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CLINICAL PROTOCOL IM140103

Open Label, Adaptive Design, Ascending, Multiple-Dose Study to Evaluate Safety and Efficacy of BMS-986004 in Adult Subjects with Primary Immune Thrombocytopenia (ITP)

Revised Protocol Number: 03
Incorporates Amendment 06

Study Director/ Medical Monitor
Marek Honczarenko, M.D., Ph.D.
[redacted]

protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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 Protocol03	08-Aug-2016	Incorporates all changes from Amendment 06
Global Amendment 06	08-Aug-2016	The purpose of this amendment is to add Long Term Extension (LTE) period to the study
Revised Protocol 02	02-Apr-2015	Incorporates all changes from Amendment 4
Amendment 04	02-Apr-2015	The purpose of this amendment is to add two follow-up visits, add Data Monitoring Committee, further clarify the Exploratory Biomarker Analyses section and update blood volume and duration of the study.
Revised Protocol 01	31-Jul-2014	Incorporates all changes from Amendment 2
Amendment 02	31-Jul-2014	The purpose of this amendment is to provide clarification and consistency on various sections in the protocol: for consistency, upper limit of age has been updated in some sections of the protocol to > 18 years old, early decision for dose escalation section has been updated and correction has been made to method of assigning subject identification section. In addition, some typographical edits, format updates and clarifications are made throughout the protocol.
Original Protocol	20-Jun-2014	Not applicable

SYNOPSIS

Clinical Protocol IM140103

Protocol Title: Open Label, Adaptive Design, Ascending, Multiple-Dose Study to Evaluate Safety and Efficacy of BMS-986004 in Adult Subjects with Primary Immune Thrombocytopenia (ITP)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Total of 40 subjects will be enrolled for the study, treated in dose panels of 10 subjects each. Four (4) dose panels are planned to be enrolled sequentially in an ascending manner, with dose intensity selected to provide increased levels of immunosuppression at steady state. Dose levels that are planned to be evaluated in this trial are expected to elicit a range of clinical response. Based on current preclinical projections, the doses range from 75 mg to 1500 mg every two weeks.

BMS-986004 will be administered once every 2 weeks as an IV infusion for a total of 7 doses. Subjects will receive investigational product on Day 1/Week 0, Week 2, Week 4, Week 6, Week 8, Week 10 and Week 12, for a total of 7 doses.

During the long term extension (LTE) period, BMS-986004 will be administered once every 2 weeks as an IV infusion for 24 weeks and during 2 Taper visits.

Study Phase: Phase 1b/2

Research Hypothesis: Because current study is an open label trial without placebo control, there is no formal research hypothesis to be statistically validated. The purpose of this study is to test if BMS-986004 will be effective in normalizing platelet counts in subjects with ITP, as well as to assess the safety, PK and immunogenicity of multiple doses of BMS-986004 in ITP subjects.

Primary Objectives:

- To assess the overall safety and tolerability of multiple doses of BMS-986004, when administered in subjects with chronic ITP.

Secondary objectives:

- To evaluate efficacy of BMS-986004 in the treatment of thrombocytopenia in subjects with chronic ITP, as measured by platelet response/complete response (R/CR) and other clinical parameters.
- To establish BMS-986004 dose response, as measured by platelet count and other clinical parameters.
- To measure the target engagement of BMS-986004 following multiple IV doses
- To assess the effect of BMS-986004 on markers associated with the risk of thromboembolism (TE) in the multiple dose setting
- To assess pharmacokinetics and immunogenicity of multiple doses of BMS-986004 in subjects with chronic ITP

[redacted]

Long Term Extension Period Objective:

To assess the long term clinical safety, tolerability and efficacy of BMS-986004.

Study Design: This is a Phase 1b/2, multicenter, open-label study to evaluate the safety, efficacy, dose response, and pharmacology (PK, target engagement and PD) of BMS-986004 in subjects with ITP.

The study will comprise a short-term period and a long-term extension (LTE) period.

The short-term period, is divided into three phases: Response Phase (6 weeks), Remission Phase (6 weeks) and Follow Up phase (8 weeks).

Screening evaluations to determine subject eligibility will be performed 21 days prior to study drug administration. The screening period may exceed 21 days but not more than 42 days total only after a discussion with and approval by the Study Director. If an extension in screening time is granted, the patient must still follow the platelet count rules for enrollment. The baseline platelet count determining enrollment eligibility will be based on the mean of two determinations taken within a week before the first dose. To be eligible for enrollment, platelet count needs to be less than 30,000/ mm^3 and show stable or declining trend. If the mean platelet count is between 30,000 - 35,000/ mm^3 the subject may be considered for enrollment on a case by case basis after discussion with and approval by the Study Director.

Following screening, a total of 40 evaluable subjects are planned for the study. Subjects are considered evaluable if they receive the first 4 doses of study drug and complete the required safety and efficacy evaluations at Day 50. Non-evaluable subjects will be replaced to maintain a count of 10 subjects in each dose panels, except subjects will not be replaced if they are discontinued from the study secondary to an adverse event unless the adverse event can be determined to be unrelated to treatment.

Subjects are treated in dose panels of 10 subjects each. Four (4) dose panels are planned to be enrolled sequentially in an ascending manner, with dose intensity selected to provide increased levels of immunosuppression at steady state. Dose levels (range from 75 mg to 1500 mg administered every two weeks) that are planned to be evaluated in this trial are expected to elicit a range of clinical response.

BMS-986004 will be administered once every 2 weeks as an IV infusion for a total of 7 doses. Four (4) doses will be administered during the Response Phase over a 6 week treatment period. The remaining 3 doses will be administered during the Remission Phase of the study over a 6 week treatment period. Subjects will receive investigational product on Day 1/Week 0, Week 2, Week 4, Week 6, Week 8, Week 10 and Week 12, for a total of 7 doses.

Each dose cohort will enroll 10 new subjects, starting with the respective dose level at Day1/Week 0, regardless of the number of subjects joining a dose cohort because of intra-subject dose escalation.

A new cohort may be opened to treat subjects at a dose lower than 75 mg if at least 6 subjects treated at the 75 mg cohort achieve platelet Response (R) (platelet count $\geq$ 30,000/mm^3 and at least 2-fold increase from the baseline count and absence of bleeding), at the end of response phase (Week 6). The new cohort would follow the same schedule as the other cohorts including intra-subject dose escalation.

The **Long-term extension (LTE)** period is optional and will include eligible subjects (defined as subjects from either cohort 3 or cohort 4 who complete 12 weeks (85-days) of treatment and who achieve a response as defined by at least a doubling of platelets from Short Term Day 1 baseline and a platelet count of $\geq$ 35,000/mm^3. If a subject has platelet counts close to a doubling of platelets and/or between 30,000-35,000 platelets/mm^3, the subject may be considered for the long term extension on a case by case basis, which will involve a review of data from the short term period and which will require approval by the Study Director.

Intra-subject dose escalation

Intra-subject dose escalation could occur after the subject has completed the Response Phase of the study. Subject will receive the next higher dose of BMS-986004 if clinically significant response has not been achieved based on measurement of platelet count on the last two consecutive counts performed at Day 43 and Day 50, and a favorable

safety profile is observed. Clinically significant response is defined as achieving platelet count ≥ 50,000/mm^3 with an increase of at least 20,000/mm^3 from baseline and absence of bleeding. Subject will then be dosed at the higher dose level for the remainder of the study (Remission Phase).

Dose frequency adjustment for responders exceeding 450,000/mm^3 (for non-splenectomized subjects) and 600,000/mm^3(for splenectomized subjects) platelet count

For both the short-term period and the long-term extension, in the event that platelet count exceeds 450,000/mm^3 for non-splenectomized subjects and 600,000/mm^3 for subjects who underwent splenectomy, in the absence of recent (administered within two weeks) rescue medication, as indicated by the two consecutive platelet count measurements, dosing of the BMS-986004 should be stopped. Subject will remain in the study and platelet counts will be then assessed based on the normal study visit schedule. Dosing of BMS-986004 could be reinitiated only after discussion between Study Director and Investigator if clinically appropriate and dictated by the medical judgment and subject's safety.

Dose escalation for dose panel and stopping rules

Decisions regarding dose escalation will be made based on the review of all cumulative safety information which includes, in general, the safety data through study Day 15 from the 10 subjects in the preceding lower dose cohort. If neither of the below stopping rules is present in dose panel, then dose escalation may proceed within the next higher dose level. However, escalation to the next higher cohort may occur when none of the stopping rules have been met and no less than 5 subjects in a cohort have been followed for at least 2 weeks under certain conditions as illustrated in the section of early decision of dose escalation for dose panel.

The stopping rules listed below will be used to determine whether it is safe to escalate to the next higher cohort. Dose escalation to the next planned dose will not proceed if any of the following criteria are met (Adverse event grading as defined by the Common Terminology Criteria for Adverse Events [CTCAE, Version 4.0]):

- Five or more subjects in a cohort have platelet counts >450,000/mm^3 for non-splenectomized subjects and >600,000/mm^3 for subjects who underwent splenectomy, and platelet count raise is not attributable to a rescue or concomitant therapy.
- Two or more subjects have serious adverse events in the same organ system (Grade 3 and above), that are determined to be related to study medication
- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the Study Team and the Investigator

If any of the above criteria are met within a dose level, the progression to a higher dose level will be put on hold and all safety data available across the study will be evaluated to estimate the risk of proceeding to the higher dose level. The review will include all of the subject(s) that experienced SAEs listed above. In addition, data set may include subjects from a dose panel, the entire dose panel, or if appropriate, all randomized subjects treated to date.

In addition, decision may be made following discussions between the Study Team and the Investigator to halt dose escalation for reasons not defined above, including but not limited to, observing a single serious adverse event in individual subjects, observing trends in a given dose panel and across dose panels, and/or it is determined that the limit of safety and/or tolerability has been reached.

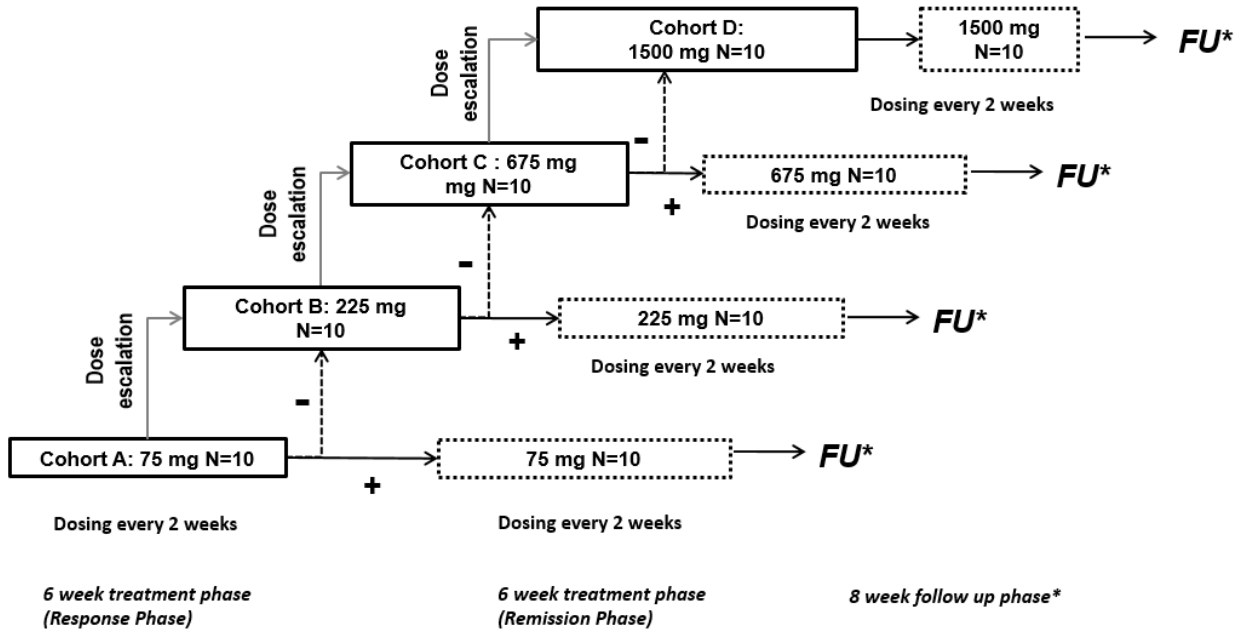
If dose escalation is stopped due to any of these findings, additional cohorts may receive the same or lower doses of the investigational compound.

At the time of dose escalation, dose levels of new cohorts may be adjusted to lower doses if the accumulated safety data so dictates.

Adaptive dose selection may be performed to adjust some pre-selected doses, e.g., the third or/and fourth cohort doses, using accumulated efficacy and dose or exposure data. Models based on response rate, such as but not limited to (Bayesian) logistic regression, (Bayesian) EMax model, may be utilized to predict a dose satisfying certain

efficacy criteria, which might be different from the standard. If there are enough responding subjects with multiple platelet measurements, changes of platelet count may be directly modeled by dose and study day to facilitate dose prediction. The selected dose for a cohort should not exceed the originally planned dose for that cohort, i.e., selected dose for cohort C should not be larger than 675mg and it should be at most 1500mg for cohort D.

Figure 3.1.3-1: Study Design Schematic: Short Term Period



**Will not apply to subjects entering LTE*

Figure 3.1.3-2: Study Design Schematic: Short Term Period

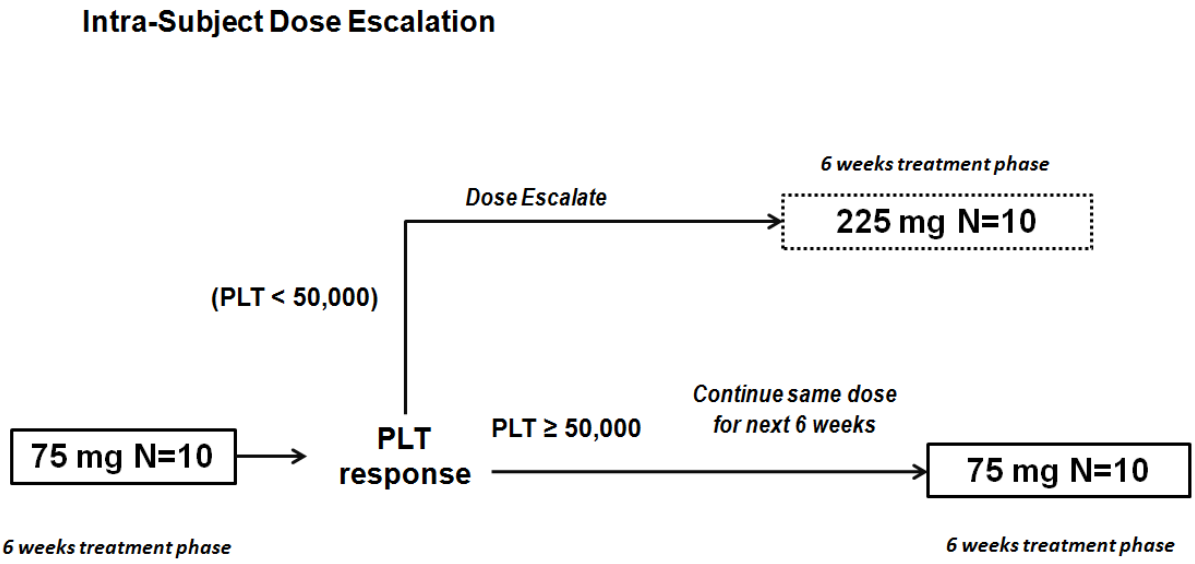
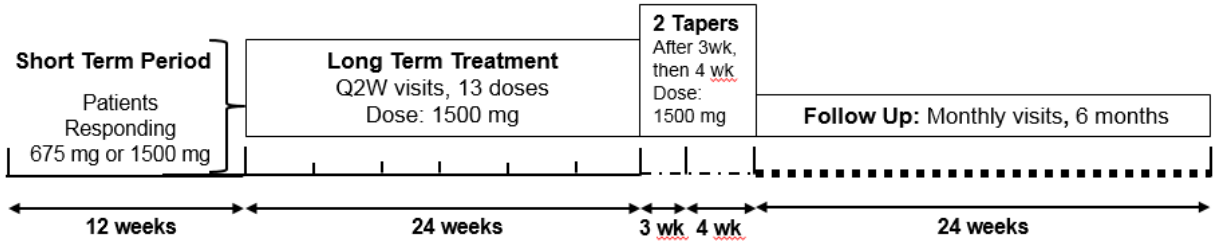


Figure 3.1.3-3: Study Design Schematic: Long term extension period



Early Decision of Dose escalation for dose panel

When a cohort is filled and a new subject is available to be treated, an early decision can be made on whether to open the next higher cohort if not all the subjects have completed the evaluation period. The early decision rule is based on controlling the probability of making a wrong early decision, called decision risk, to be at most 15%. Detailed information on deriving the decision risk is included in Appendix 1.

The early decision rule is based on the largest number of subjects who developed AE of interest which is drug-related SAE within the same organ system at grade 3 or higher. The early decision does not directly take into consideration other criteria as covered by the stopping rule. As such, its decision can be modified upon agreement from both investigators and sponsor. In case subjects are allocated to the higher cohort and at least one stopping rule as stated above is triggered toward the lower dose cohort when more events are observed at the lower cohort, decision will be made upon agreement from both investigators and sponsor after considering all safety data.

Three count numbers are used by the decision rule and are defined as follows.

- Titration-Dose Evaluable Subjects (nH): the number of subjects who are titrated and complete the evaluation period (2 weeks) starting from the first titration dose (on day 43).
- Start-Dose Evaluable Subjects (nL): the number of subjects who develop drug related SAE at grade 3 or higher or complete the evaluation period (2 weeks) from the first dose (on day 1) but haven't completed the 2 weeks evaluation period following the first titration dose (on day 43) if being titrated to a higher dose.

- Subjects with AE of Interest (k): the largest number of subjects who developed drug related SAE within the same organ system at grade 3 or higher, which could happen any time after the first dose of BMS-986004 till the decision making day. The value of k is allowed to be either 0 or 1. Note that it doesn't distinguish at which stage of treatment, prior to or post titration, that such AE happened.

Minimum Requirement for Cohort Escalation

A set of minimum safety requirement, as listed below, must be met in order to make an early decision.

- There must be at least 5 (nL+nH>=5) safety evaluable subjects (with safety data through study Day 15)
- A higher dose than the new cohort's start dose must be shown tolerated in the IM140-002 study.

Early Decision Rule:

If there is not AE of interest observed, the early decision rule is the same as the minimum requirements.

If there is one AE of interest observed, the early decision rule is shown in Table 3.1.4-1, where W represent wait, i.e., not enough evidence to enable dose panel escalation, and E represents escalate.

If there are least two subjects with AE of interest, stopping rule is triggered, and subject cannot be treated at the next higher cohort.

Study Population:

Male and Female subjects ≥ 18 years old with persistent or chronic ITP according to American Society of Hematology (ASH), with or without prior splenectomy guidelines will be eligible to participate in the study.

Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception for at least 4 weeks before dosing. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study medication

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

Study Drug for BMS-986004

Medication	Potency	IP/Non-IP
Lyophilized Cake of BMS-986004 for injection,190 mg/vial	50 mg/mL	IP

Study Assessments:

- Safety Outcome Measures: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance.
- Efficacy Assessments: Response (R) - platelet count ≥ 30,000/mm^3 and at least 2-fold increase from the baseline count and absence of bleeding, or Complete response (CR) - platelet count ≥ 100,000/mm^3 and absence of bleeding, or Overall response rate (ORR) defined as the proportion of subjects who achieved a CR or R.
- Pharmacokinetic Measures: Pharmacokinetic parameters (Cmax, Ctrough), will be derived from serum concentration versus time
- Biomarker Measures: CD40L receptor occupancy and free soluble CD40L will be measured to determine target engagement. Total soluble CD40L will be measured as a potential PD biomarker. Platelet-associated anti-

platelet antibody titers will be measured to explore possible effects on the primary pathogenic disease mechanism in ITP. Whole genome RNA profiling in the peripheral blood will be undertaken to explore CD40 pathway activation and to enumerate plasmablasts by gene expression. Peripheral blood mononuclear cells (PBMCs) will be purified from whole blood and analyzed by flow cytometry to determine if baseline leukocyte phenotypes inform on patient response to therapy and/or if leukocyte phenotypes are affected by drug therapy. Plasma molecules that may be associated with the disease or drug target pathway, including cytokines and chemokines, will be measured. The primary safety biomarkers, d-Dimer and Thrombin anti-Thrombin (TAT), will be monitored to evaluate risk of thromboembolism. Exploratory safety biomarkers to monitor possible effects on protective immunity will include immune cell enumeration by T, B, NK TruCount and phenotyping by flow cytometry.

Statistical Considerations:

Sample Size:

The number of subjects is not based on statistical power considerations. If 4 responders are observed out of 10 subjects at a dose level, a 90% confidence interval for the response rate is (0.15, 0.70).

Endpoints:

Primary endpoints of safety will be measured by AE, SAE, ECG, and laboratory abnormalities including safety biomarkers of d-Dimer and TAT.

Secondary endpoint of efficacy is measured by response rate. Secondary endpoints of PK include Cmax, CLT, AUC(TAU), Ctrough, AI_AUC, and AI_Cmax.

Exploratory endpoints include time to response, duration of response, and time to peak response.

Endpoints for the Long Term Extension Period

Primary endpoints of safety for the long-term extension period will be measured by AE, SAE, ECG, and laboratory abnormalities including safety biomarkers of d-Dimer and TAT.

The endpoint of efficacy is measured by response rate.

Analyses:

Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated. Prior therapies will be listed and summarized for each dose.

Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

Efficacy Analyses

Platelet count and change from baseline will be listed for all treated subjects. Response status will be reported together with time to respond, time to peak response, and duration of response. Response rate will be provided by cohort and treatment phase (response phase or remission phase).

Bleeding score will be listed for each subject. Bleeding events and the number of subjects experiencing any bleeding episode will be summarized by panel.

Pharmacokinetic Analyses

PK parameters will be summarized by treatment. Geometric means and coefficients of variation will be presented for Cmax (after dose 1 and dose 6), AUC(TAU), CLT, and Ctrough. Additionally, scatter plots of Cmax versus dose will be provided to assess the dependency on dose. A statistical analysis using a power model will be applied to assess dose proportionality.

Immunogenicity Analyses

Data from the assessment of immunogenicity markers (anti-BMS-986004 antibodies) will be listed by subjects. In addition, immunogenicity data will be listed separately for all the subjects who have at least one positive assay. Number and frequency of positive subjects will be summarized by dose. Definition of different positivity will be available in the study's Statistical Analysis Plan (SAP).

[redacted]

Other Analyses

Modeling analysis of PK of BMS-986004 will be conducted using a population approach as appropriate and reported separately from the clinical study report.

Long Term Extension Analyses

Similar and appropriate analyses (demographics and baseline characteristics, efficacy analyses, safety analyses, etc) will be conducted for the LTE analysis population when applicable. The analyses for the LTE analysis population are descriptive in nature.

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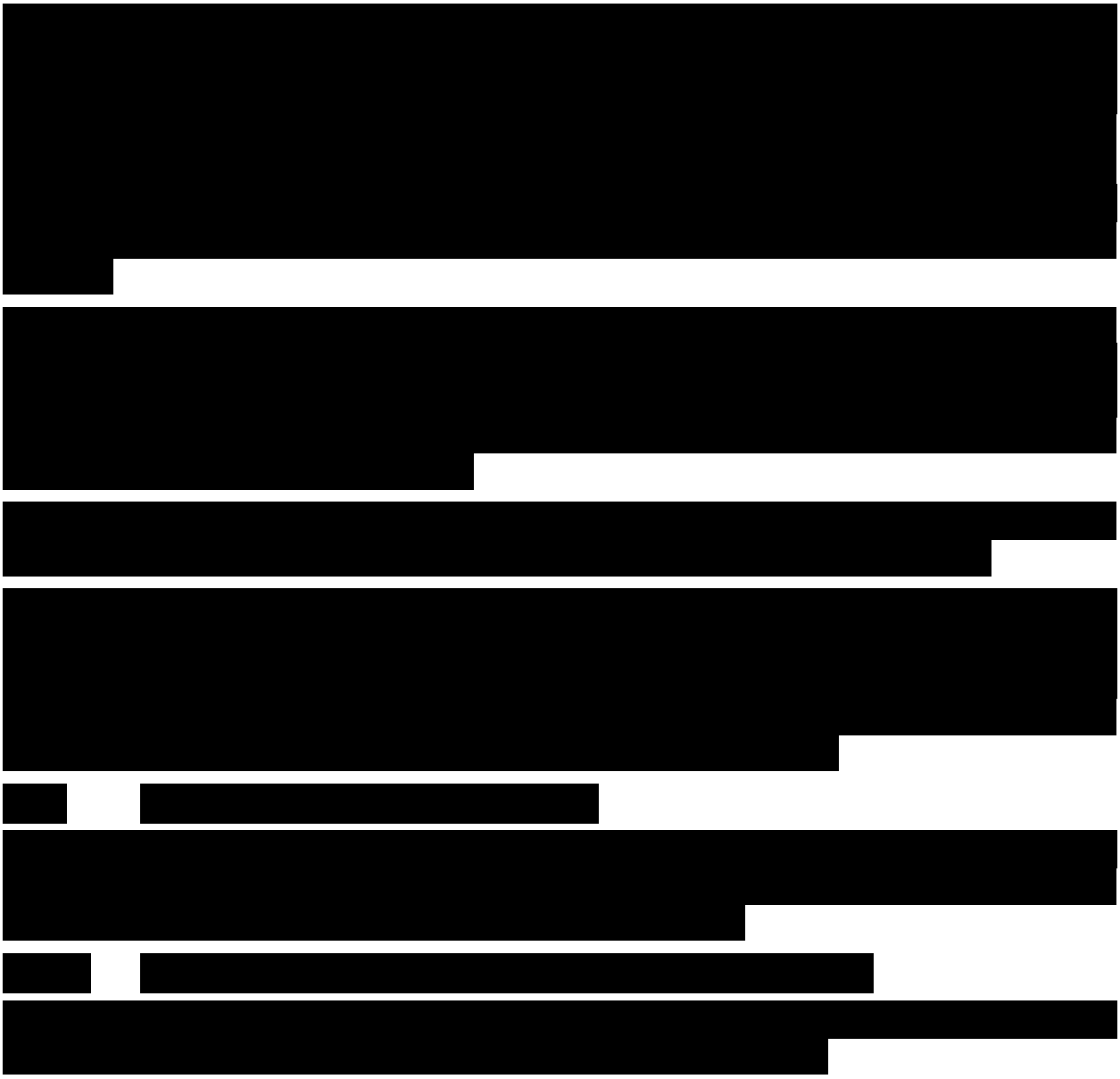


1.2 Research Hypothesis

Because current study is an open label trial without placebo control, there is no formal research hypothesis to be statistically validated. The purpose of this study is to test if BMS-986004 will be effective in normalizing platelet counts in subjects with ITP, as well as to assess the safety, PK and immunogenicity of multiple doses of BMS-986004 in ITP subjects.

1.3 Objectives(s)

1.3.1 Primary Objectives

- To assess the overall safety and tolerability of multiple doses of BMS-986004, when administered in subjects with chronic ITP.

1.3.2 Secondary Objectives

- To evaluate efficacy of BMS-986004 in the treatment of thrombocytopenia in subjects with chronic ITP, as measured by platelet response/complete response (R/CR) and other clinical parameters.
- To establish BMS-986004 dose response, as measured by platelet count and other clinical parameters.
- To measure the target engagement of BMS-986004 following multiple IV doses
- To assess the effect of BMS-986004 on markers associated with the risk of thromboembolism (TE) in the multiple dose setting
- To assess pharmacokinetics and immunogenicity of multiple doses of BMS-986004 in subjects with chronic ITP.

[redacted]

1.3.4 Long Term Extension Period Objective

- To assess the long term clinical safety, tolerability and efficacy of BMS-986004.

[redacted]

1.5 Overall Risk/Benefit Assessment

BMS-986004 is currently being evaluated in humans in a FIH SAD study which is being performed in healthy subjects to investigate the safety, tolerability, PK and PD of BMS-986004. To-date, BMS-986004 has not been studied in the ITP patient population and hence no efficacy or benefit data is established for this population. However, no clinically significant risks have been identified in the FIH study to-date and the safety margins in non-clinical studies are favorable which justifies careful evaluation of BMS-986004 in the ITP patient population. BMS-986004 could potentially provide clinical benefit by normalizing platelet counts in patients with ITP. This study will be initiating at a dose that has demonstrated relatively low immunosuppressive effect and has demonstrated no clinically significant risks in the FIH study**.** Dose panels will be enrolled sequentially in an ascending manner upon careful review of all cumulative safety information. Cumulative safety data will include all additional data that is available in the FIH study as well as data collected during the ITP study. To manage the safety risks, careful clinical and laboratory monitoring and criteria relative to dose escalation and stopping rules have been established for this protocol and include thresholds for serious infections, liver function tests, platelet counts above established thresholds, and other adverse events.

It is expected that ITP subjects will derive clinical benefit from BMS-986004 and help guide dose selection and design of future studies in the clinical development of BMS-986004. Primary efficacy assessments will include the proportion of patients achieving platelet count at least $\geq 30{,}000/mm^3$ and at least 2-fold increase from the baseline count and absence of bleeding.

The subjects planned to be enrolled in this study have limited therapeutic options since they have failed conventional therapies including immunosuppresive therapies, splenectomy and TPO mimetics. It is anticipated that efficacious doses of BMS-986004 will provide long lasting

therapeutic benefit for ITP patients. Ultimately, targeting CD40L may provide opportunity to inhibit autoimmune processes leading to thrombocytopenia and induce durable disease remission. It may thus offer novel therapeutic modality, currently not available to patients.

Given the lack of therapeutic options for ITP subjects who have failed all conventional therapies, BMS-986004 with its distinct mechanism of action and known safety profile appears to have a favorable Risk/Benefit profile.

Detailed information regarding the preclinical toxicology findings based on nonclinical studies in monkeys with BMS-986004 can be found in Section 1.5.2 and the Investigator Brochure.

1.5.1 Potential risks associated with BMS-986004

BMS-986004 is a dimeric anti-human CD40L VH dAb formatted with the Fc-tail from abatacept (modified IgG1) that is entirely inert in Fc effector function, especially in context of FcγRIIa. All data from nonclinical and NHP studies demonstrate that BMS-986004 exhibited no activity in various platelet activation assays, as well as in direct biacore binding analysis with FcγRIIa. Based on previous clinical experience with antibodies targeting costimulatory molecules and in particular with anti-CD40L antibodies, potential risks include: (1) increased probability of TE; (2) an increase in susceptibility to infection and (3) immunogenic potential including infusion reactions and formation of ADA. In addition to conventional safety assessments, general risk mitigation plan includes the following:

- To initiate dosing at 75 mg dose that has demonstrated favorable safety profile in healthy subjects in clinical evaluation. This dose is expected to elicit a sub-optimal response while ensuring very good safety profile.
- To utilize safety criteria for intra-subject dose escalation and safety criteria for dose-panel escalation and stopping rules.

1.5.2 Potential Thromboembolic Effect

To continue to mitigate the potential risk of thromboembolism, the following safety measures are included in ITP study:

- Close monitoring of any potential TE activities after BMS-986004 administration. In addition to observing clinical manifestations of both venous and arterial TE, the primary safety biomarkers, d-Dimer and Thrombin anti-Thrombin (TAT), will be monitored to evaluate risk of thromboembolism.
- TE related exclusion criteria have been added to the protocol; patients with history thromboembolic disease (including TIA, stroke, pulmonary embolism, deep vein thrombosis and thrombotic complications) or significant cardiovascular disease (including congestive heart failure, arrhythmias and other conditions known to increase risk of TE) are excluded.

1.5.3 Potential Immunosuppressive effect

As with any novel immunomodulating agent, there is a possibility of reducing normal immune function as a consequence of targeted CD40L blockade and therefore the following safety measures are included in the ITP study:

- Exclusion criteria relative to positive tests for hepatitis B and C, TB and HIV have been included in the protocol.
- Concurrent or recent use of systemic immune-modulating agents is prohibited or restricted to reduce potential risks associated with combinations of immune suppressors.
- Patients will be very closely followed and evaluated for any signs or symptoms of infection and complete blood count (CBC) differential counts, lymphocyte immunophenotyping, and measurement of serum Ig-levels (IgG, IgA and IgM) and CRP will be monitored frequently.

1.5.4 Risk of Infusion Reactions

As with any biological product, infusion reactions are a risk, even following a single dose. To reduce the risk of infusion reactions, patients will be closely monitored by trained personnel experienced with treatment of anaphylaxis and lesser infusion reactions. In addition, IV administration of study drug will not exceed infusion rate of 12.5 mg/min (Table 4-1). Furthermore, patients with history of any significant drug allergy or serious adverse reaction or hypersensitivity to any IV administered biologic will be excluded from the study.

1.5.5 Other

Risks from the PK, PD, and clinical safety phlebotomy procedures are standard and include discomfort at the injection site, bleeding, bruising, and rarely blood clot formation, infection, and fainting. Furthermore, rescue medications are permitted in the study for severe bleeding or wet purpura or if the investigator thinks the patients is at immediate risk. These medications are to be given with the intended purpose of raising platelet counts.

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 GCP 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 the 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(s) 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:

- Provide a copy of the consent form(s) 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.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.
- Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form(s) 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.
- 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.
- 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(s) must also include a statement that BMS and regulatory authorities have direct access to subject records.

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

Subjects in this trial will be invited to participate in a voluntary collection for future Medical Research. This collection is encouraged but not mandatory, and subjects who decline to participate will still be allowed to proceed with the rest of the study providing all other conditions are met.

This collection for future Medical Research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1b/2, multicenter, open-label study to evaluate the safety, efficacy, dose response, and pharmacology (PK, target engagement and PD) of BMS-986004 in subjects with ITP.

The study will comprise a short-term period and a long term extension (LTE) period.

The short-term period, is divided into three phases: Response Phase (6 weeks), Remission Phase (6 weeks) and Follow Up phase (8 weeks).

Screening evaluations to determine subject eligibility will be performed 21 days prior to study drug administration. The screening period may exceed 21 days but not more than 42 days total, and only after a discussion with and approval by the Study Director. If an extension in screening time is granted, the patient must still follow the platelet count rules for enrollment. The baseline platelet count determining enrollment eligibility will be based on the mean of two determinations taken within a week of the first dose. To be eligible for enrollment, platelet count needs to be less than 30,000/ mm^3 and show stable or declining trend. If the mean platelet count is between 30,000 - 35,000/ mm^3 the subject may be considered for enrollment on a case by case basis after discussion with and approval by the Study Director.

Following screening, a total of 40 evaluable subjects are planned for the study. Subjects are considered evaluable if they receive the first 4 doses of study drug and complete the required

safety and efficacy evaluations at Day 50. Non-evaluable subjects will be replaced to maintain a count of 10 subjects in each dose panels, except subjects will not be replaced if they are discontinued from the study secondary to an adverse event unless the adverse event can be determined to be unrelated to treatment.

Subjects are treated in dose panels of 10 subjects each. Four (4) dose panels are planned to be enrolled sequentially in an ascending manner, with dose intensity selected to provide increased levels of immunosuppression at steady state. Dose levels (range from 75 mg to 1500 mg administered every two weeks) that are planned to be evaluated in this trial are expected to elicit a range of clinical response.

BMS-986004 will be administered once every 2 weeks as an IV infusion for a total of 7 doses. Four (4) doses will be administered during the Response Phase over a 6 week treatment period. The remaining 3 doses will be administered during the Remission Phase of the study over a 6 week treatment period. Subjects will receive investigational product on Day 1/Week 0, Week 2, Week 4, Week 6, Week 8, Week 10 and Week 12, for a total of 7 doses.

Each dose cohort will enroll 10 new subjects, starting with the respective dose level at Day1/Week 0, regardless of the number of subjects joining a dose cohort because of intra-subject dose escalation.

A new cohort may be opened to treat subjects at a dose lower than 75 mg if at least 6 subjects treated at the 75 mg cohort achieve platelet Response (R) (platelet count $\geq 30{,}000/mm^3$ and at least 2-fold increase from the baseline count and absence of bleeding), at the end of response phase (Week 6). The new cohort would follow the same schedule as the other cohorts including intra-subject dose escalation.

The **long term extension (LTE)** period is optional and will include eligible subjects from either cohort 3 or cohort 4 who complete 12 weeks (85-days) of treatment and who achieve a response as defined by at least a doubling of platelets from Short Term Day 1 baseline and a platelet count of $\geq 35{,}000/mm^{3,}$ and absence of bleeding and any significant AEs as assessed on D71 or if more recent platelet count is available, based on the most recent platelet count or on the average of the two consecutive most recent platelet counts, whichever is higher. If a subject has platelet counts close to a doubling of platelets and/or between 30,000-35,000 platelets/mm^3 and absence of bleeding and any significant AEs as assessed on D71, the subject may be considered for the long term extension on a case by case basis, which will involve a review of data from the short term period and which will require approval by the Study Director.

3.1.1 Intra-subject dose escalation

Intra-subject dose escalation could occur after the subject has completed the Response Phase of the study. The intra-subject dose escalation decision will be based on review of the safety information and platelet count after 4 weeks of treatment. The decision to escalate dose for the subject will be made after evaluating platelet count at Day 50, 7 days after the 4th dose of BMS-986004 has been administered. Subject will receive the next higher dose of BMS-986004 if clinically significant response has not been achieved based on measurement of platelet count on

the last two consecutive counts performed at Day 43 and Day 50, and a favorable safety profile is observed (see Table 3.1.1-1). Clinically significant response is defined as achieving platelet count ≥ 50,000/mm^3 with an increase of at least 20,000/mm^3 from baseline and absence of bleeding. Subject will then be dosed at the higher dose level for the remainder of the study (Remission Phase), receiving investigational product at that dose on Week 8, Week 10 and Week 12. Active treatment period with BMS-986004, regardless of the dose, may not exceed 12 weeks for any individual subject.

Table 3.1.1-1: Dose Adjustment after Response Phase

Platelet Count at Day 43 and Day 50 (7 days after the 4th dose) (X /mm^3)	**Action**
< 50,000	Dose increase, as indicated by the next dose panel
≥ 50,000 with an increase of at least 20,000 from baseline	Dose remains constant on bi-weekly schedule

3.1.2 Dose frequency adjustment for responders exceeding 450,000/mm^3(for non-splenectomized subjects) and 600,000/mm^3(for splenectomized subjects) platelet count

For both the Short Term Study and the Long Term Extension plan, in the event that platelet count exceeds 450,000/mm^3 for non-splenectomized subjects and 600,000/mm^3 for subjects who underwent splenectomy, in the absence of recent (administered within two weeks) rescue medication, as indicated by the two consecutive platelet count measurements, dosing of the BMS-986004 should be stopped. Subject will remain in the study and platelet counts will be then assessed based on the normal study visit schedule. Dosing of BMS-986004 could be reinitiated only after discussion between Study Director and Investigator if clinically appropriate and dictated by the medical judgment and subject's safety.

3.1.3 Dose escalation for dose panel and stopping rules

Decisions regarding dose escalation will be made based on the review of all cumulative safety information which includes, in general, the safety data through study Day 15 from the 10 subjects in the preceding lower dose cohort. If neither of the below stopping rules is present in dose panel, then dose escalation may proceed within the next higher dose level. However, escalation to the next higher cohort may occur when none of the stopping rules have been met and no less than 5 subjects in a cohort have been followed for at least 2 weeks under certain conditions as illustrated in section 3.1.4.

The stopping rules listed below will be used to determine whether it is safe to escalate to the next higher cohort. Dose escalation to the next planned dose will not proceed if any of the following criteria are met (Adverse event grading as defined by the Common Terminology Criteria for Adverse Events [CTCAE, Version 4.0]):

- Five or more subjects in a cohort have platelet counts >450,000/mm^3 for non-splenectomized subjects and >600,000/mm^3 for subjects who underwent splenectomy, and platelet count raise is not attributable to a rescue or concomitant therapy.
- Two or more subjects have serious adverse events in the same organ system (Grade 3 and above), that are determined to be related to study medication,
- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the Study Team and the Investigator,

If any of the above criteria are met within a dose level, the progression to a higher dose level will be put on hold and all safety data available across the study will be evaluated to estimate the risk of proceeding to the higher dose level. The review will include all of the subject(s) that experienced SAEs listed above. In addition, data set may include subjects from a dose panel, the entire dose panel, or if appropriate, all randomized subjects treated to date.

In addition, decision may be made following discussions between the Study Team and the Investigator to halt dose escalation for reasons not defined above, including but not limited to, observing a single serious adverse event in individual subjects, observing trends in a given dose panel and across dose panels, and/or it is determined that the limit of safety and/or tolerability has been reached.

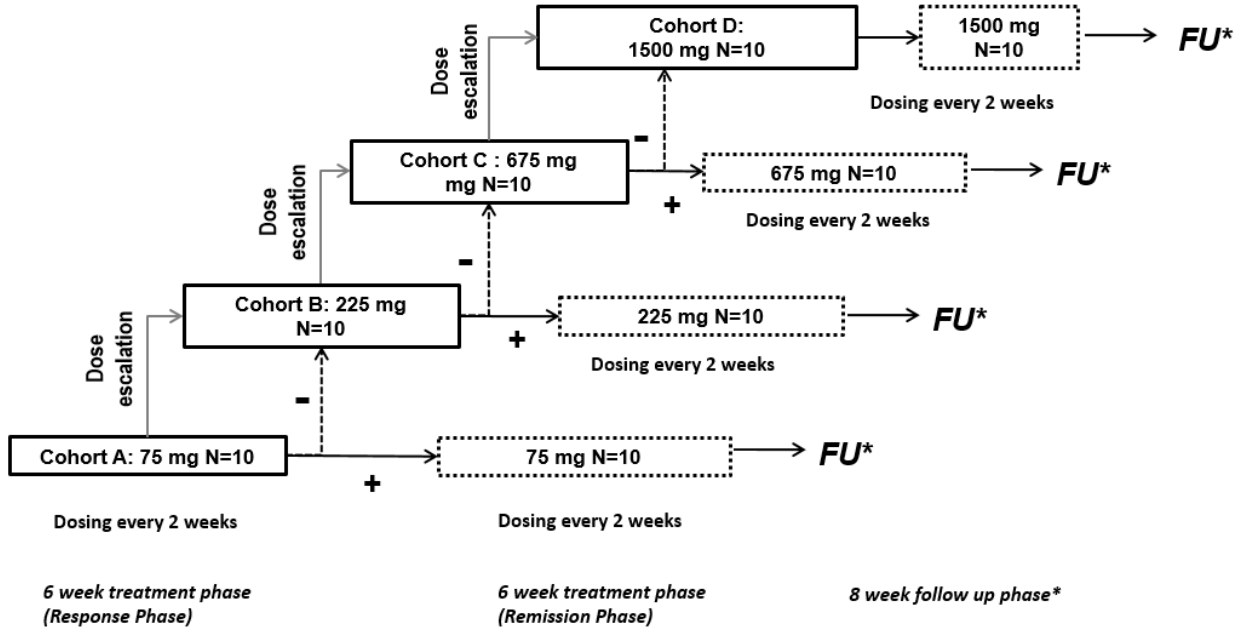
If dose escalation is stopped due to any of these findings, additional cohorts may receive the same or lower doses of the investigational compound.

At the time of dose escalation, dose levels of new cohorts may be adjusted to lower doses if the accumulated safety data so dictates.

Adaptive dose selection may be performed to adjust some pre-selected doses, e.g., the third or/and fourth cohort doses, using accumulated efficacy and dose or exposure data. Models based on response rate, such as but not limited to (Bayesian) logistic regression, (Bayesian) EMax, may be utilized to predict a dose satisfying certain efficacy criteria, which might be different from the standard. If there are enough responding subjects with multiple platelet measurements, changes of platelet count may be directly modeled by dose and study day to facilitate dose prediction. The selected dose for a cohort should not exceed the originally planned dose for that cohort, i.e., selected dose for cohort C should not be larger than 675mg and it should be at most 1500 mg for cohort D.

The study design schematic is presented in Figure 3.1.3-1.

Figure 3.1.3-1: Study Design Schematic: Short-term period



**Will not apply to subjects entering LTE*

Figure 3.1.3-2: Study Design Schematic: Short-term period

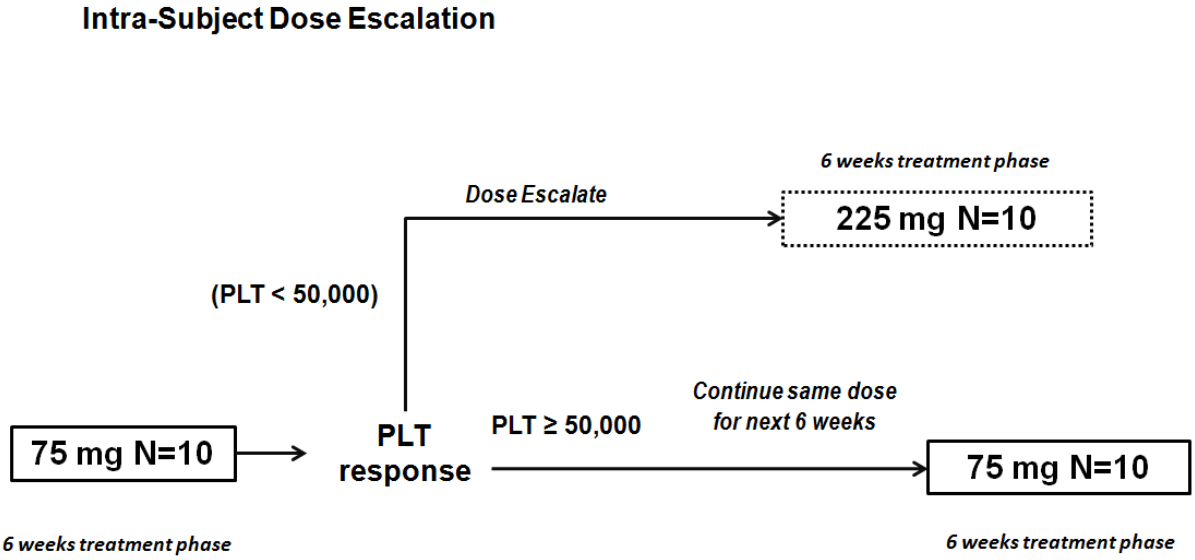
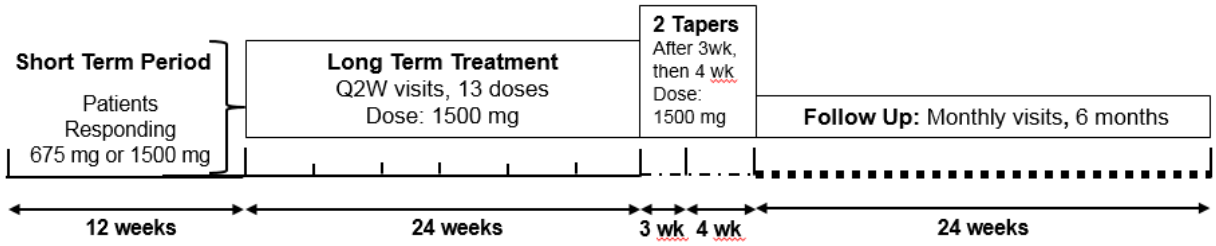


Figure 3.1.3-3: Study Design Schematic: Long term extension period



3.1.4 Early decision of dose escalation for dose panel

When a cohort is filled and a new subject is available to be treated, an early decision can be made on whether to open the next higher cohort if not all the subjects have completed the evaluation period. The early decision rule is based on controlling the probability of making a wrong early decision, called decision risk, to be at most 15%. Detailed information on deriving the decision risk is included in Appendix 1.

The early decision rule is based on the largest number of subjects who developed AE of interest which is drug-related SAE within the same organ system at grade 3 or higher. The early decision does not directly take into consideration other criteria as covered by the stopping rule. As such, its decision can be modified upon agreement from both investigators and sponsor. In case subjects are allocated to the higher cohort and at least one stopping rule as stated above is triggered toward the lower dose cohort when more events are observed at the lower cohort, decision will be made upon agreement from both investigators and sponsor after considering all safety data.

Three count numbers are used by the decision rule and are defined as follows.

- Titration-Dose Evaluable Subjects (nH): the number of subjects who are titrated and complete the evaluation period (2 weeks) starting from the first titration dose (on day 43).
- Start-Dose Evaluable Subjects (nL): the number of subjects who develop drug related SAE at grade 3 or higher or complete the evaluation period (2 weeks) from the first dose (on day 1) but haven't completed the 2 weeks evaluation period following the first titration dose (on day 43) if being titrated to a higher dose.
- Subjects with AE of Interest (k): the largest number of subjects who developed drug-related SAE within the same organ system at grade 3 or higher, which could happen any time after the first dose of BMS-986004 till the decision making day. The value of k is allowed to be either 0 or 1. Note that it doesn't distinguish at which stage of treatment, prior to or post titration, that such AE happened.

Minimum Requirement for Cohort Escalation

A set of minimum safety requirement, as listed below, must be met in order to make an early decision.

- There must be at least 5 (nL+nH>=5) safety evaluable subjects (with safety data through study Day 15)
- A higher dose than the new cohort's start dose must be shown tolerated in the IM140-002 study.

Early Decision Rule:

If there is not AE of interest observed, the early decision rule is the same the minimum requirements.

If there is one AE of interest observed, the early decision rule is shown below in Table 3.1.4-1, where W represent wait, i.e., not enough evidence to enable dose panel escalation, and E represents escalate.

If there are least two subjects with AE of interest, stopping rule is triggered, and subject cannot be treated at the next higher cohort.

Table 3.1.4-1: Decision Rule for Early Panel Escalation When There Is One Subject with AE of Interest (k=1)

Titration-Dose Evaluable Subjects (nH)[a]	Start-Dose Evaluable Subjects (nL)[b]								
	1	2	3	4	5	6	7	8	9
0	W[c]	W	W	W	W	W	W	W	E[d]
1	W	W	W	W	W	W	E	E	
2	W	W	W	W	W	E	E		
3	W	W	W	W	E	E			
4	W	W	W	E	E				
5	W	W	E	E					
6	W	E	E						
7	E	E							
8	E								

[a] the number of subjects who are titrated and complete the evaluation period (2 weeks) starting from the titration's first dose.

[b] the number of subjects who develop AE of interest or complete the evaluation period (2 weeks) from the first dose but could not be classified into the "Titration-Dose Evaluable Subjects" group.

[c] W: Wait

[d] E: Escalate

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Subjects will be closely monitored for adverse events throughout the study. Blood samples will be collected for up to 336 hours after study drug administration for pharmacokinetic (PK)

analysis. Approximately 910 mL of blood will be drawn from each subject during the short-term period (~162 days including Screening and follow up period). Less than 500mL of blood will be drawn during the LTE period.

The approximate duration of the short-term period is 23 weeks (approximately 162 Days). This includes a 21 day screening period, a 12 week treatment period and a 2 month follow up period. An extended screening period (up to 42 days) is possible but only with the approval of the Study Director, and all other eligibility rules and screening rules must still be met. If subject is eligible and opts to continue into LTE, the 2 month follow-up period will not be performed after the short-term period is completed and the subject will enter the LTE directly. If the subject opts not to enter the LTE, then a 2 month follow-up visit will be completed.

The approximate duration of the long term extension is approximately 55 weeks. This includes 24 weeks of every other week dosing of 1500 mg, two-taper visits (7 weeks total), and a 24 week follow-up period (no treatment).

3.1.5 Long Term Extension

The long term extension (LTE) period is optional and will include eligible subjects who have completed Day 85 (12-weeks of treatment) and who have consented to participate. Eligible subjects [platelet count $\geq$ 35,000/mm^3 with at least a doubling of platelets from short-term baseline, or patients approved by the Study Director on a case by case basis who are close to a two-fold increase from short term baseline and/or have 30,000-35,000 /mm^3 platelets and absence of bleeding and any significant AEs as assessed on D71 or if more recent platelet count is available, based on the most recent platelet count or on the average of the two consecutive most recent platelet counts, whichever is higher], will receive a 1500 mg dose every other week for 24 weeks. Subjects who complete 24 weeks LTE will receive a taper regimen consisting of 1500mg dose on Day 190 and a final dose on Day 218 before entering the 24 week follow-up period (no treatment).

A separate informed consent must be signed by the patients to enter the LTE period.

3.2 Post Study Access to Therapy

At the end of the 12 week treatment study period, all eligible subjects in Cohort 3 and 4 will have the option to continue into the LTE period. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the short-term period of the study, the following criteria MUST be met prior to dosing on Day 1 of the Short Term Period. No exceptions will be granted.

For entry into the long term extension, subjects must remain on study medication, complete the short-term period (up to 12 weeks of treatment), qualify per guidance for an increase in platelet count and safety, and sign a new informed consent.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) The signed written informed consent form must be obtained from the subject in accordance with requirement of the study center's IRB, prior to initiation of any protocol required procedures.

2. Target Population

a) Adults (≥18 years old), diagnosed with persistent or chronic ITP according to American Society of Hematology (ASH)/British Committee for Standards in Haematology (BCSH) guidelines, with or without prior splenectomy.

b) Subjects previously received one or more prior ITP therapies and must have had initially responded to at least one prior ITP therapy. Previous treatments for ITP include but are not limited to TPO mimetics/agonists, corticosteroids, immunoglobulins, azathioprine, danazol, cyclophosphamide and/or rituximab.

c) Subjects have had relapsed ITP i.e. failed to achieve a sustained (for more than 3 month) platelet count ≥ 50,000/mm^3 to at least one prior ITP therapy.

d) The platelet count (calculated from the mean of the 2 counts taken within a week of the first dose, during the screening and pre-treatment periods) must be less than 30,000/mm^3 with no count greater than 35,000/mm^3. If the mean of the counts is between 30,000-35,000/mm^3, the subject may still be eligible but enrollment will be on a case by case basis and require approval by the Study Director.

e) 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.

f) A complete blood count must be within the reference range (including white blood count [WBC] differential not indicative of a disorder other than ITP), with the following exceptions:

   i) subjects with hemoglobin levels between 9 g/dL for females and 10 g/dL for males and the lower limit of normal (LLN) are eligible for inclusion, if anemia was clearly attributable to ITP (excessive blood loss);

   ii) absolute neutrophil count (ANC) greater than or equal to 1500/μL (elevated WBC/ANC due to corticosteroid treatment is acceptable)

g) Prothrombin Time/International Normalized Ratio (PT/INR) and activated partial thromboplastin time (aPTT) must have been within 80% to 120% of the normal range with no known hypercoagulable state.

h) The following clinical chemistries MUST NOT exceed 2 times the normal reference range: ALT, AST, alkaline phosphatase, and bilirubin >1.5 times upper limit normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)

i) Albumin must be within 80 to 120% of normal range

3. Age and Reproductive Status

a) Males and Females, ≥ 18 years old.

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) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (84 days) plus 5 half-lives of study drug (20 days) plus 30 days (duration of ovulatory cycle) for a total of 134 days post-treatment completion.

e) 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 (84 days) plus 5 half-lives of the study drug (20 days) plus 90 days (duration of sperm turnover) for a total of 194 days post-treatment completion.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still 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 WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

  *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Secondary immune thrombocytopenia e.g. due to SLE, CLL, CVID, APS

b) Drug induced thrombocytopenia

c) History of MDS (Myelodysplastic Syndrome).

d) Subject exhibit an identifiable alternative cause of their thrombocytopenia, such as splenomegaly, family thrombocytopenia, bacteraemia, sepsis or active infection requiring or not therapy.

2. Medical History and Concurrent Diseases

a) Any severe medical condition (cardiac, hepatic or renal disorder) other than chronic ITP. (Note: "Severe" is defined as Grade 3 and above as a rule according to guidelines described by the Common Terminology Criteria for Adverse Events, Version 4.03)

b) History of thromboembolic disease within the last 24 month (e.g., transient ischemic attack [TIA], stroke [CVA], pulmonary embolism [PE]), history of deep vein thrombosis (DVT).

c) Subjects with a history of significant cardiovascular disease (e.g., congestive heart failure [CHF] New York Heart Association Grade III/IV, arrhythmia known to increase the risk of thromboembolic events [e.g., atrial fibrillation], subjects with a QT interval corrected for heart rate of > 450 msec, angina, coronary artery stent placement, angioplasty, coronary artery bypass grafting)

d) Inability to be venipunctured and/or tolerate venous access.

e) Any other sound medical, psychiatric and/or social reason as determined by the investigator.

f) Subject treated with drugs that affect platelet function, (e.g. aspirin and/or NSAIDs) or anti-coagulants for more than 3 consecutive days within 2 weeks of the study start.

3. Physical and Laboratory Test Findings

a) An abnormal (positive) direct Coombs' test in patients who have not received IVIg or IV anti-D immunoglobulin within 30 days.

b) Positive blood screen for Hepatitis C antibody

c) Positive blood screen for HIV-1, -2 antibodies or p24 antigen (HIV viral RNA test may be conducted if the investigator deems necessary).

d) Positive test for active Hepatitis B infection as indicated by screening using Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (anti-HBs) and Hepatitis B core antibody (anti-HBc) (See Appendix 3).

e) Positive quantiFERON® TB test.

f) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population.

4. Allergies and Adverse Drug Reaction

a) History of serious adverse reaction or hypersensitivity to IV administered biological therapeutic.

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

5. Other Exclusion Criteria

a) Prior exposure to BMS-986004

b) Prisoners or subjects who are involuntarily incarcerated

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

d) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4.

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 in the absence of other biological or physiological causes. In addition, Females under the age of 55 years must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/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. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can considered postmenopausal

- 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.

3.3.4 Criteria for Long Term extension

Subjects who enter the short-term period according to the eligibility criteria outlined in Sections 3.3.1 and 3.3.2, and who complete 12 weeks on study medication and at Short Term Day 71 or if more recent platelet count is available, based on the most recent platelet count or on the average of the two most recent platelet counts, whichever is higher have ≥ 35,000 platelets/mm^3 and at

least a doubling of platelets compared to Short Term Day 1 baseline, are eligible for participation in the LTE period. If a subject has completed 12 weeks on study medication and on Day 71 or if more recent platelet count is available, based on the most recent platelet count or on the average of the two consecutive most recent platelet counts, whichever is higher platelet counts are close to a doubling of platelets and/or between 30,000-35,000 platelets/mm^3 and there is an absence of bleeding and any significant AEs, the subject may be considered for the long term extension on a case by case basis, which will involve a review of data from the short term period and which will require approval by the Study Director.

A separate informed consent must be signed to enter the LTE period.

[redacted]

[redacted]

[redacted]

sponsor, subjects will continue with regularly scheduled visits

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 and/or participation in the study
- 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)
- An opportunistic or systemic fungal, viral or bacterial infection of a serious nature, that in the opinion of the investigator or medical monitor, contraindicates further dosing of investigational product after resolution.
- Malignancy, except basal cell carcinoma.
- Severe hypersensitivity reaction (anaphylaxis) to the study drug, Grade 3 or higher

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. 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 investigational product 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).

Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost-to-follow-up and any evaluations should resume according to the protocol.

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 Follow up

In this study, increase in platelet count is a key endpoint of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

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

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

BMS-986004 will be administered as a solution intravenously. Table 4-1 below indicates the total dose and number of vials per dose for each.

Table 4-1: Treatment Administration

Treatment	Total Daily Dose	Volume of Reconstituted 50 mg/mL BMS-986004	Number of BMS-986004 Vials	Prime Filter	Infusion Volume (mL)	Infusion Time (min)	Rate (mg/min)
1	75 mg IV	3 mL	1	YES	50	120	0.625
2	225 mg IV	4.5 mL	2	NO	100	120	1.875
3	675 mg IV	13.5 mL	4	NO	100	120	5.625
4	1500 mg IV	30 mL	8	NO	100	120	12.500

Table 4-2: Treatment Administration During Long Term Extension

Total Daily Dose	Volume of Reconstituted 50 mg/mL BMS-986004	Number of BMS-986004 Vials	Prime Filter	Infusion Volume (mL)	Infusion Time (min)	Rate (mg/min)
1500 mg IV	30 mL	8	NO	100	120	12.500

The study drug should be dispensed by the pharmacist or qualified designee and administered as an infusion using an infusion pump. Do not ever administer study drug by intravenous push (IVP) or bolus injection. A physician must be present at the infusion site during all administrations of study drug.

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be monitored before infusion (at anytime the day of dosing, prior to infusion), approximately every 15 minutes during infusion, at the end of the infusion (within 10 minutes after the infusion has stopped), and approximately every 30 minutes after completion of the infusion until stable, as judged by the investigator. If an anaphylactoid-like infusion reaction or anaphylactic reaction occurs, vital signs will be taken more frequently, as warranted by the severity of the reaction. Blood pressure and heart rate will also be taken prior to discharge from the site on visits in which study drug is administered.

Subjects should not be premedicated unless they have had a prior infusion reaction, since the primary objective of this study is to evaluate the expected frequency of safety events and tolerability of the study drug. However, after a reaction determined to be an infusion reaction has been documented, the investigator may elect to administer prophylactically an anti-histamine or Tylenol for the comfort and safety of the subject prior to subsequent infusions.

Product description and storage information is described in Table 4-3.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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.

In this protocol, investigational product is: BMS-986004 Injection. BMS-986004 is a clear to slightly opalescent, colorless to pale yellow solution; may contain particulate matter upon visual inspection. The drug product is a preservative free, ready to use solution contained in a 10 cc vial with 20 mm opening, Type I flint glass, 1-panel, open label.

Each vial of drug product contains the labeled amount of BMS-986004, 190 mg/vial (50 mg/mL) in 10 mM Sodium Phosphate, pH 6.5, 25 mM Arginine HCl, 250 mM Sucrose. A 13% overfill is included in each vial to account for vial, needle syringe (VNS) holdup. This drug product can be used for intravenous administration only

4.2 Non-investigational Product

Not Applicable.

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).

Preparation for Intravenous Use

Dilution of BMS-986004 Injection for IV use must be performed using sterile disposable syringes. Prior to IV administration, BMS-986004 Injection is diluted with 0.9% Sodium Chloride Injection (NS) to prepare dosing solutions with BMS-986004 concentrations ranging from 1.5 to 15 mg/mL. The product is to be infused over 2 hours for each panel, using a volumetric pump at the protocol specific dose(s) and rate(s) through the IV infusion set as indicated in Table 4-1. Care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain anti-microbial preservatives or bacteriostatic agents.

BMS-986004 Injection should be stored refrigerated at 2° - 8°C (36° - 46°) with protection from light. After withdrawal into an appropriate sized syringe and dilution with NS (in the concentration range of 1.5 to 15 mg/mL), the product must be administered intravenously within two hours. The diluted BMS-986004 solutions may be stored in PVC, IV bags for up to 24 hours at refrigerated and protected from light, (2° - 8°C) or up to 4 hours (which includes the infusion time of two hours) at room temperature (15° - 25°C) and ambient lighting conditions. Regardless of the storage condition, the BMS-986004 infusion must be completed within 24 hours after transfer of the reconstituted BMS-986004 solution to an infusion container and dilution in normal saline.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets. Partially used or empty vials of BMS-986004 Injection should be discarded as per the site procedures

4.4 Method of Assigning Subject Identification

During the Screening visit, the investigative site will call into the enrollment option of the Interactive Voice Response System (IVRS) designated by BMS for assignment of a 5-digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, eg, 00001, 00002, 00003.... 00010. The patient identification number (PID) will ultimately be comprised of the site number and subject number. For example, the first subject screened (ie, enrolled) at site number 1, will have a PID of 0001 00001.

Enrolled subjects meeting all eligibility criteria will be assigned to a dose cohort. Specific instructions regarding enrollment and dose cohort assignment will be provided to the investigational sites in their training materials.

Specific instructions for using IVRS will be provided to the investigational sites in a separate document.

Subjects will not be replaced if they are discontinued from the study secondary to an adverse event unless the adverse event can be determined to be unrelated to treatment. The replacement subject will receive the same treatment as the subject being replaced.

4.5 Selection and Timing of Dose for Each Subject

Dose escalation and modifications will be guided by the approach described in Section 3.1.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance. After administration of BMS-986004, an examination of the injection site is required.

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 BMS 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 BMS 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.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2 and Table 5.1-3

Table 5.1-1: Screening Procedural Outline (IM140103)

Procedure	Screening Visit	Day -8 Visit	Day -1 Visit	Notes
Eligibility Assessments				
Informed Consent	X			A subject is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X	X	X	
Medical History	X	X	X	Include any toxicities or allergy related to previous treatments.
Safety Assessments				
Physical Examination (PE)	X		X	If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and predose evaluation.
Physical Measurements	X		X	Includes height, weight, and BMI.
Vital Signs	X	X	X	Includes body temperature, respiratory rate, seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Electrocardiogram (ECGs)	X			ECGs should be recorded after the subject has been supine for at least 5 minutes.
Laboratory Tests	X	X	X	Includes blood and urine samples. Platelet count included in this test. Eligibility requires an average of the screening, D-1 and Predose platelet counts to be in accordance with inclusion criteria 2d. (Hematology, Serum Chemistry, Urinalysis)
Serology	X			To include Hepatitis C antibody, Hepatitis B surface antigen (Ag), Hepatitis B anti-surface Ag antibody, Hepatitis B anti-core Ag antibody, HIV-1, HIV-2 antibody. Results must be available prior to Day 1 dosing.
Urine Drug Screen	X			7-panel UDS
Direct Coomb's	X			
Pregnancy Test/FSH	X	X	X	For women only (urine or serum)
QuantiFERON Test	X			Unless documented negative test was performed within 6 months of screening
ITP-BAT	X	X	X	

Table 5.1-1: Screening Procedural Outline (IM140103)

Procedure	Screening Visit	Day -8 Visit	Day -1 Visit	Notes
Prothrombin Time (PT)	X			Screen for hypercoagulable state; also known as International Normalized Ratio (INR)
Activated Partial Thromboplastin Time (aPTT)	X			Screen for hypercoagulable state; must be within 80% to 120% of the normal range
Exploratory PD Biomarker Assessment				
Whole Blood Gene Expression			X	Whole blood sample will be collected to provide a double baseline for enrolled patients and control ITP B cell repertoire data from patients who do not enroll (screening sample only)
Plasma Soluble Free CD40L Level			X	See Section 5.6
Plasma Soluble Total CD40L Level			X	See Section 5.6
Platelet-Associated Anti-platelet Antibodies (WB)		X		See Section 5.6
Platelet Ag-specific B cells by ELISPOT assay (WB)		X		See Section 5.6
B cell Repertoire Analysis (WB)	X		X	See Section 5.6
Immune Cell Counts (T, B, and NK) and Phenotypes (WB)		X		See Section 5.6
Adverse Event Reporting				
Monitor for Serious Adverse Events	X	X	X	All SAEs must be collected that occur during the screening period and within 3 months of discontinuation of dosing.

Table 5.1-2: On Treatment Procedural Outline (IM140103)

Procedure	D 1	D 2	D 4	D 8	D 15	D 29	D 43	D 50	D 57	D 71	D 72, 75, and 78	D 85 / ET	FU1 (D99)[a]	FU2 (D113)[a]	FU3 (D127)[a]	FU4 (D141)[a]	Notes
Safety Assessments																	
Physical Examination (PE)	X											X					
Physical Measurements	X				X	X	X		X	X		X	X	X		X	Weight only
Vital Signs	X	X	X	X	X	X	X		X	X		X	X	X	X	X	See note in screening procedures.
Electrocardiogram (ECGs)	X									X		X					See note in screening procedures.
Laboratory Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See note in screening procedures and Section 5.3.2. Pre-dose on Day 1. Platelet count included in this test as an efficacy parameter. (Hematology, Serum Chemistry, and Urinalysis)
Pregnancy Test	X								X	X		X	X	X		X	For women only (urine or serum)
ITP-BAT (SMOG Score)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Subjects will be graded according to the ITP-BAT - Bleeding Assessment Tool
Adverse Event Reporting																	
Monitor for Non-Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Monitor for	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See note in screening

Table 5.1-2: On Treatment Procedural Outline (IM140103)

Procedure	D 1	D 2	D 4	D 8	D 15	D 29	D 43	D 50	D 57	D 71	D 72, 75, and 78	D 85 / ET	FU1 (D99)[a]	FU2 (D113)[a]	FU3 (D127)[a]	FU4 (D141)[a]	Notes
Serious Adverse Events																	procedures.
Pharmacokinetic (PK) Assessments																	
Serial Blood PK Sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 5.5.
Immunogenicity Sampling	X				X	X	X		X	X		X	X	X	X	X	See Section 5.5
Exploratory PD Biomarker Assessments																	
CD40L Receptor Occupancy (WB)	X	X			X		X			X		X	X	X	X	X	See Section 5.6. On Dosing days Receptor Occupancy samples must be collected prior to dosing.
Whole Blood Gene Expression				X		X			X		X*			X	X		See Section 5.6. (* day 78 only)
Plasma Soluble Free CD40L Level				X		X			X	X		X	X	X	X	X	See Section 5.6.
Plasma Soluble Total CD40L Level				X		X			X	X		X	X	X	X	X	See Section 5.6.
Platelet-Associated Anti-platelet Antibodies (WB)								X			X*		X				See Section 5.6. (* day 72 only)

Table 5.1-2: On Treatment Procedural Outline (IM140103)

Procedure	D 1	D 2	D 4	D 8	D 15	D 29	D 43	D 50	D 57	D 71	D 72, 75, and 78	D 85 / ET	FU1 (D99)[a]	FU2 (D113)[a]	FU3 (D127)[a]	FU4 (D141)[a]	Notes
Platelet Ag-specific B cells by ELISPOT assay (WB)								X			X*		X				See Section 5.6 (* day 72 only)
B cell Repertoire Analysis (WB)												X					See Section 5.6
Whole blood for PBMC isolation	X				X		X					X					See Section 5.7
Plasma for cytokine and chemokines	X				X		X					X					See Section 5.6
Primary Safety (TE) Biomarker Assessments																	
Plasma d-Dimer	X	X	X	X	X	X	X	X	X	X	X*	X	X	X	X	X	See Section 5.6. (* day 78 only)
Plasma Thrombin Anti-thrombin (TAT)	X	X	X	X	X	X	X	X	X	X	X*	X	X	X	X	X	See Section 5.6. (* day 78 only)
Serum Troponin I	X	X	X	X	X	X	X	X	X	X	X*	X	X	X	X	X	See Section 5.6. (* day 78 only)
Exploratory Safety Biomarker Assessments																	
C-reactive Protein (CRP)	X		X	X	X	X	X	X	X	X	X*	X	X	X	X	X	See Section 5.6. (* day 78 only)
Immunoglobulin (IgM, IgG, IgA)	X		X	X	X	X	X	X	X	X	X*	X	X	X	X	X	See Section 5.6. (* day 78 only)

Table 5.1-2: On Treatment Procedural Outline (IM140103)

Procedure	D 1	D 2	D 4	D 8	D 15	D 29	D 43	D 50	D 57	D 71	D 72, 75, and 78	D 85 / ET	FU1 (D99)[a]	FU2 (D113)[a]	FU3 (D127)[a]	FU4 (D141)[a]	Notes
Immune Cell Counts (T, B, and NK) and Phenotypes (WB)						X			X		X*			X	X	X	See Section 5.6. (* day 78 only)
Clinical Drug Supplies																	
Study Drug Administration	X				X	X	X		X	X		X					
Report to study site	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] Only if subject is not entering the LTE after completing 12-weeks of study medication

Abbreviations: D = Day, FU=follow-up, ET=early term visit

Table 5.1-3: Long term Extension Procedural Outline (IM140103)

Procedure / Visit Day (± 3 days is allowed for all visits, including LTE Day 1)	**LTE D1[a]**	**Every-other week Visits (Q2W) LTE D15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169 (±3 days)**	**Taper Period Visit 1 LTE D190 (±3 days)**	**Taper Period Visit 2 LTE 218 (±3 days)**	**Monthly Follow-up Period LTE D248, 278, 308, 338, 368, 398 (±3 days)**	**Notes**
Confirm subject has completed 12 weeks of treatment and has signed informed consent to participate in the LTE	X					
Safety Assessments						
Physical Examination (PE)	X	X	X	X	X	
Physical Measurements	X	X*		X	X (On D248 and 398 only)	Weight only. *LTE D85 only
Vital Signs	X	X	X	X	X	Includes body temperature, respiratory rate, seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Electrocardiogram (ECGs)	X	X*		X		ECGs should be recorded after the subject has been supine for at least 5 minutes. *On Day 71 only.
Laboratory Tests	X	X	X	X	X	Includes blood and urine samples. Platelet count

Table 5.1-3: Long term Extension Procedural Outline (IM140103)

Procedure / Visit Day (± 3 days is allowed for all visits, including LTE Day 1)	**LTE D1[a]**	**Every-other week Visits (Q2W) LTE D15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169 (±3 days)**	**Taper Period Visit 1 LTE D190 (±3 days)**	**Taper Period Visit 2 LTE 218 (±3 days)**	**Monthly Follow-up Period LTE D248, 278, 308, 338, 368, 398 (±3 days)**	**Notes**
						included in this test. (Hematology, Serum Chemistry, Urinalysis)
Pregnancy Test	X	X*	X	X	X	For women only (urine or serum) must be negative to continue dosing. *On LTE D29, D57, D85, D113, D141, D169 only
Adverse Event Reporting						
Monitor for Non-Serious Adverse Events	X	X	X	X	X	
Monitor for Serious Adverse Events	X	X	X	X	X*	∗All SAEs must be collected within 3 months of discontinuation of dosing
PK & Immunogenicity Assessments						
PK Sampling	X	X	X	X	X*	*On LTE D248, D278, D308 only
Immunogenicity Sampling	X	X	X	X	X*	*On LTE D248, D278, D308 only

Table 5.1-3: Long term Extension Procedural Outline (IM140103)

Procedure / Visit Day (± 3 days is allowed for all visits, including LTE Day 1)	**LTE D1[a]**	**Every-other week Visits (Q2W) LTE D15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169 (±3 days)**	**Taper Period Visit 1 LTE D190 (±3 days)**	**Taper Period Visit 2 LTE 218 (±3 days)**	**Monthly Follow-up Period LTE D248, 278, 308, 338, 368, 398 (±3 days)**	**Notes**
Biomarker Assessments						
Plasma Soluble Free CD40L Level		X	X	X		
Plasma Soluble Total CD40L Level		X	X	X		
Plasma Collection		X	X	X		
Clinical Drug Supplies						
Contact IVRS	X	X	X	X		
Study drug administration (1500 mg)	X	X	X	X		
Report to Study Site	X	X	X	X	X	(+/- 3 days visit window for all visits)

[a] Study procedures performed on Day 85 of the short term period will be used as the starting point for LTE Day 1 procedures. They do not need to be performed twice. Patient in LTE, the Day 85 of the short term period and Day 1 of the LTE study dose are the same.

In the event of multiple procedures are required at a single timepoint, the following is a list of procedures from highest priority to low:

1) Pharmacokinetic Sampling

2) Safety (ECG)

3) Safety (clinical labs)

5.1.1 Retesting During Screening or Lead-in Period

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

Any new result will override the previous result (i.e., 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.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully stocked advanced cardiac life support (ACLS) cart will be immediately available on the premises. The site will have a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. BMS will provide a BMS approved protocol and any amendments or administrative letters (if required), The Bleeding Assessment Tool (ITP-BAT), BMS-986004 Investigator Brochure, Pregnancy surveillance forms, NCI CTCAE version 4.0 and a Pharmacy Manual. Case report forms (electronic or hard copy) will be provided by BMS. The Central Laboratory will provide a lab manual, labels and tubes for the collection and handling of blood (including PKs, biomarker and immunogenicity) specimens.

5.3 Safety Assessments

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests and clinical tolerability of the drug.

The safety of BMS-986004 will be assessed primarily by summarizing treatment emergent AEs/SAEs and by evaluating laboratory and biomarker safety assessment, including hematology, clinical chemistry and coagulation.

The occurrence of treatment-emergent AEs and SAEs will be summarized from the first administration of study drug through Study Day 85. Treatment-emergent AEs and SAEs that occur after the first administration of study drug will be summarized by system organ class and preferred terms, by severity, and by relationship to study drug and reviewed for potential significance and clinical importance. Treatment-emergent AEs and SAEs will be summarized for each of the BMS-986004 dose cohorts, and for all BMS-986004 doses combined.

5.3.1 Imaging Assessment for the Study

Not applicable.

5.3.2 Laboratory Test Assessments

A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.

The following clinical laboratory tests will be performed:

Hematology (Local Lab)

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count
RBC
Reticulocyte percent

Prothrombin Time (PT) / International Normalized Ratio (INR) (Screening only)
Activated Partial Thromboplastin Time (aPTT) (Screening only)

Peripheral Blood Biomarkers
CD40L Receptor occupancy (by flow cytometry)
Platelet-associated anti-platelet antibody titers
Platelet Ag-specific B cells by ELISPOT
Immune cell counts (T, B and NK cells) and phenotypes (by flow cytometry)
Gene expression
PBMC

Plasma biomarkers
D-dimer
Thrombin anti-Thrombin (TAT)
Free and Total soluble CD40L
Cytokines and Chemokines

Serum biomarkers
Troponin I
Immunoglobulin panel (IgG, IgA, IgM)
CRP

Serum Chemistry (Local Lab)

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Direct bilirubin
Alkaline phosphatase (AP)
Lactate dehydrogenase (LDH)
Creatinine
Blood Urea Nitrogen (BUN)
Uric acid
Glucose
Total Protein
Albumin
Sodium
Potassium
Chloride
Calcium
Phosphorus
Magnesium
Creatine kinase
Creatine Clearance (CLcr)- screening only

Urinalysis (Local Lab)

Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

Serology (Local Lab)
Serum for hepatitis C antibody, hepatitis B surface antigen (Ag), hepatitis B anti-surface Ag antibody, hepatitis B anti-core Ag antibody, HIV-1, -2 antibody (screening only).

Other Analyses (Local Lab)

Pregnancy test (WOCBP only)
Direct Coombs (Screening Only)
Urine for Drug of Abuse (UDS, Screening only)

QuantiFERON TB test (screening only)

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3 Laboratory Test Result Abnormalities).

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

Proportion of subjects achieving:

- Response (R) - platelet count ≥ 30,000/mm^3 and at least 2-fold increase from the baseline count and absence of bleeding, or
- Complete response (CR) - platelet count ≥ 100,000/mm^3 and absence of bleeding, or

Overall response rate (ORR) defined as the proportion of subjects who achieved a CR or R.

5.4.2 Secondary Efficacy Assessments

- Proportion of subjects achieving platelet count ≥ 50,000/mm^3 with an increase of at least 20,000/mm^3 from Short Term Day 1 and absence of bleeding
- Percent of visits with platelet count above 30,000/mm^3 (50,000/mm^3 or 100,000/mm^3). If subject entered study with baseline between 30,000-35,000/mm^3 at Short Term Day 1,

determine percent of visits with platelet count above subject's Short Term Day 1 platelet count.

- Mean platelet count at each visit
- Mean change from baseline in platelet counts at each visit
- Mean fold change from baseline in platelet counts at each visit
- Time to response: time from starting treatment to achievement of CR or R.
- No response (NR): platelet count < 30,000/mm^3 or less than 2-fold increase of baseline platelet count or bleeding.
- Percentage of participants experiencing any bleeding episode and the total number of bleeding events.
- Subject's Bleeding Score (measured by the ITP-BAT Bleeding Assessment Test)
- Corticosteroid-dependence - the need for ongoing or repeated doses administration of corticosteroids for at least 2 months to maintain a platelet count at or above 30,000/mm^3 and/or to avoid bleeding.
- The duration of response is measured from the achievement of a first measured CR or R until the loss of CR or R.
- Ability to maintain Response or Complete Response after stopping treatment.

5.4.3 Long Term Extension Period Efficacy Assessments

5.4.3.1 Primary Efficacy Assessment

- Response (R) - platelet count ≥ 35,000/mm^3 and at least 2-fold increase from the Short-Term baseline (Day 1) count and absence of bleeding, or
- Complete response (CR) - platelet count ≥ 100,000/mm^3 and absence of bleeding, or

Overall response rate (ORR) defined as the proportion of subjects who achieved a CR or R by visit.

5.5 Pharmacokinetic Assessments

Pharmacokinetics of BMS-986004 will be derived from serum concentration versus time data. The pharmacokinetic parameters to be assessed include:

Cmax	Maximum observed serum concentration
AUC(TAU)	Area under the concentration-time curve in one dosing interval
Ctrough	Trough observed serum concentration
CLT	Total body clearance
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady-state to Cmax after the first dose

Individual subject pharmacokinetic parameter values will be derived by non compartmental methods by a validated pharmacokinetic analysis program. Actual times will be used for the analysis.

5.5.1 Pharmacokinetics: Collection and Processing

Table 5.5.1-1 lists the sampling schedule to be followed for the assessment of pharmacokinetics. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 5.5.1-1: Pharmacokinetic Sampling Schedule for BMS-986004

Study Day/Month of Sample Collection	Event	Time (Relative To BMS-986004 Dose) Hour: Min	BMS-986004 Blood Sample	BMS-986004 Immunogenicity Sample
Collections During Short-Term Period				
1	Predose	00:00	X	X
1	EOI[a]	02:00	X	
2		24:00	X	
4		72:00	X	
8		168:00	X	
15	Predose	00:00	X	X
29	Predose	00:00	X	X
43	Predose	00:00	X	X
50		168:00	X	
57	Predose	00:00	X	X
57	EOI[a]	02:00	X	
71	Predose	00:00	X	X
71	EOI[a]	02:00	X	
72		24:00	X	
75		96:00	X	
78		168:00	X	
85	Predose	00:00	X	X
FU 1 (Day 99)		336:00	X	X
FU 2 (Day 113)		672:00	X	X
FU 3 (Day 127)		1008:00	X	X
FU 4 (Day 141)		1344:00	X	X

Table 5.5.1-1: Pharmacokinetic Sampling Schedule for BMS-986004

Study Day/Month of Sample Collection	Event	Time (Relative To BMS-986004 Dose) Hour: Min	BMS-986004 Blood Sample	BMS-986004 Immunogenicity Sample
Collections During Long Term Extension				
LTE Day 15	Predose	00:00	X	X
LTE Day 29	Predose	00:00	X	X
LTE Day 43	Predose	00:00	X	X
LTE Day 57	Predose	00:00	X	X
LTE Day 71	Predose	00:00	X	X
LTE Day 85	Predose	00:00	X	X
LTE Day 99	Predose	00:00	X	X
LTE Day 113	Predose	00:00	X	X
LTE Day 127	Predose	00:00	X	X
LTE Day 141	Predose	00:00	X	X
LTE Day 155	Predose	00:00	X	X
LTE Day 169	Predose	00:00	X	X
Taper V1 LTE 190	Predose	00:00	X	X
Taper V2 LTE 218	Predose	00:00	X	X
LTE FU D248			X	X
LTE FU D278			X	X
LTE FU D308			X	X
Other Samples				
AE[b]	AE		X	X

[a] EOI=End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. The PK serum sample of EOI must be taken on the contralateral arm.

[b] For subjects who are prematurely discontinued due to AEs, the listed samples should be taken

It is expected that every effort be made to collect PK samples at the times indicated in the protocol. The following windows serve as a guideline for PK and Biomarker sample collections:

- +/- 2 minutes for samples within the first 2 hours after dose
- +/- 1 day for the 24 hour post dose time point (Day 2, Day 72)
- +/- 2 days for sparse sampling for Day 4, Day 8, Day 75 and Day 78 visit
- +/- 3 days for all Long Term Extension samplings

For the long term extension, immunogenicity and PK serum samples and plasma samples will be obtained at every visit during treatment and at the end of the first, second and third months of follow up.

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for BMS-986004 by a validated ligand binding assay. In addition, serum samples will be archived for potential exposure-biomarker or other exploratory analysis, if the need arises and to the extent possible. Exploratory biomarker analysis may include assessment of markers associated with inflammatory or autoimmune disease, molecules associated with ITP or disease mechanism of action and signaling pathways, with the drug target, CD40L, or drug target mechanism of action and signaling pathways, and/or with patient response to drug treatment.

5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

5.6 Biomarker Assessments

Blood and will be drawn at the times indicated in Table 5.7.1-1 and Table 5.7.1-2 for the measurement of target engagement, PD and disease-related biomarkers. Further details of blood collection and processing will be provided to the site in the procedure manual.

5.6.1 Primary Safety (TE) Biomarker Assessments

Previous molecules in clinical development targeting CD40L have demonstrated the potential to induce thromboembolism (TE). All data from nonclinical, NHP and single ascending dose clinical study of BMS-986004 are consistent with the conclusion that BMS-986004 does not possess platelet activating or other activity associated with the induction of TE. To further mitigate the risk of TE in subjects dosed with BMS-986004, a set of primary, accepted markers of platelet activation and TE potential will be monitored at frequent intervals and analyzed in real-time. Plasma and serum will be collected to monitor the risk and minimize impact of a potential TE event. Prothrombin time (PT) and activated Partial thromboplastin time (aPTT) will be assessed at screening as measures of a hypercoagulable state. D-dimer and thrombin anti-thrombin (TAT) in plasma will be quantified as measures of TE risk. Serum troponin I will be monitored as an indicator of potentially TE-related subclinical myocardial infarction. Data from these primary safety biomarker measurements will be collected and carefully evaluated in the context of a thorough review of all available clinical data and used to formulate go/no-go decisions prior to dose escalation.

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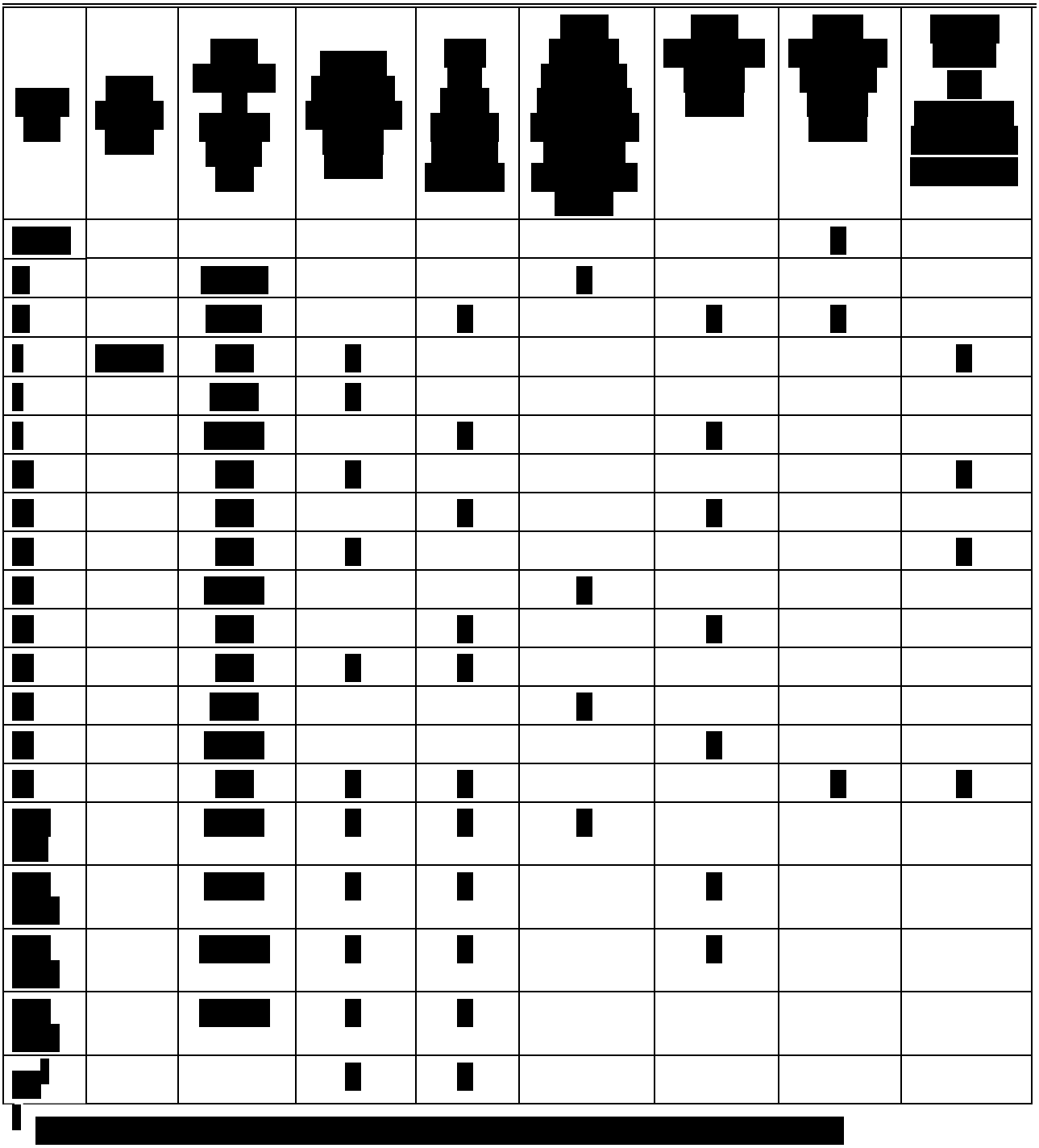

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5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

5.9.1 Immunogenicity Assessments

The immunogenic potential of the study medication will be assessed based on levels of anti-BMS-986004 antibodies.

5.9.1.1 Immunogenicity Sample Collection and Analysis

Serum samples will be collected as described in Table 5.5.1-1. Samples will be assayed for the presence of anti-BMS-986004 antibodies by a validated electrochemiluminescence (ECL) immunoassay method.

5.10 Results of Central Assessments

Not applicable.

5.11 Sampling for Medical Research

Where individual subjects have provided separate consent for Medical Research collection, residual samples of serum, plasma, RNA and PBMCs will be retained by the BMS Biobank for medical research purposes. No additional sampling is required for residual collections. Medical research collections and retention should be presented to all subjects, except where prohibited by local laws or regulations. However, enrollment into the main study is not contingent upon consent to participate in future medical research sample banking.

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

Sections 5.6.1 and 5.6.2 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 3 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 should 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 should 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 should 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. 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. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. 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 should 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, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should 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 investigational product, 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 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).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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 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)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

The key responsibilities for investigators during p-DILI assessment include: (i) Early detection, medical evaluation (including the exclusion of other potential causes) and rapid laboratory confirmation of liver-related abnormalities, and (ii) Sponsor notification of p- DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information the sponsor is responsible for: (iii) Timely evaluation and triaging of p-DILI cases, (iv) Expedited reporting of p-DILI cases and (v) Expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a subject meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a Hepatic Laboratory Panel (ALT, AST, TB, AP). Any subject with an abnormal Hepatic Laboratory Panel that meets p-DILI criteria is a candidate for study drug discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to BMS as an SAE within 24hrs of confirmation.

An extensive clinical history, examination and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include,

non-exhaustively and by way of example only: infectious diseases (such as active hepatitis -A, -B and -C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases (such as hepatocellular carcinoma), automimmune diseases (such as primary biliary cirrhosis) and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the subject's age, gender, clinical history, and signs and symptoms. If necessary, after discussion with Sponsor's safety team, Investigator may perform additional diagnostic tests/procedures to further diagnose pDILI (e.g. ultrasound, MRI/MRS, liver biopsy).

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 perform safety and efficacy assessments at regularly scheduled times as well as on an ad hoc basis if needed. The DMC will review relevant safety data from preceding Cohorts before the study progresses to the next Cohort. In addition, formal DMC monitoring meetings will occur when a maximum of 20 subjects have had at least 6 weeks of exposure during the Response Period or 6 months after the first subject is randomized to the study (whichever comes first).

Thereafter, DMC monitoring will be performed at approximately 4 month intervals or after each additional 10 subjects have had at least 11 weeks of exposure (whichever comes first) until all subjects are enrolled into the study. At that time, the DMC will meet every 6 months. With the agreement of DMC and BMS this schedule may be modified depending on the rate of subject accrual.

The DMC will review safety data including serious adverse events and events of special interest, focusing on early signal detection. The DMC will also evaluate the rates of clinical response compared to the background rates expected in this study population based on a review of the relevant literature. Further details on the content and methods of data reports to the DMC will be outlined in the charter of that committee along with the processes and procedures the committee will follow. These reviews will be conducted by an internal data monitoring committee made up of representatives of the sponsor who are not involved in the day-to-day conduct of the study.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The number of subjects is not based on statistical power considerations. If 4 responders are observed out of 10 subjects at a dose level, a 90% confidence interval for the response rate is (0.15, 0.70).

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who sign an informed consent form.
- All Treated Subjects: All subjects who receive at least one dose of study medication, either BMS-986004 or placebo.
- Pharmacokinetic Subjects: All subjects who receive at least one dose of BMS-986004 and have available serum concentration data.

Biomarker Subjects: All treated subjects for whom pharmacodynamic measurements are available at both Short Term Day 1 baseline and at least one other time after treatment

LTE:

- LTE Analysis Population: All subjects who have received at least one dose of LTE medication of 1500 mg.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective to establish safety will be measured by the primary endpoints of AEs, SAEs, ECG, and laboratory abnormalities including safety biomarkers of d-Dimer and TAT. These endpoints will be based on medical reviews of AE reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, and ECG parameters including heart rate, PR interval, QRS interval, and QTcF interval (QT interval corrected for heart rate).

8.3.2 Secondary Endpoint(s)

The first secondary objective of efficacy will be measured by the following secondary endpoints:

- Response Rate (RR): Response rate is defined as the proportion of subjects who are responders.

The second secondary objective of assessing pharmacokinetics of BMS-986004 after one and multiple doses will be measured by the following secondary endpoints:

- Cmax: Maximum observed serum concentration
- AUC(TAU): Area under the concentration-time curve in one dosing interval
- Ctrough: Trough observed serum concentration
- CLT: Total body clearance
- AI_AUC: AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose

- AI_Cmax: Cmax Accumulation Index; ratio of Cmax at steady-state to Cmax after the first dose

[redacted]

8.3.4 Endpoint for the Long Term Extension Period

During the Long Term Extension period, the following endpoints will be assessed cumulatively (safety) and over time (efficacy).

8.3.4.1 Primary Endpoints for LTE

The primary objective to establish safety will be measured by the primary endpoints of AEs, SAEs, ECG, and laboratory abnormalities including safety biomarkers of d-Dimer and TAT. These endpoints will be based on medical reviews of AE reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, and ECG parameters including heart rate, PR interval, QRS interval, and QTcF interval (QT interval corrected for heart rate).

Response Rate (RR): Response rate at each visit of the LTE is defined as the proportion of LTE subjects who are responders on that visit day of the LTE (i.e., achieved or maintained CR or R).

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated. Prior therapies will be listed and summarized for each dose.

8.4.2 Efficacy Analyses

Platelet count and change from baseline and fold change from baseline will be listed for all treated subjects and summarized by panel and visit. Response status will be reported together with time to respond, time to peak response, and duration of response. Response rate will be provided by panel and treatment phase (response phase or remission phase). Different efficacy criteria will be used to evaluate each subject's responding status.

Bleeding score will be listed for each subject. Bleeding events and the number of subjects experiencing any bleeding episode will be summarized by panel.

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

8.4.4 Pharmacokinetic Analyses

PK parameters will be summarized by treatment. Geometric means and coefficients of variation will be presented for Cmax (after dose 1 and dose 6), CLT, AUC(TAU), and Ctrough. Additionally, scatter plots of Cmax versus dose will be provided to assess the dependency on dose. A statistical analysis using a power model will be applied to assess dose proportionality.

8.4.5 Immunogenicity Analyses

Data from the assessment of immunogenicity markers (anti-BMS-986004 antibodies) will be listed by subjects. In addition, immunogenicity data will be listed separately for all the subjects who have at least one positive assay. Number and frequency of positive subjects will be summarized by dose. Definition of different positivity will be available in the study's Statistical Analysis Plan (SAP).

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8.4.8 Long Term Extension Analyses

Similar and appropriate analyses (demographics and baseline characteristics, efficacy analyses, safety analyses, etc) will be conducted for the LTE analysis population when applicable. The analyses for the LTE analysis population are descriptive in nature.

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8.4.10 Outcomes Research Analyses

Not applicable.

8.4.11 Other Analyses

8.4.11.1 Immunogenicity Analysis

Serum samples will be assayed for the presence of anti-BMS-986004 antibodies. The incidence of a positive response will be summarized by treatment group. Similar work will be performed for the Long Term Extension.

8.4.11.2 Population PK Analysis

Modeling analysis of PK and/or exposure-response analysis of BMS-986004 will be conducted using a population approach as appropriate and reported separately from the clinical study report.

8.5 Interim Analyses

Data emerging from each panel of this exploratory study may be used for timely decisions about adjustments to procedures in subsequent panels, including but not limited to, dose of next higher panel, an intermediate dose, and early termination of the study. No formal inferences requiring any adjustment to statistical significance level will be performed.

Models, including but not limited to Bayesian logistic regression, Bayesian EMax, and linear or nonlinear regression models, will be examined and built to predict a dose to achieve certain efficacy outcomes such as desired response rate or platelet count. Exposure data or PK parameters may be included in the model. Efficacy data obtained during the remission phase after a subject has been intra-subject dose escalated to a titration dose may be used to provide robust and reliable prediction. Timing of dose prediction could be as early as efficacy results becoming available for an enough number of subjects treated in the second cohort. Refer to Appendix 2 for more discussions and some simulation results.

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

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.

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.

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 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 subject recruitment and enrollment into the study.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse 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 (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
Medical Research	Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which we would like to collect and/or retain samples from study participants. Examples of Medical Research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BRt	Total amount recovered in bile

Term	Definition
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration

Term	Definition
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
%FE	percent fecal excretion
fu	fraction of unbound drug
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
G criteria	adjusted R^2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen

Term	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
kg	kilogram
$\lambda\sigma z$	terminal disposition rate constant
L	liter
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm
Lz_Start	The time point starting the log-linear elimination phase defining ther terminal half life
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life
mg	milligram

Term	Definition
Mg^{++}	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR	medical research
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRT	mean residence time
MS	mass spectrometry
MTD	maximum tolerated dose
μg	microgram
N	number of subjects or observations
Na^{+}	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time

Term	Definition
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout

Term	Definition
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

APPENDIX 1 ADAPTIVE EARLY DECISON FOR DOSE PANEL ESCALATION

Introduction

A model-based cohort escalation rule is established to help decide on opening the next cohort for newly enrolled subjects when current cohort is filled but not all of its subjects are monitored for 2 whole weeks regarding drug toxicity and tolerability. The decision rule would allow treating subject, once available, at the next cohort without waiting for the completion of every subject's AE evaluation period at the current cohort and at the same time keeping decision risk acceptably low.

Please note that AE would be closely monitored throughout the trial for each subject, and the 2 weeks' AE evaluation period mentioned here is for the purpose of cohort escalation only. During the evaluation period, the numbers of subjects who developed drug-related SAE within the same organ system at grade 3 or higher, called AE of interest are counted and the largest number will be used.

Decision Risk

The decision risk is mathematically defined as the probability of observing enough number of event(s) in the still non-evaluable subjects given data collected from evaluable subjects such that cohort escalation is not allowed. Evaluable subjects are those who are observed an AE of interest or complete the AE evaluation period. To enroll subject into the next cohort, the non-adaptive cohort escalation rule requires, among others, no more than one subject being reported drug-related serious adverse event or serious infection and infestation within the evaluation period. Therefore, if one subject is observed with an AE of interest, the decision risk would be the probability of observing at least one more AE of interest in the non-evaluable subjects; if no AE of interest is reported, the decision risk is thus the probability of observing at least two AEs of interest from the non-evaluable subjects.

Decision Data

To take advantage of the titration design, in which subjects could possibly take a higher dose that is to be used initially in the next cohort, the adaptive decision rule makes use of the following three statistics:

- Titration-Dose Evaluable Subjects (nH): the number of subjects who are titrated and complete the evaluation period (2 weeks) starting from the titration's first dose (on day 43).
- Start-Dose Evaluable Subjects (nL): the number of subjects who develop drug related SAE at grade 3 or higher or complete the evaluation period (2 weeks) from the first dose (on day 1) but haven't completed the 2 weeks evaluation period following the first titration dose (on day 43) if being titrated to a higher dose.
- Count of AE of Interest (k): number of subjects with AE of interests, which could happen any time after the first dose of BMS-986004 till the decision making day. Apparently, k=0 or 1. Please note that it doesn't distinguish at which stage, prior to or post titration, that such AE happened.

With sample size of 10 for each cohort, the number if non-evaluable subjects is 10-nH-nL.

Decision Risk Estimation

Calculation of decision risk is based on the method of Bayesian constrained rate estimate with ascending beta prior. It assumes that the rate of AE of interest increases with doses, however, no specific mathematical form is given governing the relationship between dose and rate. In this way, robustness is achieved by avoiding possible model misspecification. It also assumes that rate depends on the maximum dose subject takes, i.e., titrated subjects are equally likely in developing AE of interest as subjects who take the titrated dose right in the beginning. The prior information is solicited from a phase III study of Abatacept IM101174, in which 12 out 721 subjects (1.7%) were reported to experience drug related SAEs within short term period (half year treatment). The prior used is Beta(0.01, 0.49), which indicates 2% rate and is equivalent of contributing 0.5 subject at each dose.

Decision risk for k=1 is listed below (values are provided only for when the number evaluable subjects, nH+nL, is at least 5, and at most 9). Bayesian MCMC simulation is performed to compute the posterior predictive probability under R version 3.1.0 with a random seed of 20140625.

Titration-Dose Evaluable Subjects (nH)	Start-Dose Evaluable Subjects (nL)								
	1	2	3	4	5	6	7	8	9
0					43.2	34.1	25.4	16.6	8.3
1				38.6	30.0	22.7	14.6	7.2	
2			36.0	29.1	21.1	13.9	6.8		
3		34.9	27.4	20.0	13.1	6.5			
4	33.9	25.9	19.3	12.9	6.2				
5	25.7	19.3	12.5	6.0					
6	18.4	11.9	5.9						
7	11.8	5.7							
8	5.7								

When k=0, decision risk is close to zero, therefore not provided.

Minimum safety requirement:

Other conditions, as listed below, have to meet to open a new cohort

There must be at least 5 evaluable subjects

The start dose of the new cohort or a higher dose must be shown tolerated in the IM140-002 study if such dose was or will be tested.

Decision Rule

Decision rule is derived by comparing decision risk to a pre-selected threshold value when the current cohort is filled and a newly enrolled subject is available to be allocated to the next cohort. If decision risk is less than the threshold value, the subject will be treated at the next cohort (denoted as E in the following table), otherwise, the subject need to wait for more evidence coming up (denoted as W).

An example of decision rule for k=1 is shown below with decision risk being 15%.

Titration-Dose Evaluable Subjects (nH)	Start-Dose Evaluable Subjects (nL)								
	1	2	3	4	5	6	7	8	9
0	W	W	W	W	W	W	W	W	E
1	W	W	W	W	W	W	E	E	
2	W	W	W	W	W	E	E		
3	W	W	W	W	E	E			
4	W	W	W	E	E				
5	W	W	E	E					
6	W	E	E						
7	E	E							
8	E								

Decision rule for k=0 is same as the Minimum safety requirement for any reasonable small threshold value.

APPENDIX 2 ADAPTIVE DOSE SELECTION

Introduction

Bayesian logistic regression model is used to predict an adaptive dose for a given response rate. Simulations of both logistic regression and Bayesian logistic regression are provided to show their performance in predicting dose for pre-selected response rate. New method of analyzing data obtained from the study with titration design is also included. More detailed discussion will be available in the study's statistical analysis plan (SAP).

Adaptive dose selection is not limited to the Bayesian logistic regression model described in this appendix. Alternative modeling includes, for example, nonlinear or linear mixed effect regression of longitudinal platelet count. Specifically, when PK exposure data are available, model based on PK exposure may be a better choice than that on dose only since there are only a few distinct values of doses.

Adaptive dose selection can be performed as early as when the third cohort is about to enroll subjects. However, it is advised that the predicted dose would be more reliable when more data are available, e.g., when the fourth cohort is about to enroll. For safety reasons, the selected dose to be administered at a higher cohort cannot be larger than what is planned for that cohort.

Bayesian Logistic Model Description

The model is described below:

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1(\log(d_i) - \log(75))$$

$$y_i \sim \text{Binomial}(n_i, p_i)$$

$$\beta = \begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix} \sim N(\mu, \Psi)$$

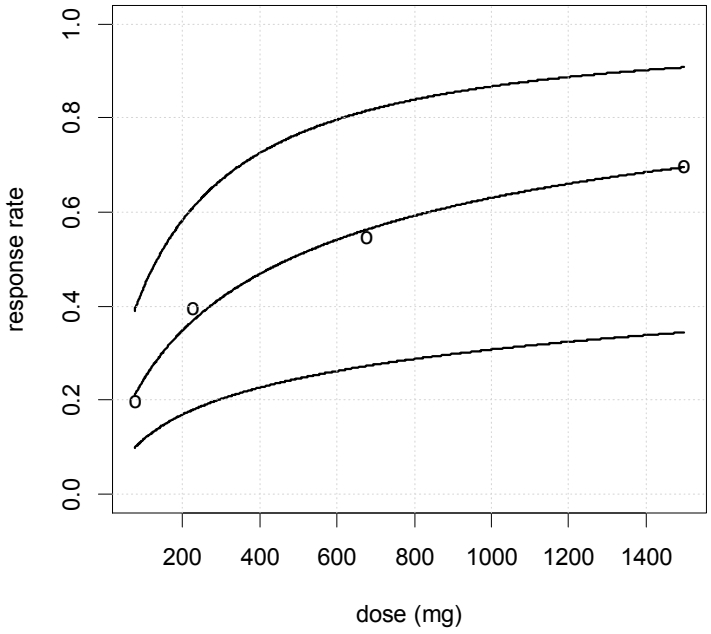
where, at each dose level i, d_i is dose in mg, p_i is the expected response rate, n_i is the number of subjects treated at dose d_i, and y_i is the number of responders. Model parameters β are assumed a normal distribution with mean μ and variance ψ. Explaining variable, dose, is in log scale, and is subtracted by an offset of log(75), where 75 is the minimum dose administered at cohort 1. By subtracting such an offset value, intercept parameter μ alone can be interpreted as the log odd value of the expected response rate for cohort 1, and as such it is easy to set prior distribution parameters (shown below).

Prior of the model parameters is set under the following guidelines:

- Model-predicted response rate at each dose level matches the expected rate.
- A 97.5% quantile of the response rate at the lowest dose is around 0.4.
- A 2.5% quantile of the response rate at the highest dose is around 0.35.
- Extremely small probability for β_2 being negative

It is assumed that the response rate at dose of 75mg, 225mg, 675mg, and 1500mg to be 0.2, 0.4, 0.55 and 0.7 respectively. A linear regression using the above data will give prior mean μ to be (-1.33, 0.72) with rounding error. The second and third bullets of the guidelines would make the stand deviation of β_1 to be 0.45, and β_2 to be 0.2. Prior distributions of β_1 and β_2 are assumed to be independent. A 95% credible interval of response rates under prior and without observation data is shown in Figure 1, where the top curve is the upper 97.5% quantile, the center is the mean, and the bottom is the lower 2.5% quantile. The circles represent the expected response rates at the selected doses. It can be seen that the chosen prior would lead to a mean response rate estimate being very close to the expected or assumed, and at the same time the wide region of 95% credible interval indicates that the prior's weak impact on the posterior estimation of response rate when data are observed.

Figure 1: 95% Credible Interval of Response Rate under Prior Only



Special consideration for titration

Non-responders at each cohort other than the maximum 1500mg cohort would be administered higher dose with the hope of becoming responders. Therefore, two response status data may be observed for those non-responders. Due to relative small sample size of each cohort, making use of status data after the titration dose is believed to increase the accuracy of model-based prediction under some reasonable assumptions. Listed in the below are two assumptions used in the adaptive dose selection:

- If a subject responses to a dose, the subject would respond to higher dose with probability 1.

- If a subject does not respond to a dose after 3 administrations, additional dosing at the same dose would not make a subject change from non-responder to responder.

Based on the above assumptions, a new approach is proposed to combine the subjects at two adjacent cohorts to estimate the response rate at the higher dose which is shared by the two cohorts.

Simulation

Trial simulation is done to show the performance of logistic regression and Bayesian logistic regression with starting dose data only or with titration data included. The Settings of simulation parameters are listed below for convenience:

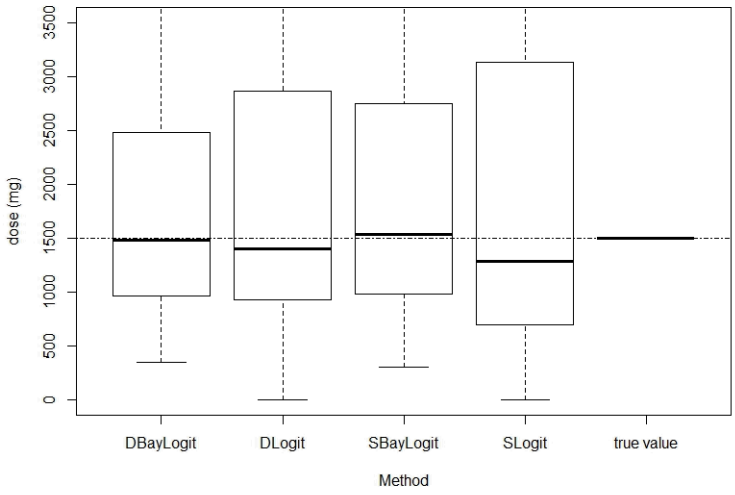
- Doses: 75, 225, 675, 1500
- Rate: 0.2, 0.4, 0.55, 0.7
- Conditional response rate for non-responder after titration:0.25, 0.25, 0.33
- Response rate used to predict dose: 0.7 (equivalently the fourth cohort)
- Number of simulated trials: 1000

Prediction results from four different methods are compared with each other.

- SLogit: Logistic regression with response status from starting dose only
- SBayLogit: Bayesian logistic regression with response status from starting dose only
- DLogit: Logistic regression with response status from both starting dose and titration dose
- DBayLogit: Bayesian logistic regression with response status from both starting dose and titration dose

Simulation results are shown in Figure 2. It can be seen that Bayesian modeling provides less variant and seemingly closer-to-true-value predictions compared to the usual logistic regression. In addition, variation of the predicted dose is smaller by including titration data when same modeling is used.

Figure 2: Predicted Dose from Different Methods



APPENDIX 3 INTERPRETATION OF HEPATITIS B SEROLOGICAL TEST RESULTS

As our study drug is expected to demonstrate immunosuppressive effects, we find it necessary to carefully evaluate and exclude subjects with potentially active Hepatitis B infection. For this reason, in order to fully evaluate subject's eligibility for enrollment, Exclusion Criterion 3f requires interpretation of data from three standard tests for hepatitis B i.e. measurement of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs) and Hepatitis B core antibody (anti-HBc).

Subject's eligibility for enrollment should be assessed as described below:

- Subjects that are negative for all three markers are allowed into the study
- Subjects that are HBsAg (neg), anti-HBc (neg) and anti-HBs (pos) are allowed into the study (immunized subjects)
- Subjects that are HBsAg (neg), anti-HBc (pos) and anti-HBs (pos) are allowed into the study (Hep B immune most likely due to natural exposure)
- Subjects that are HBsAg (pos) are excluded from the study
- Subjects that are HBsAg (neg), anti-HBc (pos) and anti-HBs (neg) may be included after additional discussion with Medical Monitor in order to evaluate subject's full clinical status and medical history.

Please also refer to the below "Interpretation of Hepatitis B Serologic Test Results" provided by the Department of Health and Human Services, CDC.