Title Page

Protocol Title: A randomized, diagnostic, Phase 3, double-blind, 2-arm study to investigate the efficacy of Drug B tablet in participants aged 30 to 60 years with urogenital diseases

Protocol Number: s3324323

Amendment Number: 2

Compound: tre54

Brief Title: Efficacy of Drug B Tablet in Urogenital Diseases: A Phase 3, Randomized, Double-Blind Study

Study Phase: Early Phase 1

Sponsor Name: weer

Legal Registered Address: Click or tap here to enter text.

Regulatory Agency Identifier Number(s): 22324

Registry	ID

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
[Amendment X]	*[Day-Mon-Year]*
[Amendment X]	*[Day-Mon-Year]*
[Amendment X]	*[Day-Mon-Year]*
Original Protocol	*[Day-Mon-Year]*

Amendment [X] (Day-Month-Year)

Overall Rationale for the Amendment:

[INSERT rationale statement]

Section # and Name	Description of Change	Brief Rationale
[INSERT]	[INSERT]	[INSERT]
[INSERT]	[INSERT]	[INSERT]
[INSERT]	[INSERT]	[INSERT]

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A randomized, diagnostic, Phase 3, double-blind, 2-arm study to investigate the efficacy of Drug B tablet in participants aged 30 to 60 years with urogenital diseases

Brief Title: Efficacy of Drug B Tablet in Urogenital Diseases: A Phase 3, Randomized, Double-Blind Study

Regulatory Agency Identifier Number(s):

Registry	ID
	22324

[Pediatric Investigational Plan Number]:

Click or tap here to enter text.

Rationale:

On January 11, 2017, Eisai notified study investigators of the decision to discontinue further enrollment in the study and significantly amend the protocol to discontinue all ongoing study procedures and conduct, while providing a mechanism for patients already randomized to the amatuximab (MORAb-009) arm to continue receiving ongoing study treatment until discontinuation for disease progression or tolerability issues. Per the amendment, only core information necessary for safety monitoring and reporting will be collected, and no efficacy data will be reported. Subjects who were randomized to placebo and all subjects in follow-up have been discontinued from the study.

The principal factor driving this business decision was significant delays in initiating the program, which led to a significant shift in the timing of the primary and final analyses. Consequently, the original rationale for the study is now compromised by the introduction of newer treatment regimens (e.g., bevacizumab) and the rapid clinical development of several investigational agents (e.g., immune checkpoint inhibitors), such that the program no longer aligns with the developing standard of care. It is important to note that there have been no new safety issues identified during the conduct of this study to date that are driving this decision. There is also no new efficacy data that informed this decision.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To assess the efficacy and dose-response of Drug A tablet in participants with immune system diseases.	Click or tap here to enter text.
Secondary	
To compare the efficacy and dose-response of Drug A tablet in participants with immune system diseases.	Click or tap here to enter text.

Overall Design Synopsis:

This is an interventional, early Phase 1 clinical trial with a primary purpose of treatment. The study employs a randomized, double-blind, crossover assignment design with two arms. The control method used is a placebo control group. The study will be conducted at multiple centers.The study population includes patients aged 18 to 60 years with immune system diseases. Healthy volunteers are not included in this trial. Both male and female participants are eligible for inclusion.Blinding will be maintained at a double-blind level, ensuring that both participants and investigators are unaware of the treatment assignments. This method minimizes bias and maintains the integrity of the study results.Participants will be randomly assigned to one of the two study arms. Randomization will occur after the screening phase and before the initiation of the intervention. The intervention involves the administration of Drug A in tablet form.The total duration of study participation for each participant includes a screening period, followed by the intervention phase, and a follow-up period. The sequence and duration of these periods will be specified in the detailed study protocol.Provisions for extending the study or entry into rollover studies will be considered based on interim results and participant response. Long-term follow-up information regarding the participant's safety or survival status will be obtained as noted in the informed consent form (ICF) and assent form.The design of this interventional, early Phase 1 clinical trial is well established and follows best practices for evaluating the safety and efficacy of new treatments. The use of a placebo control group is justified as it allows for a clear comparison between the intervention and no treatment, thereby providing a reliable measure of the intervention's effect. This is particularly important in early-phase trials where the primary goal is to assess safety and preliminary efficacy.The primary endpoint of this study is clinically relevant as it directly measures the intervention's impact on the condition or disease being treated. In this case, the primary endpoint will likely involve clinical markers or patient-reported outcomes that reflect how the participant feels, functions, or survives. This endpoint provides a reliable and valid measurement of the intended intervention effect, ensuring that the results are meaningful and applicable to real-world settings.The primary endpoint measures direct benefit by assessing improvements in symptoms, functional status, or survival rates. A clinically meaningful effect would be demonstrated by a statistically significant improvement in these measures compared to the placebo group. This would indicate that the intervention has a tangible

positive impact on the participants' health and quality of life.Given that the study population includes patients with immune system diseases, the inclusion of both male and female participants aged 18 to 60 years is justified. This age range is appropriate as it encompasses the adult population most likely to be affected by these conditions. Excluding healthy volunteers ensures that the study results are applicable to the target patient population. If a specific sex or age group is excluded, it would be due to known differences in disease prevalence, response to treatment, or safety concerns, which would be clearly justified in the protocol.The use of Drug A in tablet form as the intervention is appropriate for this study. If Drug A is a marketed compound but is not used as per the approved label, a justification for its classification as an auxiliary medicinal product (AxMP) or noninvestigational medicinal product (NIMP) will be provided. This ensures that the intervention is used in a manner that is scientifically and ethically sound, while still allowing for the collection of valuable data on its safety and efficacy in the study population.The 5-mg/kg dose of amatuximab was selected based on the results of the MORAb-009-003 study and on the results of exposure-response analysis. The selection of the dose of pemetrexed as well as cisplatin is based on the country-specific labeling requirements. The decision to proceed to the next dose level of amatuximab (either an increase or a decrease) will be made by the study team and the investigator based on safety, tolerability, and preliminary pharmacokinetic data obtained in at least 10 participants at the prior dose level. The dosing schedule may be adjusted to expand a dosing cohort to further evaluate safety and pharmacokinetic findings at a given dose level or to add cohorts to evaluate up to 3 additional dose levels. The study procedures for these additional participants/cohorts will be the same as those described for other study participants/cohorts. Dose escalation will be temporarily halted and no further participants will be dosed until completion of a full safety review if moderate or severe adverse events are consistently observed across participants in a cohort. Relevant reporting and discussion with the medical monitor, relevant study personnel, and the IRB/IEC will take place before resumption of dosing. If the same serious adverse event occurs in more than 2 participants in a cohort, then dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the medical monitor, relevant study personnel, and the IRB/IEC will take place before resumption of dosing. The above criteria will apply even if measured pharmacokinetic parameters are below the prespecified pharmacokinetic stopping criteria, and every effort will be made to take a blood sample at the time of the adverse event for pharmacokinetic analysis.The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

Brief Summary:

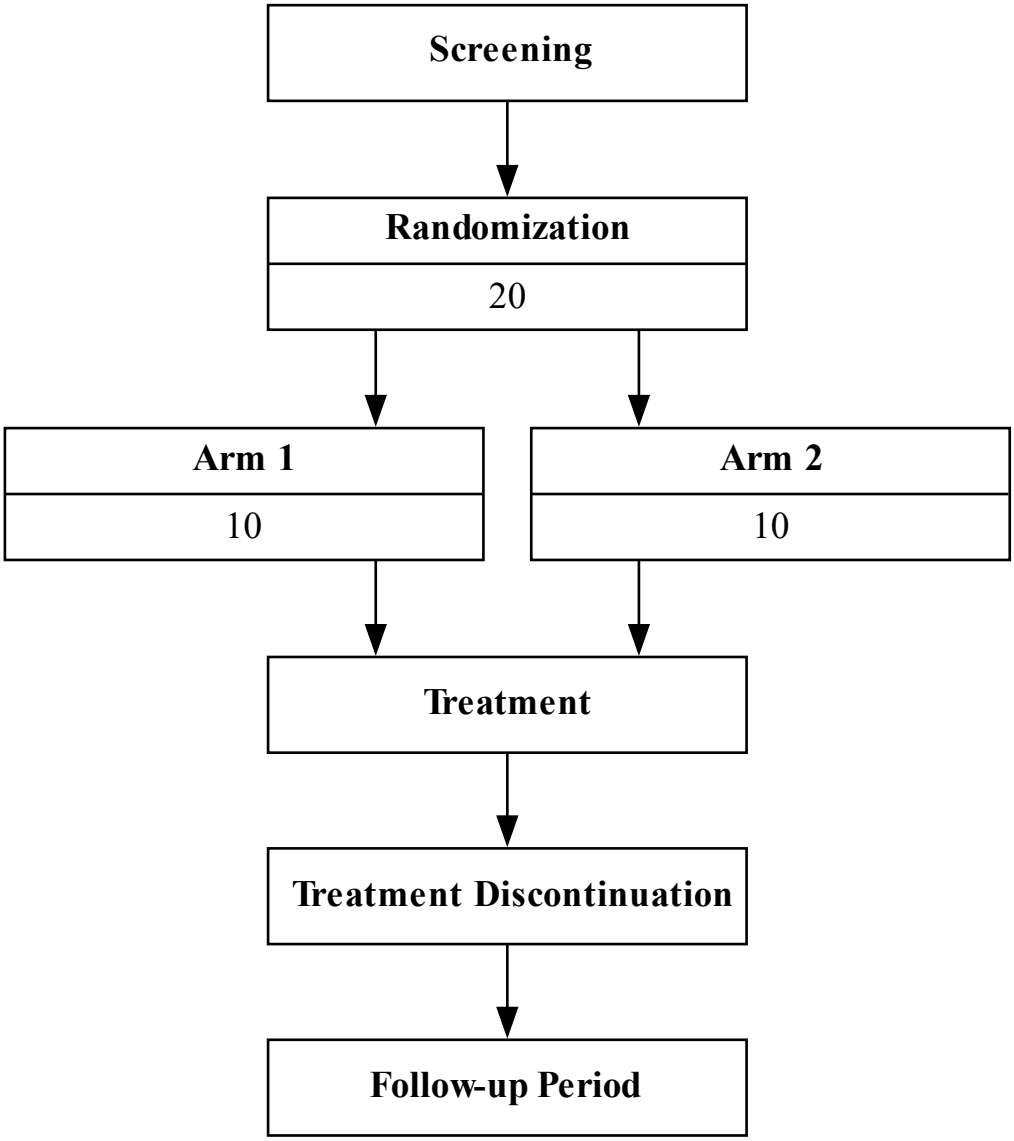
Click or tap here to enter text.This early Phase 1 interventional clinical trial aims to evaluate the safety and preliminary efficacy of Drug A in patients aged 18 to 60 with immune system diseases. The study uses a randomized, double-blind, crossover design with two arms, including a placebo control group, and will be conducted at multiple centers. Both male and female participants are eligible, but healthy volunteers are excluded.Participants will be randomly assigned to one of the two study arms after a screening phase. The intervention involves

administering Drug A in tablet form. The study includes a screening period, an intervention phase, and a follow-up period, with provisions for extending the study based on interim results and participant response.The primary endpoint measures the intervention's impact on the condition, focusing on clinical markers or patient-reported outcomes. The study design minimizes bias through double-blinding and randomization, ensuring reliable and valid results.Dose selection and adjustments for Drug A, amatuximab, pemetrexed, and cisplatin are based on prior studies and country-specific labeling requirements. Dose escalation will be carefully monitored, with safety reviews conducted if adverse events occur. The study will end after the last participant's final visit, and participants are considered to have completed the study after all scheduled procedures.Overall, the trial follows best practices for early-phase studies, ensuring scientific and ethical integrity while aiming to provide meaningful data on the intervention's safety and efficacy.

Number of Participants:

Click or tap here to enter text.Approximately 100 participants will be screened to achieve 100 enrolled.

1.2. Schema



1.3. Schedule of Activities (SoA)

Procedures	-2	-1	0	1	2	3	4	5	6
Informed consent	X	X							
Genetic Testing	X	X							
Hematologic Tests	X	X						X	
Histological Techniques			X					X	
Immunologic Tests			X					X	
Microbiological Techniques			X					X	
Pregnancy Tests	X	X						X	
Rapid Diagnostic Tests			X					X	
Semen Analysis	X	X						X	
Sex Determination Analysis	X	X							

2. Introduction

This section provides an overview of the indication for the study, current therapeutic options, details about the investigational product (Amatuximab), its mechanism of action, clinical experience from Phase 1 and Phase 2 studies, expected adverse events, and the rationale for conducting the study.

2.1. Study Rationale

On 11 January 2017, Eisai notified study investigators of the decision to discontinue further enrollment in the study and significantly amend the protocol to discontinue all ongoing study procedures and conduct, but provide a mechanism for patients already randomized to the amatuximab (MORAb-009) arm to continue to receive ongoing study treatment until discontinuation for disease progression or tolerability issues. Per the amendment, only core information necessary for safety monitoring and reporting will be collected. No efficacy data will be reported. Subjects who were randomized to placebo and all subjects in follow-up have been discontinued from the study. The principal factor driving this business decision was significant delays in initiating the program, which led to a significant shift in the timing of the primary and final analyses. As a result, the original rationale for the study is now compromised by the introduction of newer treatment regimens (eg, bevacizumab) and the rapid clinical development of several investigational agents (eg, immune checkpoint inhibitors), such that the program no longer aligns with the developing standard of care. It is important to note that there have been no new safety issues identified during the conduct of this study to date that are driving this decision. There is also no new efficacy data that informed this decision.

2.2. Background

The objective of the study is to evaluate the safety and tolerability of amatuximab in combination with pemetrexed and cisplatin in subjects with unresectable malignant pleural mesothelioma.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To assess the efficacy and dose-response of Drug A tablet in participants with immune system diseases.	Click or tap here to enter text.
Secondary	
To compare the efficacy and dose-response of Drug A tablet in participants with immune system diseases.	Click or tap here to enter text.
Tertiary	
To determine the efficacy and dose-response of Drug A tablet in participants with immune system diseases.	Click or tap here to enter text.

4. Study Design

4.1. Overall Design

This is an interventional, early Phase 1 clinical trial with a primary purpose of treatment. The study employs a randomized, double-blind, crossover assignment design with two arms. The control method used is a placebo control group. The study will be conducted at multiple centers.

The study population includes patients aged 18 to 60 years with immune system diseases. Healthy volunteers are not included in this trial. Both male and female participants are eligible for inclusion.

Blinding will be maintained at a double-blind level, ensuring that both participants and investigators are unaware of the treatment assignments. This method minimizes bias and maintains the integrity of the study results.

Participants will be randomly assigned to one of the two study arms. Randomization will occur after the screening phase and before the initiation of the intervention. The intervention involves the administration of Drug A in tablet form.

The total duration of study participation for each participant includes a screening period, followed by the intervention phase, and a follow-up period. The sequence and duration of these periods will be specified in the detailed study protocol.

Provisions for extending the study or entry into rollover studies will be considered based on interim results and participant response. Long-term follow-up information regarding the participant’s safety or survival status will be obtained as noted in the informed consent form (ICF) and assent form.

4.2. Scientific Rationale for Study Design

The design of this interventional, early Phase 1 clinical trial is well established and follows best practices for evaluating the safety and efficacy of new treatments. The use of a placebo control group is justified as it allows for a clear comparison between the intervention and no treatment, thereby providing a reliable measure of the intervention's effect. This is particularly important in early-phase trials where the primary goal is to assess safety and preliminary efficacy.

The primary endpoint of this study is clinically relevant as it directly measures the intervention's impact on the condition or disease being treated. In this case, the primary endpoint will likely involve clinical markers or patient-reported outcomes that reflect how the participant feels,

functions, or survives. This endpoint provides a reliable and valid measurement of the intended intervention effect, ensuring that the results are meaningful and applicable to real-world settings.

The primary endpoint measures direct benefit by assessing improvements in symptoms, functional status, or survival rates. A clinically meaningful effect would be demonstrated by a statistically significant improvement in these measures compared to the placebo group. This would indicate that the intervention has a tangible positive impact on the participants' health and quality of life.

Given that the study population includes patients with immune system diseases, the inclusion of both male and female participants aged 18 to 60 years is justified. This age range is appropriate as it encompasses the adult population most likely to be affected by these conditions. Excluding healthy volunteers ensures that the study results are applicable to the target patient population. If a specific sex or age group is excluded, it would be due to known differences in disease prevalence, response to treatment, or safety concerns, which would be clearly justified in the protocol.

The use of Drug A in tablet form as the intervention is appropriate for this study. If Drug A is a marketed compound but is not used as per the approved label, a justification for its classification as an auxiliary medicinal product (AxMP) or noninvestigational medicinal product (NIMP) will be provided. This ensures that the intervention is used in a manner that is scientifically and ethically sound, while still allowing for the collection of valuable data on its safety and efficacy in the study population.

4.2.1. Patient Input into Design

Patient involvement in the design of the clinical study for immune system diseases included consultations with patient advocacy groups and individual patients who have experienced the condition. Feedback was gathered through surveys and focus groups to understand patient perspectives on study procedures, potential burdens, and outcomes of interest. This input was instrumental in shaping the study design to ensure it aligns with patient needs and preferences, thereby enhancing recruitment, retention, and overall study feasibility.

4.3. Justification for Dose

The 5-mg/kg dose of amatuximab was selected based on the results of the MORAb-009-003 study and on the results of exposure-response analysis. The selection of the dose of pemetrexed as well as cisplatin is based on the country-specific labeling requirements. The decision to proceed to the next dose level of amatuximab (either an increase or a decrease) will be made by the study team and the investigator based on safety, tolerability, and preliminary pharmacokinetic data obtained in at least 10 participants at the prior dose level. The dosing

schedule may be adjusted to expand a dosing cohort to further evaluate safety and pharmacokinetic findings at a given dose level or to add cohorts to evaluate up to 3 additional dose levels. The study procedures for these additional participants/cohorts will be the same as those described for other study participants/cohorts. Dose escalation will be temporarily halted and no further participants will be dosed until completion of a full safety review if moderate or severe adverse events are consistently observed across participants in a cohort. Relevant reporting and discussion with the medical monitor, relevant study personnel, and the IRB/IEC will take place before resumption of dosing. If the same serious adverse event occurs in more than 2 participants in a cohort, then dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the medical monitor, relevant study personnel, and the IRB/IEC will take place before resumption of dosing. The above criteria will apply even if measured pharmacokinetic parameters are below the prespecified pharmacokinetic stopping criteria, and every effort will be made to take a blood sample at the time of the adverse event for pharmacokinetic analysis.

4.4. End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

5. Study Population

This interventional study will include participants of all sexes, aged 18 to 60 years, who are diagnosed with immune system diseases. Healthy volunteers will not be eligible for participation.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

Participant must be 18 to 60 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

Participants who are immune system diseases.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. **Autoimmune Diseases**: Subjects with a history of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, or multiple sclerosis.

2. **Immunodeficiency Disorders**: Subjects with primary or secondary immunodeficiency disorders, including but not limited to HIV/AIDS.

3. **Allergic Reactions**: Subjects with a history of severe allergic reactions or anaphylaxis to any component of Drug A.

4. **Chronic Infections**: Subjects with chronic infections such as tuberculosis, hepatitis B, or hepatitis C.

5. **Organ Transplantation**: Subjects who have undergone organ transplantation and are on immunosuppressive therapy.

6. **Lymphoproliferative Disorders**: Subjects with a history of lymphoproliferative disorders, including lymphoma or leukemia.

7. **Severe Asthma or Eczema**: Subjects with severe asthma or eczema requiring systemic corticosteroids or other immunosuppressive treatments.

8. **Recent Vaccination**: Subjects who have received a live vaccine within 4 weeks prior to the start of the study.

9. **Uncontrolled Diabetes**: Subjects with uncontrolled diabetes mellitus, as it may affect immune function.

10. **Current Use of Immunosuppressive Drugs**: Subjects currently using immunosuppressive drugs, including corticosteroids, methotrexate, or biologics, within 4 weeks prior to the study.

6. Study Intervention(s) and Concomitant Therapy

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices, and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the study conduct. Drug A, a tablet, will be administered to study participants as part of the investigational treatment regimen. Concomitant therapy includes any additional medications or treatments that are necessary for the participant's health and are not expected to interfere with the evaluation of or interact with the investigational product. All concomitant therapies administered during the study period will be recorded in the participant's medical record.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of Drug A will occur if subjects experience intolerable toxicity, disease progression, or withdraw consent. Additionally, the study may be discontinued if significant safety concerns arise or if the sponsor decides to terminate the study for business or strategic reasons. All discontinuation details are documented in Appendix 1.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue Drug A. If Drug A is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for safety and efficacy outcomes. See the Schedule of Activities (SoA) for data to be collected at the time of discontinuation of Drug A and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention with Drug A (tablet) is required by the investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in the best interest of the participant.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Assessments (SoA). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to the first participant's first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Primary Endpoint

The primary endpoint of this study is the safety and tolerability of Drug A in subjects with immune system diseases. Descriptive statistics will be used to summarize the incidence, severity, and type of adverse events. The number and percentage of subjects experiencing each type of adverse event will be presented.

Secondary Endpoints

Secondary endpoints include pharmacokinetic (PK) parameters of Drug A. PK parameters such as C_max, T_max, AUC, and half-life will be calculated using non-compartmental methods. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be provided for each PK parameter.

Sample Size Determination

As this is an early phase 1 study, no formal sample size calculation is required. The sample size is based on practical considerations and is deemed sufficient to achieve the study objectives.

Interim Analysis

No interim analysis is planned for this study.

Safety Analyses

Safety analyses will include all subjects who receive at least one dose of Drug A. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term. Laboratory values, vital signs, and electrocardiograms will be summarized using descriptive statistics.

Data Handling and Quality Assurance

All data will be collected and managed using validated electronic data capture (EDC) systems. Data quality assurance procedures will be implemented to ensure the accuracy and completeness of the data.

Statistical Software

All statistical analyses will be performed using SAS® or other validated statistical software as required.

This section provides an overview of the statistical considerations for this early phase 1 study of Drug A in subjects with immune system diseases. Detailed methodologies and additional analyses will be described in the statistical analysis plan.