

All reported AEs and SAEs will be listed, indicating the subject ID, treatment group, age, gender, race, day of onset relative to start of dosing, resolution date, investigator-assessment of relationship to study drug, investigator-assessment of intensity of event, action taken regarding study drug and whether treatment was required for the event.

All adverse events with an outcome of death will be listed.

Selected AE summaries will be generated for the double-blind period and cumulative abatacept safety period which include SAEs, AEs leading to study drug discontinuation, most common related AEs (reported in at least 2% of subjects) and most common (serious or non-serious) AEs (reported in at least 5% of subjects).

AE summaries by age group (adults versus pediatrics) will be presented for serious AEs, AEs leading to study drug discontinuation, most common related AEs (reported in at least 2% of subjects in any treatment group for each age group separately).

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Summary information (the number and percent of subjects) regarding AEs (for serious or non-serious events) will be tabulated by SOC, PT and treatment group for:

- Serious adverse events (SAE).
- AEs leading to study drug discontinuation.
- AEs related to study drug.
- Related events categorized by intensity.
- Most common related AEs (reported in at least 2% of subjects in any treatment group).
- AEs by intensity.
- All AEs (serious or non-serious).
- Most common (serious or non-serious) AEs (reported in at least 5% of subjects in any treatment group).
- Serious adverse events and related serious adverse events with death as an outcome following EudraCT requirements.

Laboratory AEs are laboratory results identified by the Investigator as AEs and thus reported on the AE pages of the CRF. Any such AE will be included in the respective AE summaries.

7.6.2 Adverse Events of Interest

7.6.2.1 Renal Related Events

All reported renal-related events during treatment will be summarized by preferred term and treatment group. Renal-related events will be defined using the MedDRA Maintenance and Support Services Organization (MSSO) Chronic Kidney Disease Structured MedDRA Query (SMQ), MSSO Embolic and Thrombotic Disease SMQ, and BMS custom Renal Supplement SMQ. The listing will include all renal-related events up to the database lock.

7.6.2.2 Infections

All reported infections and infestations within the SOC: Infections and infestations occurring during treatment will be summarized by preferred term and treatment group. The listing will include all reported infections and infestations up to the database lock. Summary of infections and infestations AEs by intensity will also be summarized. A Kaplan-Meier plot of time to first serious infection during treatment will also be presented by treatment group.

In addition to the SOC of infections and infestations, all events in the cSMQ of Opportunistic Infections will be summarized by preferred term and treatment group. The listing will include all reported events up to the database lock.

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7.6.2.3 Malignancy

All events in the MSSO malignancies SMQ list will be summarized. These events will be summarized by preferred term and treatment group. The listing will include all reported events up to the database lock.

7.6.2.4 Autoimmune Disorders

The frequency of pre-specified autoimmune disorders, defined using a BMS custom Autoimmune Disorder SMQ will be provided. Autoimmune disorders will also be summarized by intensity. All reported autoimmune disorders reported up to the database lock will be listed.

7.6.2.5 Infusional Reactions

1) Peri-infusional AEs of interest are defined as those AEs occurring within the first 24 hours after the start of each study drug infusion that are included in the pre-specified MedDRA list of peri-infusional events of interest.
2) Acute infusional AEs of interest are defined as those AEs occurring within the first hour after the start of each study drug infusion that are included in the pre-specified MedDRA list of peri-infusional events of interest.

   The pre-specified MedDRA code of peri-infusional AEs of interest will be provided prior to database lock and will be included in the CSR.
3) Other peri-infusional AEs are defined as other AEs occurring during the first 24 hours after the start of each study drug infusion but not included in the pre-specified list of peri-infusional AEs defined in 1) above.

The number and percent of subjects experiencing the infusional AEs defined in 1) above through 3) above will be summarized by SOC, PT and treatment group. The distribution of the infusional AEs of interest by intensity will also be provided except for the AEs defined in C above. All reported peri-infusional AEs of interest reported up to the database lock will be listed.

7.6.3 Incidence Rate Analyses

Incidence rate is defined as the quotient of number of subjects with event and exposure (patient-years), where the exposure (patient-years) is the sum over all subjects' exposure during a pre-specified study period (censored at the time of the first occurrence of event) divided by 365. The resulting incidence rate is multiplied by 100 to express the rate per 100 p-y. Incidence rates per 100 p-y and associated 95% Poisson confidence intervals will be calculated for each treatment group.

Incidence rate analyses will be performed for SAEs, Renal Related AEs, Opportunistic Infections, Malignancy and Autoimmune disorders, the point estimate and 95% CI of incidence rate (per 100 patient-years) of each endpoint will be provided by system organ class and preferred term, separately for each treatment group.

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The analyses will be performed for events that occurred in double-blind period up to 56 days post last dose in double-blind period or first dose date in OLE whichever is earlier.

For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, the analyses will be performed for events that occurred in Period 1 up to the first dose in Period 2.

7.6.4 Multiple Adverse Events

Several descriptive summaries of adverse events that takes into account the number of occurrences that an AE was reported by individual patients will be provided. In order to prepare these summaries, the CRF data will be processed according to standard BMS algorithms to categorize each line of patient data as a new occurrence or a continuation of an existing event. This determination will be based upon onset and resolution dates. Each line of patient data will represent the maximum severity observed as well as the last known assessed relationship to study medication by the investigator.

This data will be presented as the rate per 100 years of patient exposure. Exposure to study medication will be calculated according to approved standard BMS algorithms as well.

As an example, if 5 patients report 7 unique episodes of headache and had a combined cumulative exposure of 20 years to study medication, the incidence rate is reported as 7/20 *(100) or 35 cases per 100 patient years of exposure.

For adverse events with multiple occurrences, the following will be provided:

- A table showing the total number and rate (exposure adjusted) of occurrences for general AEs occurring in at least 5% of the subjects treated. AEs will be organized by System Organ Class (SOC) and Preferred Term (PT), and reported by and treatment group.
- A listing displaying the unique instances of all AEs (i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event have been collapsed).

No formal comparisons are made between treatments. No formal statistical testing will be performed, only summary statistics of adverse events with multiple occurrences for double-blind period, cumulative abatacept safety period and OLE period as described in APPENDIX 2 will be provided.

7.6.4.1 EudraCT Summaries

Exposure adjusted adverse event summaries including multiple occurrences of unique adverse events for EudraCT reporting requirements will be presented by treatment group in the cumulative abatacept safety period. These summaries include serious adverse events, drug related serious adverse events and non-serious adverse events using a global cutoff of 5 percent.

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7.6.5 Laboratory Data

Safety summaries based on laboratory test results include evaluation of laboratory abnormalities and changes in laboratory test values from baseline (baseline definition is provided in Section 8.3).

Laboratory abnormalities will be summarized by treatment group for double-blind period and cumulative abatacept safety period as described in Section 7.6.

Laboratory abnormalities are identified using a pre-defined set of marked abnormality (MA) criteria (listed in Safety Data Convention). The frequency of subjects with laboratory MAs during treatment based on pre-specified criteria will be tabulated by treatment group, for each analyte.

Laboratory measurements and their changes from baseline will be summarized by study day and treatment group, for protocol specified analytes. Subjects who have laboratory measures at baseline and corresponding measure on at least one scheduled visit following administration of study drug will be included in the laboratory analyte assessment. Note that not all subjects have laboratory determinations for all analytes at all visits, and therefore the sample size may vary from analyte to analyte at each time point.

In addition shift tables for the following laboratory tests will be provided. The categorical classifications of these tests will be determined based on the cut points specified below and cross-tabulation of classification between baseline and each of the scheduled visits will be presented by treatment group.

Selected laboratory safety summaries will be generated for the double-blind period and the cumulative abatacept safety period separately as described in APPENDIX 2.

Table 7.6.5-1: Definitions of Analytes Cut Points

Analytes (Test Code)	Cut Point
Platelet Count (PLAT)	$< 100 \times 10^9$c/L
	$\geq 100 \times 10^9$c/L
Alanine Aminotransferase (ALT)	< 3 x ULN
	3 - ≤ 5 x ULN
	> 5 x ULN
Aspartate Aminotransferase (AST)	< 3 x ULN
	3 - ≤ 5 x ULN
	> 5 x ULN
Neutrophils (absolute)	$< 0.5 \times 10^9$c/L
	0.5×10^9c/L - $\leq 15 \times 10^9$c/L
	$\geq 15 \times 10^9$c/L
G-Glutamyl Transferase (GGT)	< 3 x ULN
	3 - ≤ 5 x ULN
	> 5 x ULN

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Table 7.6.5-1: Definitions of Analytes Cut Points

Analytes (Test Code)	Cut Point
Serum albumin	≤ ULNA (normal)
	> ULNA (abnormal)
[redacted]	[redacted]
[redacted]	[redacted]
eGFR	< 60mL/min/1.73m²
	60 - 89mL/min/1.73m²
	≥ 90mL/min/1.73m²

7.6.6 Vital Signs

Summary statistics for vital sign measurements (seated systolic BP, seated diastolic BP, heart rate and body temperature) will be presented at study baseline, and prior and after infusion by scheduled visit and treatment group. At the end of the study report, summary statistics of vital signs measurements collected during OLE will be provided.

7.7 Other Analyses

7.7.1 Immunogenicity

Serum for anti-abatacept antibody titers are drawn at Days 1 and 113 during the double-blind period and at Day 56, 84 and 168 during the follow-up period. For this assay, for all summaries and listings unless specified otherwise, a positive relative to baseline immunogenicity response for 'CTLA4 and possibly Ig', 'Ig and/or Junction Region', respectively, is defined as:

- A missing baseline immunogenicity measurement and a positive laboratory reported immunogenicity response post-baseline.
- A negative laboratory reported baseline immunogenicity response and a positive laboratory reported immunogenicity response post-baseline.
- A positive laboratory reported baseline immunogenicity response and a positive laboratory reported immunogenicity response post-baseline that has a titer value strictly greater than the baseline titer value.

This definition will be applied for each antibody-reactivity separately.

All other ECL immunogenicity measurements will be classified as lack of positive (relative to baseline) immunogenicity response or negative immunogenicity response.

The number (and percentage) of subjects with positive samples relative to baseline will be provided. These summaries will be provided by antibody specificity, and overall. These summaries

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will include frequencies by scheduled visit (including on-treatment, off-treatment and overall) and by treatment group and age group. The Day 1 measurement will be the baseline measurement for all subjects.

Immunogenicity during the follow up period will be analyzed as above and will be provided at the end of study report.

7.7.2 Pharmacokinetic Endpoints

Serum PK:

- Cmin (μ g/mL): Trough level serum concentration of abatacept on Days 1, 15, 29, 57, 85 and 113 will be tabulated by age group and study day. Geometric means and coefficients of variation will be presented.
- Cmax (μ g/mL): Maximum observed serum concentration on Day 85 in subjects receiving abatacept IV will be obtained and tabulated by age group. Geometric means and coefficients of variation will be presented.
- Tmax (h): Time to reach peak serum concentration of abatacept will be obtained and tabulated by age group. Medians and ranges will be presented by age group.
- AUC (TAU) (μ g·h/mL): Area under the serum concentration time curve over a dosing interval between Days 85 and 113 will be tabulated by age group. Geometric means and coefficients of variation will be presented.
- Urine PK: Xu (μ g): Amount of abatacept excreted in urine for Days 1, 15, 29, 57, 85 and 113 will be tabulated by age group. Geometric means and coefficients of variation will be presented.

[redacted]

8 CONVENTIONS

8.1 Definitions

8.1.1 Renal Response

The renal response at a specific time point will be present if all the following criteria (composite renal index) are met at that time point:

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 within normal range if normal at baseline or ≥ 75% baseline value if below normal at baseline.

Approved v2.0 930132602 2.0

eGFR determination will be based on the CKD-EPI[6] for adults and the new Schwartz equation[7] for children.

The CKD-EPI formula will be used to determine the eGFR for the adults and will be expressed as mL/min per 1.73m^2. The CKD-EPI formula is:

$$eGFR = 141 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.209} \times 0.993^{Age} \times (1.018\ [\text{if female}]) \times (1.159\ [\text{if black}])$$

Where Scr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1, age in years.

The new Schwartz formula for use in children to determine eGFR, also expressed as mL/min per 1.73m^2, is:

$$eGFR = 39.1[\text{height(m)/Scr(mg/dl)}]^{0.516} \times [1.8/\text{cystatinC(mg/L)}]^{0.294} \times [30/\text{BUN(mg/dl)}]^{0.169} \times [1.099]^{\text{gender}} \times [\text{height (m)}/1.4]^{0.188}$$

Gender = 1 if male and 0 if female

Normal eGFR is defined as eGFR equal or greater than the lower limit of normal (LLN) eGFR. For this study, the LLN eGFR for both adults and children is defined as 90mL/min per 1.73m^2.

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 (i.e., spot urine) will be utilized, preferably in the morning. For all other time points, the assessment will require a single void spot urine.

8.1.2 Complete remission

Complete remission at a specific time point will be present if all the following criteria are met at that time point:

PROTEINURIA: UPCR ≤ 0.3.

RENAL FUNCTION: No worsening of baseline (Study Day 1) estimated glomerular filtration rate (eGFR) defined as within normal range if normal at baseline, 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 as indicated in Section 8.1.1 above.

8.1.3 Prednisone or Prednisone Equivalent Use

Systemic prednisone or prednisone equivalent medication (oral, intramuscular or intravenous) will consist of the following generic names of CS on the CRF page. Before unblinding a final review

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of all medications will be performed to identify all prednisone equivalent medications and dose conversion if there is any.

- Prednisolone
- Prednisone
- Deflazacort
- Methylprednisolone
- Dexamethasone
- Hydrocortisone
- Betamethasone

The conversions of dosages of the prednisone equivalents are as follows:

- 1mg of prednisolone = 1mg of prednisone
- 1mg of deflazocort = 0.83mg of prednisone
- 1mg of methylprednisolone = 1.25mg of prednisone
- 1mg of dexamethasone = 6.67mg of prednisone
- 1mg of hydrocortisone = 0.25mg of prednisone
- 1mg of Betamethasone = 8.33mg of prednisone

For subjects who discontinued the double-blind period early, the last prednisone dose reported will be carried to Day 113.

Prednisone use at each scheduled infusion visit:

- Day 1: the total daily dose at Day 1.
- Day 15: average daily dose in mg from one day after Day 1 to the infusion date of Day 15.
- Day 29: average daily dose in mg from one day after infusion date of Day 15 to the infusion date of Day 29.
- Day 57 to Day 113: average daily dose in mg from one day after the date of prior infusion to the date of current infusion.
- If a scheduled infusion is missed, the target day will be used for the visit when calculating the average total daily dose at this visit.

8.2 Determination of Responders

For analyses of treatment differences in the proportions of subjects achieving a renal response or complete remission at specific time point, a conservative approach will be taken for subjects who prematurely discontinue prior to achieving the efficacy endpoint. That is, regardless of treatment group, these discontinued subjects will be considered as non-responders. Subjects with any missing renal response component will also be considered as non-responders.

Approved v2.0 930132602 2.0

8.3 Baseline Measurements

For all outcome measures, unless otherwise specified, the baseline value is the last assessment taken prior to the first infusion of double-blind treatment. In general, this is the assessment taken on or just before the administration of study medication (Day 1). For some variables that are also measured during screening such as vital signs and laboratory data, if Day 1 assessments are unavailable, then screening assessments will be used as baseline measurements. Adult BMI will be calculated from the screening height and the Day 1 weight while the pediatric BMI will be calculated from the Day 1 height and weight.

8.4 Missing Measurements

For determination of renal response, handling of missing values is addressed in Section 8.2. For the analysis of individual components of other outcome research endpoints (Adult: SF Physical Function v1.2 8b, SF Fatigue v1.0 Adult 8a and SF Pain Interference v1.0 Adult 8a, Pediatric: SF Physical Function - Mobility v1.0 Peds 8a, SF Fatigue v1.0 Peds 10a and SF Pain Interference v1.0 Peds 8a), other efficacy measures and biomarkers, missing values will not be imputed. See the Safety Analysis Guidelines and Safety Data Conventions for the CTLA4IG program (Referenced earlier) for conventions related to the handling of missing or partial dates and the determination of appropriate default values in such cases and in particular for concomitant medication dose start-dates and end-dates and AE onset dates. All of these rules also apply when deriving efficacy data sets.

8.5 Multiple Measurements

When lab samples are inadvertently taken or analyzed multiple times, this produces multiple measures for the same date (and time in the case of labs) for the same subject.

In such cases, the average of such multiple assessments or lab results will be used for this time point for this subject.

When clinical measurements are assessed multiple times at the same date for the same subject, the record with the latest ‘last change time stamp’ will be used for this time point for this subject.

8.6 Day Ranges for Analysis Time Points

Subjects do not always adhere strictly to the visit schedule timing in the protocol. Therefore the designation of visits during treatment will be based on the day of evaluation relative to the study (day of first infusion = study Day 1) rather than the nominal visit recorded in the case report form (CRF). Mutually exclusive relative day windows are defined in the following table to provide derived visits that correspond to the post-baseline time points specified in the protocol.

Designation of visits for efficacy assessments and outcomes research performed at every scheduled visit is tabulated in Table 8.6-1.

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Table 8.6-1: Day Ranges for Components of Renal Response, Component of Completed Remission and Outcomes Research Assessments at Every Scheduled Visit During the Double-Blind Period and OLE Period

Visit	Target Day	Component of Renal Response/ Complete Remission (UPCR, eGFR)	eGFR (Provided by Lab)	Outcomes Research Day Ranges
Double-blind period				
Screening	< 1	< 1	< 1	< 1
Day 1 (Baseline)	1	1	1	1
Day 15	15	8 - 22		
Day 29	29	23 - 43		
Day 57	57	44 - 71		
Day 85	85	72 - 99		2 - 99
Day 113*	113	100 - 127	50 - 177	100 - 127
OLE period				
Day 141	141	128 - 155		
Day 169	169	156 - 183		
Day 197	197	184 - 211		
Day 225	225	212 - 239		
Day 253	253	240 - 267		
Day 281	281	268 - 295		

* Day 113 assessment for subjects continuing in OLE, the upper inclusive limit of this window is the first infusion in OLE or 42 days after last dose in double-blind period, whichever comes earlier. Assessments within 42 days after last dose in double-blind period are included for subjects discontinuing during double-blind period.

For subjects who completed Period 1 and entered Period 2 prior to the protocol revision:

Table 8.6-2: For Subjects who Completed Period 1 and Entered Period 2 prior to the Protocol Revision

Visit	Target Day	Component of Renal Response/ Complete Remission (UPCR, eGFR)	eGFR (Provided by Lab)	Outcomes Research Day Ranges
Double-blind (Period 1 and Period 2)				
Screening	**< 1**	**< 1**	**< 1**	**< 1**

Approved v2.0 930132602 2.0

Table 8.6-2: For Subjects who Completed Period 1 and Entered Period 2 prior to the Protocol Revision

Visit	Target Day	Component of Renal Response/ Complete Remission (UPCR, eGFR)	eGFR (Provided by Lab)	Outcomes Research Day Ranges
Day 1 (Baseline)	1	1	1	1
Day 15	15	8 - 22		
Day 29	29	23 - 43		
Day 57	57	44 - 71		
Day 85	85	72 - 99		2 - 99
Day 113*	113	100 - 120	50 - 141	100 - 127
Day 128	128	121 - 134		
Day 141	141	135 - 155		
Day 169	169	156 - 183-	142 - 183	
Day 197	197	184 - 211	184 - 211	
Day 225*	225	212 - 239	212 - 239	
OLE period				
Day 253	253	240 - 267		
Day 281	281	268 - 295		
Day 309	309	296 - 323		
Day 337	337	324 - 351		
Day 365	365	352 - 379		
Day 393	393	380 - 407		

* Day 113 assessment for subjects continuing in Period 2, the upper inclusive limit of this window is the first infusion in Period 2 or 42 days after last dose in Period 1, whichever comes earlier. Day 113 assessment extends 42 days after last dose in Period 1 for subjects discontinuing during Period 1. Similarly, Day 225 assessment for subjects continuing in OLE, the upper inclusive limit of this window is the first infusion in OLE or 42 days after last dose in Period 2, whichever comes earlier. Assessments within 42 days after last dose in Period 2 are included for subjects discontinuing during Period 2.

Table 8.6-3: Day Ranges for Laboratory Assessments at Every Scheduled Visit During the Double-Blind Period and OLE Period

Visit	Target Day	Chemistry	CBC	Total Cholesterol and Triglycerides, fasting
Double-blind period				
Screening	**< 1**	**< 1**	**< 1**	**< 1**
Day 1 (Baseline)	1	1	1	1

Approved v2.0 930132602 2.0

Table 8.6-3: Day Ranges for Laboratory Assessments at Every Scheduled Visit During the Double-Blind Period and OLE Period

Visit	Target Day	Chemistry	CBC	Total Cholesterol and Triglycerides, fasting
Day 15	15	8 - 22		
Day 29	29	23 - 43	15- 57	
Day 57	57	44 - 71		28 - 56
Day 85	85	72 - 99	58 - 99	
Day 113*	113	100 - 141	100 - 197	57 - 197
OLE period				
Day 169	169	142 - 197		
Day 225	225	198 - 253		
Day 281	281	254 - 309	198 - 309	198 - 309

* Day 113 assessment for subjects continuing in OLE, the upper inclusive limit of this window is the first infusion in OLE or 42 days after last dose in double-blind period, whichever comes earlier. Assessments within 42 days after last dose in double-blind period are included for subjects discontinuing during double-blind period.

For subjects who completed Period 1 and entered Period 2 prior to the protocol revision:

Table 8.6-4: For Subjects who Completed Period 1 and Entered Period 2 prior to the Protocol Revision

Visit	Target Day	Chemistry	CBC	Total Cholesterol and Triglycerides, fasting
Double-blind (Period 1 and Period 2)				
Screening	< 1	< 1	< 1	< 1
Day 1 (Baseline)	1	1	1	1
Day 15	15	8 - 22		
Day 29	29	23 - 43	15 - 57	
Day 57	57	44 - 71		28 - 56
Day 85	85	72 - 99	58 - 99	
Day 113*	113	100 - 120	100 - 141	57 - 169
Day 128	128	121 - 134		
Day 141	141	135 - 155		
Day 169	169	156 - 183-	142 - 197	
Day 197	197	184 - 211		
Day 225*	225	212 - 253	198 - 309	170 - 309
OLE period				

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Table 8.6-4: For Subjects who Completed Period 1 and Entered Period 2 prior to the Protocol Revision

Visit	Target Day	Chemistry	CBC	Total Cholesterol and Triglycerides, fasting
Day 281	281	254 - 309		
Day 337	337	310 - 365		
Day 393	393	366 - 421	310 - 421	310 - 421

* Day 113 assessment for subjects continuing in Period 2, the upper inclusive limit of this window is the first infusion in Period 2 or 42 days after last dose in Period 1, whichever comes earlier. Day 113 assessment extends 42days after last dose in Period 1 for subjects discontinuing during Period 1. Similarly, Day 225 assessment for subjects continuing in OLE, the upper inclusive limit of this window is the first infusion in OLE or 42 days after last dose in Period 2, whichever comes earlier. Assessments within 42 days after last dose in Period 2 are included for subjects discontinuing during Period 2.

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Table 8.6-5: Day Ranges for Immunogenicity Assessments at Every Scheduled Visit During the Double -Blind Period and Follow-Up Period

Visit	Target Day	Immunogenicity Day Ranges*
Double-blind period		
Day 1 (Baseline)	1	≤ 1
Day 113	113	8 - 169*
Follow-up period		
Day 56	56	1 - 70
Day 84	84	71 - 126
Day 168	168	127 - 168

* For Day 113 assessment, the upper inclusive limit of this window is the first infusion in OLE or 56 days after last dose in double-blind period, whichever comes earlier.

For subjects who completed Period 1 and entered Period 2 prior to the protocol revision:

Table 8.6-6: For Subjects who Completed Period 1 and Entered Period 2 prior to the Protocol Revision

Visit	Target Day	Immunogenicity Day Ranges*
Double-blind period		
Day 1 (Baseline)	1	≤ 1
Day 113	113	8 - 169*
Day 225	225	170 - 281
Follow-up period		
Day 56	56	1 - 70
Day 84	84	71 - 126
Day 168	168	127 - 168

*For Day 113 assessment, the upper inclusive limit of this window is the first infusion in Period 2 or 56 days after last dose in Period 1, whichever comes earlier

If a subject has more than one visit where a measurement is recorded within a window, the measurement closest to the target day will be used. In case of two visits being equidistant from the target, the later measurement will be used in the analyses. Exceptions to these rules apply to immunogenicity, where the least favorable value (toward a positive response) in the window will be used.

For subjects who discontinue from study therapy prematurely, assessments performed after the last infusion of study drug will be included in the efficacy and safety data sets provided that these assessments are made within 42 and 56 days respectively of the last infusion.

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9 CONTENT OF REPORTS

The results of this study will be presented in a standard BMS Clinical Study Report (CSR). Prior to completion of the CSR an Initial Data Assessment will be prepared briefly identifying the key results and any unanticipated findings that are unusual for a study within this program. Prior to completion of the Initial Data Assessment, a meeting for the Initial Data Assessment of study results will be held after database lock and unblinding. Attendees at this meeting will review efficacy and safety summaries and listings and will identify key results that should be highlighted in the Initial Data Assessment and CSR.

At the end of the study, when all subjects complete the follow-up period or discontinue prematurely, a final closeout report will be prepared. The reports will be mainly presenting safety summaries based on the OLE and the cumulative period. It will include the following summaries and the associated listings indicated in the respective sections in this analysis plan:

- Subject Disposition.
- Exposure summaries presented in Section 7.4.
- Efficacy: Changes from baseline in UPCR and serum albumin.
- Adverse Events:
  - Serious adverse events (SAE).
  - AEs leading to study drug discontinuation.
  - AEs related to study drug.
  - Related events categorized by intensity.
  - Most common related AEs (reported in at least 2% of subjects in any treatment group).
  - AEs by intensity.
  - All AEs (serious or non-serious).
  - Most common (serious or non-serious) AEs (reported in at least 5% of subjects in any treatment group).
  - Serious adverse events and related serious adverse events with death as an outcome following EudraCT requirements.
  - Multiple AEs summaries including the required EudraCT summaries in Section 7.6.4.1 (based on cumulative abatacept safety period).
- Laboratory Summaries:
  - Laboratory abnormalities.
  - Shift tables.
- Vital Signs based on OLE period only.
- Immunogenicity.
- Pharmacokinetics.

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APPENDIX 1 DOCUMENT HISTORY

Table 9-1: Document History

Version	Statistician	Date	Notes/Revisions
1.0	[redacted]	16 January 2018	Original version
2.0	[redacted]	13 September 2018	Incorporates Protocol Amendment 2 - Period 2 is eliminated and the previous Period 1 is renamed as the double-blind period. - [redacted] - For subjects who completed Period 1 and entered Period 2 prior to the protocol revision, the Period 1 is analyzed as part of the double-blind, the Period 2 data are only listed. Period 2 data are not part of any summaries except for safety summaries at the end of the study on the cumulative abatacept safety period.

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APPENDIX 2 RELEVANT PROTOCOL DEVIATIONS

Pre Randomization:

- UPCR < 2.7 at screening.
- eGFR below the following level at screening:
  - 50 for subjects < 18 years (new Schwartz equation).
  - 50 for subjects ≥ 18 years (CKD-EPI equation).
- Body mass index (BMI): > 45 in subjects ≥ 18 years of age and ≥ 99% percentile for subjects < 18 years of age at screening.
- Hemoglobin (Hgb) < 7.0g/dl at screening.
- White Blood Count (WBC) < 2,000/mm3 (2 x 109/L) at screening.
- Platelets < 75,000/mm3 (75 x 109/L) at screening.
- Serum ALT or AST > 3 times upper limit of normal at screening.
- Subjects systemically using any of CS (low dose, prednisone or equivalent at doses ≤ 15mg/day), calcineurin inhibitors (cyclosporine and tacrolimus), MMF and MPA for treatment of TRNS (use for other medical indications [e.g. asthma] is allowed), satisfying any of the following:
  - Started using one of the above agents within 8 weeks of enrollment.
  - Not using the standard dose or
  - Have not been on stable dose for at least 4 weeks prior to randomization.

Post Randomization:

- FSGS or MCD diagnosis not confirmed by a pathology report.
- Use of prohibited medication:
  - Any systemic immunosuppressive or immunomodulator per protocol including, but not limited to cyclophosphamide, methotrexate, belimumab, azathioprine, leflunomide, rituximab, experimental therapies, everolimus, sirolimus, corticotropin injection gel (ACTH) or plasmapheresis.
  - Combined use of two or more renin-angiotensin system (RAS) inhibitors.
- Missed two or more doses of investigational product for any reason during double-blind period.

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APPENDIX 3 CLINICAL REPORTS CONTENT

Table 9-2: Safety Analysis by Period

	End of Double-Blind Period CSR	End of Study CSR	
	Double-Blind Period	Cumulative Abatacept Safety Period	OLE Period
Serious Adverse Events	X	X	X
AEs leading to study drug discontinuation	X	X	X
AEs related to study drug	X	X	X
Related events categorized by intensity	X	X	X
Most common related AEs (reported in at least 2% of subjects in any treatment group)	X	X	X
All AEs (serious or non-serious)	X	X	X
AEs by intensity	X	X	X
Most common (serious or non-serious) AEs (reported in at least 5% of subjects in any treatment group)	X	X	X
Serious adverse events and related serious adverse events with death as an outcome (EudraCT)		X	
AEs of Special Interest (Renal Related Events, Infections, Malignancy, Autoimmune Disorder, Infusional Reactions)	X	X	
Multiple Adverse Events	X	X	
EudraCT summaries - Exposure adjusted summaries		X	
Laboratory abnormalities	X	X	X
Laboratory Shift Tables	X	X	X
Mean Change from Baseline in Lab Parameters	X		
Vital Signs	X		X
Immunogenicity	X	X	

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[redacted]

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