Official Title: **A Phase 2, Open-Label Study of INCB050465 in Participants With Autoimmune Hemolytic Anemia**

NCT Number: NCT03538041

Document Date: Statistical Analysis Plan Version 1.0: 03-March-2022

STATISTICAL ANALYSIS PLAN

INCB 50465-206

A Phase 2, Open-Label Study of INCB050465 in Participants With Autoimmune Hemolytic Anemia

IND Number:	**121,474**
EudraCT Number	**2017-003652-22**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803** **USA**
Protocol Version:	**Protocol Amendment (Version) 5 dated 02 NOV 2020**
CRF Approval Date:	**04 JUN 2020**
SAP Version:	**Amendment 1**
SAP Author:	[redacted] [redacted]**, Biostatistics**
Date of Plan:	**03 MAR 2022**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AESI	adverse events of special interest
AIHA	autoimmune hemolytic anemia
AUC_{0-t}	area under the concentration-time curve from time = 0 to the last measureable concentration at time = t
BMI	body mass index
CAD	cold agglutinin disease
CL/F	apparent oral dose clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration over the dose interval
CMV	cytomegalovirus
CR	complete response
CRF	case report form
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAT	direct antiglobulin test
ECG	electrocardiogram
eCRF	electronic case report form
FACIT-F	The Functional Assessment of Chronic Illness Therapy - Fatigue
FAS	full analysis set
IgG	immunoglobulin G
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PD	pharmacodynamic
PJP	*Pneumocystis jiroveci* pneumonia
PK	pharmacokinetic
PR	partial response
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TE	treatment extension
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
WHO	World Health Organization

1. INTRODUCTION

This is a multicenter, open-label study designed to evaluate the safety and efficacy of INCB050465 administered orally to participants with AIHA who have decreased hemoglobin and evidence of ongoing hemolysis that requires treatment intervention. Participants with primary warm, cold (CAD), and mixed-type AIHA, without an underlying lymphoproliferative malignancy or other autoimmune disease and have failed at least 1 prior treatment for AIHA will be eligible for enrollment. Participants will be treated for 12 weeks. There are 2 cohorts in this study: Cohort 1, with up to 10 participants, with no more than 3 cold (CAD)/mixed-type AIHA participants to appropriately reflect response in the overall population, which is predominantly warm AIHA; and Cohort 2, with approximately 15 participants, with approximately 5 CAD AIHA, up to 8 warm AIHA, and the remainder from any of the 3 AIHA types. Cohort 2 distribution and increased number of participants are intended to better evaluate CAD AIHA patients and possible signal observed in Cohort 1, as well as account for higher baseline variability seen in the warm AIHA subpopulation. The first cohort (Cohort 1, $n = 10$ participants) enrolled will initially receive INCB050465 1 mg QD. At Week 6, participants who continue to require transfusions or do not attain a meaningful clinical response (at least a stabilization ≥ 2 g/dL increase in hemoglobin from baseline to Week 6) may have their dose increased, with sponsor preapproval, to 2.5 mg QD of INCB050465 until Week 12. If there are any tolerability issues in individual participants who received 2.5 mg, the dose may be decreased to 1 mg. Following enrollment of a minimum of 6 warm AIHA participants in the first cohort and review of safety and efficacy data through Week 6, Cohort 2 may begin enrollment. Participants in Cohort 2 ($n \approx 15$) will receive INCB050465 2.5 mg QD for 12 weeks. If there are any tolerability issues, the dose may be decreased to 1 mg. The investigator and sponsor should review and agree any dose increases or decreases. Following the last dose of INCB050465, participants will be eligible for a 12-week (3 months) follow-up for evaluation of the safety and durability of response.

Autoimmune hemolytic anemia is a rare acquired disorder in which autoantibodies directed against red blood cell membrane antigens lead to their accelerated destruction. The estimated incidence of AIHA in adults is 0.8 to 3 per 100,000 per year, with a mortality rate of 11% (Zanella and Barcellini 2014).

Currently, there is no approved and effective targeted therapy for treatment of AIHA. In addition to showing efficacy in a number of B-cell–related cancers, treatment with INCB050465 has shown significant improvement in animal models of AIHA and lupus nephritis, as well as other antibody-mediated diseases. The purpose of Study INCB 50465-206 is to evaluate the efficacy and safety of INCB050465 in the treatment of participants with AIHA.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 50465-206 Protocol Amendment (Version) 5. The scope of this plan includes the final analyses that are planned and will be executed by the Department of Biostatistics or designee.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 50465-206 Protocol Amendment (Version) 5 dated 02 NOV 2020 and CRFs approved 04 JUN 2020. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol Amendments and CRF versions.

2.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of INCB050465 in the treatment of participants with AIHA.	• Proportion of participants attaining a CR (defined as hemoglobin ≥ 12 g/dL not attributed to transfusion effect*) at any visit from Week 6 to Week 12. • Proportion of participants attaining a PR (defined as hemoglobin 10-12 g/dL or at least ≥ 2 g/dL increase from baseline not attributed to transfusion effect) at any visit from Week 6 to Week 12. *No transfusion effect definition: > 1 week since last transfusion.
• To evaluate the safety of INCB050465 administered as repeat doses in participants with AIHA.	• Safety and tolerability will be assessed by monitoring AEs, measuring vital signs and ECGs, and conducting clinical laboratory blood and urine sample assessments.
Secondary	
• To further evaluate the efficacy of INCB050465 in the treatment of participants with AIHA.	• Proportion of participants attaining a CR during postbaseline visits. • Proportion of participants attaining a PR during postbaseline visits. • Proportion of participants attaining a ≥ 2 g/dL increase in hemoglobin from baseline. • Mean, change, and percentage change from baseline of hemoglobin. • Proportion of participants requiring transfusions. • Proportion of participants who achieve normalization of hemolytic markers. *(Hemolysis markers: hemoglobin, haptoglobin, LDH, reticulocyte count, total bilirubin, and direct/indirect bilirubin.)* • Change of daily usage of prednisone. • FACIT-F subscale assessment.
• To evaluate the PK effects of INCB050465.	• PK endpoints: C_{max}, t_{max}, C_{min}, AUC_{0-t}, and CL/F.

Objectives	Endpoints
• To evaluate the PD effects of INCB050465.	• Change from baseline in PD markers: reticulocyte count, DAT for IgG and C3b, cold agglutinin levels, haptoglobin, total bilirubin, direct/indirect bilirubin, LDH, and complement assessment (CH50, C3, and C4).
[redacted]	

3. STUDY DESIGN

This is a multicenter, open-label study designed to evaluate the safety and efficacy of INCB050465 administered orally to participants with AIHA who have decreased hemoglobin and evidence of ongoing hemolysis that requires treatment intervention. Participants with primary warm, cold (CAD), and mixed-type AIHA, without an underlying lymphoproliferative malignancy or other autoimmune disease and have failed at least 1 prior treatment for AIHA will be eligible for enrollment. Participants will be treated for 12 weeks. There are 2 cohorts in this study: Cohort 1, with up to 10 participants, with no more than 3 cold (CAD)/mixed-type AIHA participants to appropriately reflect response in the overall population, which is predominantly warm AIHA; and Cohort 2, with approximately 15 participants, with approximately 5 CAD AIHA, up to 8 warm AIHA, and the remainder from any of the 3 AIHA types. Cohort 2 distribution and increased number of participants are intended to better evaluate CAD AIHA patients and possible signal observed in Cohort 1, as well as account for higher baseline variability seen in the warm AIHA subpopulation. The first cohort (Cohort 1, $n = 10$ participants) enrolled will initially receive INCB050465 1 mg QD. At Week 6, participants who continue to require transfusions or do not attain a meaningful clinical response (at least a stabilization ≥ 2 g/dL increase in hemoglobin from baseline to Week 6) may have their dose increased, with sponsor preapproval, to 2.5 mg QD of INCB050465 until Week 12. If there are any tolerability issues in individual participants who received 2.5 mg, the dose may be decreased to 1 mg. Following enrollment of a minimum of 6 warm AIHA participants in the first cohort and review of safety and efficacy data through Week 6, Cohort 2 may begin enrollment. Participants in Cohort 2 ($n \approx 15$) will receive INCB050465 2.5 mg QD for 12 weeks. If there are any tolerability issues, the dose may be decreased to 1 mg. The investigator and sponsor should review and agree any dose increases or decreases. Following the last dose of INCB050465, participants will be eligible for a 12-week (3 months) follow-up for evaluation of the safety and durability of response.

3.1. Randomization

Not applicable.

3.2. Control of Type I Error

All statistical analyses are exploratory in nature. No alpha control will be implemented. Unless otherwise specified, all confidence intervals provided will be at the 95% confidence level.

3.3. Sample Size Considerations

The sample size is based on the precedent of other studies and is not based on statistical power calculations (Go et al 2017, Hill et al 2017, Lechner and Jäger 2010). The study is not powered for statistical comparison of efficacy endpoints; the sample size is based on the demonstration of preliminary findings of clinical response. It is anticipated that a sample size of approximately 25 participants will permit sufficient data to warrant further investigation. Also, the sample size depends on the occurrence of safety findings. Approximately 10 participants will be enrolled in Cohort 1, and approximately 15 participants in Cohort 2, which will provide > 89% chance of detecting at least 1 AE of interest (eg, colitis, exfoliative dermatitis, infections) if the underlying AE rate is 20% for Cohort 1 and > 96% chance for Cohort 2.

3.4. Schedule of Assessments

Refer to Protocol Amendment (Version) 5 dated 02 NOV 2020 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations

4.1.1. Day 1

Day 1 is the date that the first dose of study drug INCB050465 is administered to the participants.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of -1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of INCB050465.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in relevant sections.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCB050465.

Concomitant medication is defined as any nonstudy medication that is:

- Started before the date of first administration of INCB050465 and is ongoing throughout the study or ends on/after the date of first administration of INCB050465.
- Started on/after the date of first administration of INCB050465 and is ongoing or ends during the course of study treatment.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first administration of INCB050465. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; Version 9.1 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum, and both the actual value and change and/or percentage from baseline (if available) will be analyzed. Descriptive summaries for categorical variables will include the number and percentage of participants in each category. All by-visit analyses will include the follow-up period if the data are available.

5.2. Treatment Groups

This is a multicenter, open-label, increasing dose strength study of INCB050465 administered as 1 tablet QD. There are 2 cohorts and approximately 10 participants will be enrolled in Cohort 1, and approximately 15 participants in Cohort 2.

Cohort 1: INCB050465 1 mg QD for up to 12 weeks. At Week 6, participants who fulfill dose increase criteria (see definition below) will be offered INCB050465 2.5 mg QD for up to 6 weeks. If there are any tolerability issues in individual participants who received 2.5 mg, the dose may be decreased to 1 mg.

Cohort 2: INCB050465 2.5 mg QD for up to 12 weeks. If there are any tolerability issues in individual participants, the dose may be decreased to 1 mg.

Criteria for dose increase: (1) Continue to require transfusions by Week 6 visit, or (2) do not attain a meaningful clinical response (at least a stabilization $\geq$ 2 g/dL increase in hemoglobin from baseline to Week 6). Dose increases require sponsor preapproval (refer to Protocol, Section 6.6).

Participants will be summarized overall and based on the dose regimen initially assigned in the study.

5.3. Analysis Populations

5.3.1. Full Analysis Set

The FAS includes all participants enrolled in the study who receive at least 1 dose of INCB050465.

The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy and safety data.

5.3.2. Treatment Extension Evaluable Population

Participants who apply at least 1 dose of INCB050465 in the extension period will constitute the TE evaluable population.

5.3.3. Pharmacokinetic/Pharmacodynamic Evaluable Population

The PK/PD population will include all participants who received at least 1 dose of study drug and provided at least 1 postdose blood sample (1 PK/PD measurement). The study pharmacokineticist will review data listings of participant dosing and sample records to identify participants to be excluded from the analysis.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of data displays and sample data displays.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographics

The following demographics will be summarized for the FAS: age, sex, race, ethnicity, weight, height, and BMI.

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the FAS:

- Years since first onset of AIHA (< 2 years, 2-5 years, > 5 years)
- Type of AIHA (warm/cold/mixed type/other)
- Number of hospitalizations due to hemolytic anemia in the past year
- Failed therapies (no/yes [prednisone/rituximab/other])
- Transfusions in the past year (no/yes)
- Splenectomy received (no/yes)

6.1.3. Prior Therapy

Prior medication information for AIHA will be used to identify medication received by participants before enrollment into the study. Prior medications for AIHA will be summarized.

6.1.4. General Medical History

For participants in the FAS, general medical history will be summarized by assigned cohort. This summation will include the number and percentage of participants with significant medical history for each body system/organ class as documented on the eCRF.

6.2. Disposition of Participants

The number and percentage of participants who were treated, completed the study, discontinued study treatment with a primary reason for discontinuation, and discontinued from the study with a primary reason for withdrawal will be summarized for the treatment period (FAS) and the extension period (TE) separately. The number of participants enrolled by site will also be provided.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be presented in the participant data listings. A summary table of major Protocol deviations will also be provided for the treatment period (FAS) and extension period (TE) separately.

6.4. Exposure

For participants in the FAS and TE, descriptive statistics will be provided for duration of treatment, average daily dose, and total dose separately. Duration of treatment with INCB050465 is defined as the number of days from Day 1 to the date of last record of INCB050465 administration. In addition, daily usage of prednisone (or equivalent) will be summarized using descriptive statistics.

6.5. Study Drug Compliance

For participants in the FAS, overall compliance (%) for INCB050465 will be calculated for all participants as:

Compliance (%) = 100 × [total dose taken] / [total intended dose].

The total intended dose will be based on the earliest study day of permanent discontinuation of the study medication. Intended dose is defined as the sum of the doses prescribed by the investigator accounting both for planned dose reductions as well as those reductions or increases mandated by the investigator.

6.6. Prior and Concomitant Medication

For participants in the FAS, prior medications and concomitant medications will be coded using the WHO Drug Dictionary and summarized by WHO drug class and WHO drug term. Results will be summarized as number and percentage of participants with prior and concomitant medications by WHO drug term and WHO drug class.

7. EFFICACY

Sample data displays are provided in Appendix A. All efficacy analyses are exploratory. Hence, no p-values will be provided and no multiple adjustment will be made.

7.1. Efficacy Hypotheses

Not applicable.

7.2. Efficacy Parameters

A CR for a given visit is attained if the following 2 conditions are satisfied:

1. Hemoglobin ≥ 12 g/dL.
2. Last transfusion occurred > 1 week before the date of visit.

A PR for a given visit is achieved if the following 2 conditions are satisfied:

1. Hemoglobin 10-12 g/dL or ≥ 2 g/dL increase from baseline.
2. Last transfusion occurred > 1 week before the date of visit.

7.3. Analysis of Primary Efficacy Parameters

The primary endpoints include:

1. Proportion of participants attaining a CR at any visit from Week 6 to Week 12 and
2. Proportion of participants attaining a PR at any visit from Week 6 to Week 12

The primary endpoints will be summarized using descriptive statistics.

7.4. Analysis of Secondary Efficacy Parameters

The secondary endpoints include:

1. Proportion of participants attaining a CR during postbaseline visits.
2. Proportion of participants attaining a PR during postbaseline visits.
3. Proportion of participants attaining a ≥ 2 g/dL increase in hemoglobin from baseline.
4. Mean, change, and percentage change from baseline of hemoglobin.
5. Proportion of participants requiring transfusions, defined as "Yes" if the last transfusion is within 7 days of the visit date and "No" otherwise.
6. Proportion of participants who achieve normalization of hemolytic markers *(*hemolysis markers: hemoglobin, haptoglobin, LDH, reticulocyte count, total bilirubin, and direct/indirect bilirubin).
7. Daily usage of prednisone.
8. FACIT-F subscale assessment.

All secondary endpoints will be summarized using descriptive statistics.

7.5. FACIT-F Subscale

FACIT-F subscale is a 13-item instrument designed to assess fatigue/tiredness and its impact on daily activities and functioning in a number of chronic diseases. The 13 items are shown in Figure 1, where the gray bar on the left is the item code. If 7 or more item scores are nonmissing, then the FACIT-F subscale score will be calculated as shown in Figure 2; otherwise, the FACIT-F subscale score will be set to missing. Actual measurements, change, and percentage change from baseline will be summarized for the fatigue subscale score.

Figure 1: FACIT-F Subscale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Figure 2: FACIT-F Subscale Calculation

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE SUBSCALE	HI7	4	-	_____	=_____
	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered:

_____=**Fatigue Subscale score**

7.6. Pharmacokinetic Analyses

The data will be analyzed by standard population PK methods using appropriate software (eg, NONMEM®). An attempt will be made to evaluate the effect of demographic characteristics and baseline characteristics (eg, age, weight, sex, race, renal function) on the population PK profile. Additionally, exposure-response analyses for key efficacy and safety parameters may also be considered if there are sufficient data available.

7.7. Pharmacodynamic Analyses

[redacted]

Biomarkers from blood samples will be summarized using descriptive statistics by treatment group. Additionally, subgroup analysis will include participants with other baseline characteristics, including duration of autoimmune hemolytic anemia, concomitant autoimmune disease, and prior treatments.

8. SAFETY AND TOLERABILITY

Sample data displays are provided in Appendix A.

8.1. General Considerations

The analyses in this section will be provided for the FAS in the treatment period and TE evaluable population in the extension period. Safety tables will be summarized for the treatment period and extension period separately.

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE. The CTCAE v5 is used for this study. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. The incidence of AEs and treatment-related AEs will be tabulated. Serious AEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

8.2.2. Adverse Events of Special Interest

Adverse events of special interest will be summarized in the following categories by treatment and extension periods separately:

- Colitis
- CMV infection
- Diarrhea
- Exfoliative dermatitis
- Febrile neutropenia
- Herpes simplex
- Intestinal perforation
- PJP
- Pneumonia
- Pneumonitis
- Rash
- Varicella zoster virus infection

8.2.3. Adverse Event Summaries

An overall summary of AEs will include:

- Number (%) of participants reporting any TEAEs.
- Number (%) of participants reporting any SAEs.
- Number (%) of participants reporting any Grade 3 or 4 TEAEs.
- Number (%) of participants who had a TEAE leading to death.
- Number (%) of participants reporting any treatment-related TEAEs.
- Number (%) of participants who temporarily interrupted study treatment because of TEAEs.
- Number (%) of participants who permanently discontinued study treatment because of TEAEs.

The following summaries will be produced by MedDRA term (if 2 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT.
- Summary of TEAEs by PT in decreasing order of frequency.
- Summary of TEAEs by SOC, PT, and maximum severity.
- Summary of treatment-related AEs by SOC and PT.

- Summary of treatment-related AEs by PT in decreasing order of frequency.
- Summary of treatment-related AEs by SOC, PT, and maximum severity.
- Summary of Grade 3 or 4 TEAEs by SOC and PT.
- Summary of Grade 3 or 4 treatment-related TEAEs by SOC and PT.
- Summary of TEAEs leading to death by SOC and PT.
- Summary of treatment-emergent SAEs by SOC and PT.
- Summary of treatment-emergent SAEs by PT in descending order of frequency.
- Summary of treatment-related SAEs by SOC and PT.
- Summary of TEAEs leading to dose interruption by SOC and PT.
- Summary of TEAEs leading to discontinuation of treatment by SOC and PT.
- Summary of nonserious TEAEs by SOC and PT.
- Summary of AESI by SOC and PT.

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

All laboratory assessments will be performed using a central laboratory, with the exception of the following, in which case the investigative site laboratory or an accredited local laboratory may be used:

- Hematology panels, including complete blood count and differential count, will be sent to a local laboratory for analysis (refer to Protocol, Section 8.2.1).
- For local laboratory assessments deemed necessary by the investigator for participant management (ie, dose modification, SAE, or COVID-19 restrictions affecting travel to the site for extension visits). Note: Such assessment data and reference ranges must be recorded in the participant's eCRF.

In the case of both local laboratory and central laboratory assessments are available, local lab will be used for analysis. Laboratory values, change from baseline values, and percent change from baseline values will be summarized descriptively by visit. Baseline values will be determined using the nonmissing values collected before the first administration, prioritizing scheduled assessments over unscheduled visits. For baseline laboratory candidates with the same date and time in the same priority category, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

8.3.2. Laboratory Value Summaries

Clinical laboratory tests, including hematology, serum chemistry, urinalysis, coagulation, pregnancy testing, and serology (refer to Protocol, Section 8, Table 5), will be performed for each participant during the study in accordance with study schedule of assessments. If specific safety issues arise, additional unscheduled laboratory tests/analyses may be performed at the discretion of the investigator.

All test results and associated normal ranges from central laboratories will be reported in SI units. All tests with numeric values will have a unique unit per test.

Laboratory hematology and serum chemistry parameters identified in Protocol Section 8, Table 5 will be summarized. Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary. In addition, box-and-whisker plots will be provided for laboratory parameters if applicable.

For test results that will be summarized with available normal ranges, the number and percentage of participants with the laboratory values being low, normal, high, and missing will be tabulated for each test and each visit.

8.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and body temperature will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 1. The abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed along with their assigned cohort. Alert vital signs are defined as an absolute value outside the defined range and percentage change greater than 25%. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 1: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 160 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Respiratory rate	> 24 breaths/min	< 8 breaths/min
Temperature	> 38°C	< 35.5°C

8.5. Electrocardiograms

Twelve-lead ECGs including PR, QRS, QT, QTcB, QTcF, and RR intervals will be obtained for each participant during the study. Change and percentage change from baseline will be calculated at each postbaseline assessment time. Descriptive statistics will be determined for each ECG parameter.

Incidences of clinically notable ECG abnormalities are defined in Table 2. Participants exhibiting clinically notable ECG abnormalities will be listed with study visit and assigned treatment group. Abnormal values for subjects with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed.

Table 2: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold	Percent Change
PR	> 220 ms	< 75 ms	± 25%
QRS	> 120 ms	< 50 ms	± 30%
QT	> 500 ms	< 300 ms	± 25%
QTcB	> 460 ms	< 295 ms	± 25%
QTcF	> 460 ms	< 295 ms	± 25%
RR	> 1330 ms	< 600 ms	± 25%

QTcF = Fridericia correction.

9. INTERIM ANALYSES

An interim analysis will be performed when all participants have completed the Week 12 treatment period.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 3.

Table 3: Statistical Analysis Plan Versions

SAP Version	Date
Original	13 SEP 2018
Amendment 1	03 MAR 2022

10.1. Changes to Protocol-Defined Analyses

A portion of the primary endpoints that relate to hemolysis factors was removed as well as a change in the range for hemoglobin. This is a change from the Protocol in order to react to the evolving regulatory interactions and more useful information from other developments in this area.

The addition of the treatment extension evaluable population is for analysis of participants who enrolled into the open-label extension period.

An interim analysis was added for when all participants have complete Week 12 treatment. This change from the Protocol was made to support publications and a possible Phase 3 development plan for CAD participants.

10.2. Changes to the Statistical Analysis Plan

10.2.1. Amendment 1

The primary purpose of this amendment is to update the definition of the primary endpoints. Section 2.2, Section 5.3.2, Section 6.2 through Section 6.4, Section 7.2, Section 7.4, and Appendix A have been modified to address edits made to the SAP based on Section 10.1.

- Section 1, Section 3, Section 3.3, Section 5.2, Section 8.3.1 were updated to align with Protocol Amendments 3, 4, and 5.
- Section 8.1 was updated to provide more details for the safety analysis.
- Section 8.2.2, AESIs were added in align with parsaclisib program.
- Section 4.2.1, the definition of age was removed due to date of birth cannot be collected according to the new requirement from agency and CRF was updated to collect age instead.
- Section 4.1.4, Last Available Value was removed since it is not applicable to this study.
- Other minor changes have been incorporated throughout the SAP.

11. REFERENCES

Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. Blood 2017;129:2971-2979.

Hill QA, Stamps R, Massey E, et al. The diagnosis and management of primary autoimmune haemolytic anaemia. Br J Haematol 2017;176:395-411.

Lechner K, Jäger U. How I treat autoimmune hemolytic anemias in adults. Blood 2010;116:1831-1838.

Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemias. Haematologica 2014;99:1547-1554.

APPENDIX A. PLANNED TABLES AND LISTINGS

This appendix provides a list of the planned tables and listings for the clinical study report. Standard tables will follow the conventions in the Standard Safety Tables initial version. Shells are provided for nonstandard tables. In-text tables are identical in structure and content as appendix tables, but follow a Rich Text Format.

The list of tables, listings, and the shells are to be used as guideline. Modifications of the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population
Baseline and Demographic Characteristics		
1.1 Disposition		
1.1.1	Analysis Populations	FAS
1.1.2.1	Summary of Participant Disposition in the Treatment Period	FAS
1.1.2.1	Summary of Participant Disposition in the Extension Period	TE
1.1.3	Summary of Number of Participants Enrolled by Site	FAS
1.2 Demography		
1.2.1	Summary of Demographics	FAS
1.3 Baseline Characteristics		
1.3.1	Summary of Baseline Disease Characteristics	FAS
1.4 Prior Medication and Concomitant Medication		
1.4.1	Summary of Prior Medications	FAS
1.4.2	Summary of Prior Medications for AIHA	FAS
1.4.3	Summary of Concomitant Medications	FAS
1.5 Others		
1.5.1	Summary of General Medical History	FAS
1.5.2.1	Summary of Protocol Deviations by Category in the Treatment Period	FAS
1.5.2.2	Summary of Protocol Deviations by Category in the Extension Period	TE
Efficacy		
2.1 Primary Efficacy		
2.1.1	Summary of Participants Attaining a Complete Response at any Visit From Week 6 to Week 12	FAS
2.1.2	Summary of Participants Attaining a Partial Response at any Visit From Week 6 to Week 12	FAS
2.2 Secondary Efficacy		
2.2.1	Summary of Participants Attaining a Complete Response by Visit	FAS
2.2.2	Summary of Participants Attaining a Partial Response by Visit	FAS
2.2.3	Summary of Participants Attaining a $\geq$ 2 g/dL Increase in Hemoglobin From Baseline	FAS
2.2.4	Summary of Hemoglobin by Visit	FAS

Table No.	Title	Population
2.2.5	Summary of Participants Requiring Transfusions	FAS
2.2.6	Summary of Participants Achieving Normalization of Hemolytic Markers by Visit	FAS
2.2.7	Summary of Daily Usage of Prednisone by Visit	FAS
2.2.8	Summary of FACIT-F Subscale by Visit	FAS
Safety		
3.1 Study Drug Exposure		
3.1.1.X	Summary of Drug Compliance	FAS
3.1.2.X	Summary of Study Drug Exposure	FAS
3.2 Adverse Events		
3.2.1.X	Overall Summary of Treatment-Emergent Adverse Events	FAS
3.2.2.X	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.3.X	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS
3.2.4.X	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	FAS
3.2.5.X	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.6.X	Summary of Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS
3.2.7.X	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	FAS
3.2.8.X	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.9.X	Summary of Grade 3 or 4 Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term	FAS
3.2.10.X	Summary of Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class and Preferred Term	FAS
3.2.11.X	Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.12.X	Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS
3.2.13.X	Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.14.X	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption by MedDRA System Organ Class and Preferred Term	FAS
3.2.15.X	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term	FAS
3.2.16.X	Summary of Nonserious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.1.X	Summary of Colitis by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.2.X	Summary of CMV infection by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.3.X	Summary of Diarrhea by MedDRA System Organ Class and Preferred Term	FAS

Table No.	Title	Population
3.2.17.4.X	Summary of Exfoliative Dermatitis by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.5.X	Summary of Febrile Neutropenia by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.6.X	Summary of Herpes Simplex by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.7.X	Summary of Intestinal Perforation by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.8.X	Summary of PJP by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.9.X	Summary of Pneumonia by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.10.X	Summary of Pneumonitis by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.11.X	Summary of Rash by MedDRA System Organ Class and Preferred Term	FAS
3.2.17.12.X	Summary of Varicella Zoster Virus Infection by MedDRA System Organ Class and Preferred Term	FAS
3.3 Laboratory		
3.3.1.X	Summary of Laboratory Values - Hematology	FAS
3.3.2.X	Summary of Laboratory Values - Chemistry	FAS
3.3.3.X	Shift Summary of Hematology Values in CTC Grade - to the Worst Abnormal Value	FAS
3.3.4.X	Shift Summary of Chemistry Values in CTC Grade - to the Worst Abnormal Value	FAS
3.4 Vital Signs		
3.4.1.X	Summary of Systolic Blood Pressure	FAS
3.4.2.X	Summary of Diastolic Blood Pressure	FAS
3.4.3.X	Summary of Pulse	FAS
3.4.4.X	Summary of Respiratory Rate	FAS
3.4.5.X	Summary of Body Temperature	FAS
3.5 ECG		
3.5.1.X	Summary of 12-Lead ECG: PR Interval Values	FAS
3.5.2.X	Summary of 12-Lead ECG: QRS Interval Values	FAS
3.5.3.X	Summary of 12-Lead ECG: QT Interval Values	FAS
3.5.4.X	Summary of 12-Lead ECG: QTcB Interval Values	FAS
3.5.5.X	Summary of 12-Lead ECG: QTcF Interval Values	FAS
3.5.6.X	Summary of 12-Lead ECG: RR Interval Values	FAS

Note: For tables ending with "X," separate tables will be provided for the treatment period (FAS) and extension period (TE).

Listings

Listing No.	Title
Demographic and Baseline Characteristics	
1.1.1	Participant Enrollment and Disposition Status
1.1.2	Participant Inclusion and Exclusion Criteria Violations
1.1.3	Protocol Deviations
1.2.1	Demographic

Listing No.	Title
1.2.2	Baseline Disease Characteristics
1.3	General Medical History
1.4.1	Prior and Concomitant Medications
1.4.2	Prior Medications for AIHA
1.5	Study Drug Compliance
Efficacy	
2.1	Hemoglobin
2.2	Transfusion
2.3	Daily Usage of Prednisone
2.4	FACIT-F Subscale
Adverse Events and Exposure	
3.2.1	Adverse Events
3.2.2	Serious Adverse Events
3.2.3	Grade 3 or 4 Adverse Events
3.2.4	Adverse Events Leading to Death
3.2.5	Treatment-Related Adverse Events
3.2.6	Adverse Events Leading to Interruption of Study Drug
3.2.7	Adverse Events Leading to Discontinuation of Study Drug
Laboratory Data	
3.3.1	Clinical Laboratory Values – Hematology
3.3.2	Clinical Laboratory Values – Serum Chemistry
3.3.3	Abnormal Clinical Laboratory Values – Hematology
3.3.4	Abnormal Clinical Laboratory Values – Serum Chemistry
Vital Signs	
3.4.1	Vital Signs
3.4.2	Abnormal Vital Sign Values
3.4.3	Alert Vital Sign Values
ECG	
3.5.1	12-Lead ECG Values
3.5.2	Abnormal 12-Lead ECG Values
3.5.3	Alert 12-Lead ECG Values