109MS310

Biogen - BG00012 in MS

Statistical Analysis Plan

BIOGEN

Statistical Analysis Plan

Version No.: Final Version 1.0

Study Title: An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis

Name of Study Treatment: BG00012

Protocol No.: 109MS310 / NCT02525874

Study Phase: Phase 3b

APPROVAL

This document has been reviewed and approved by:

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[redacted] Study Medical Lead (Printed Name)	[redacted]	02/23/2018 Date

Table of Contents

List of Abbreviations

AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine transaminase
AST	aspartate transaminase
BID	twice daily
BUN	Blood Urea Nitrogen
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CRF	case report form
DMF	dimethyl fumarate
DNA	deoxyribonucleic acid
ECG	electrocardiogram
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HIV	human immunodeficiency virus
ICF	informed consent form
Ig	immunoglobulin
IgG	Immunoglobulin G
IVMP	intravenous methylprednisolone
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
NK	natural killer
[redacted]	[redacted]
PT	preferred term
PML	Progressive multifocal leukoencephalopathy
RBC	Red blood cell
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
ULN	upper limit of normal
US	United States
WBC	white blood cell

1 STUDY OBJECTIVES AND ENDPOINTS

1.1 Primary Objective and Endpoint

The primary objective of the study is to evaluate the effect of BG00012 on lymphocyte subset counts during the first year of treatment in subjects with relapsing-remitting multiple sclerosis (RRMS).

The primary endpoint that relates to this objective is the change in lymphocyte subset counts for up to 48 weeks.

1.2 Secondary Objectives and Endpoints

A secondary objective is to evaluate the pharmacodynamic effect of BG00012 on absolute lymphocyte counts (ALCs) and immunoglobulins (Igs) during the first year of treatment.

The endpoints that relate to this objective are the changes in Igs isotypes and ALCs for up to 48 weeks.

[redacted]

2 STUDY DESIGN

2.1 Study Overview

This is an open-label, multicenter study to evaluate the effects of BG00012 on lymphocyte subtypes and Ig isotypes. Approximately 200 subjects were treated in approximately 100 sites in North America and Europe.

After the Screening Visit (up to 28 days) if required per local guidelines and if not already available within the previous 3 months, a magnetic resonance imaging (MRI) scan should be performed locally before starting therapy with BG00012 as per local guidelines. Subjects will then receive BG00012 treatment for 96 weeks (Treatment Period). Blood samples for lymphocyte subset analysis, as well as blood samples for the determination of each subject's complete blood count with differential, will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 12, 24, 36, 48, 60 (complete blood count [CBC only]), 72, 84 (CBC only), and 96. Clinical samples for the analysis of blood chemistries will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 24, 48, and 96. A post-treatment follow-up visit, at which safety assessments will be performed, will occur 4 weeks after the final dose of BG00012.

Subjects who temporarily withhold or permanently discontinue study treatment for any other reason than lymphopenia and have a lymphocyte count <LLN will continue protocol-required visits and assessments and will also be followed every 4 weeks for 24 weeks, then every 12 weeks (unless clinically indicated more often or at the Investigator's discretion) until the lymphocyte count is ≥LLN or for up to 48 weeks following drug discontinuation, whichever occurs sooner.

Subjects who develop a confirmed lymphocyte count of <500 cells/mm3 at any time during the study will be monitored every 4 weeks. If the lymphocyte count stays <500 cells/mm3 for 24 weeks, the subject will temporarily withhold study treatment. If the lymphocyte count does not recover to LLN within 24 weeks while study treatment is temporarily withheld, study treatment will be discontinued permanently.

Subjects whose lymphocyte counts remain <LLN at the end of the study (Week 96) will complete the final Follow-Up Visit and will then be followed up outside of this study at the Investigator's discretion.

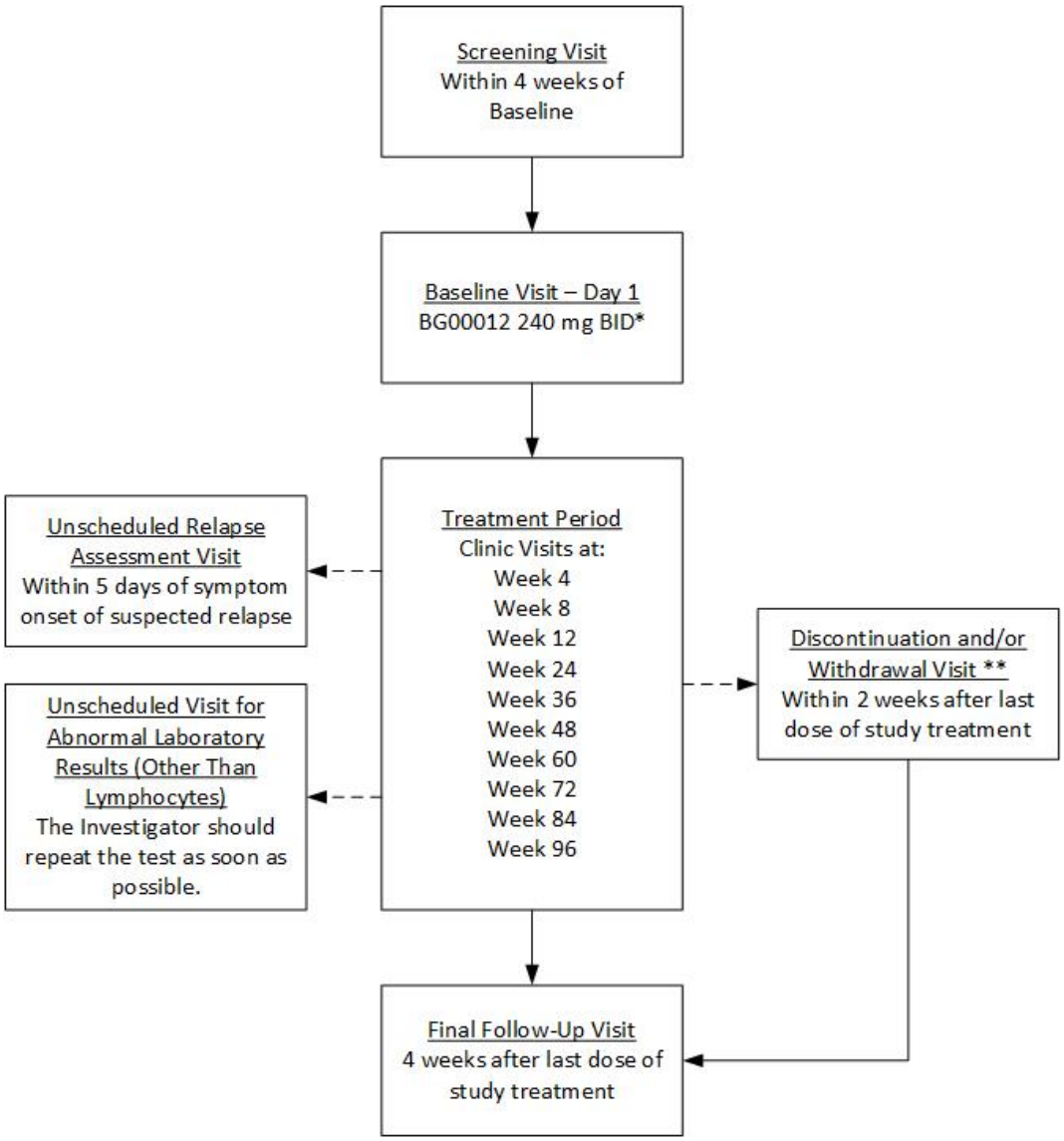
Therapies directed toward the treatment of MS are permitted, at the discretion of the treating physician and only after consulting with the Medical Monitor, for subjects who have permanently discontinued BG00012 for any reason.

Subjects who withdraw from the study while on study treatment will complete the Discontinuation and/or Withdrawal Visit as soon as possible but no later than 2 weeks after their last dose of study treatment and will complete the final Follow Up Visit 4 weeks after their last dose of study treatment unless consent has been withdrawn.

Subjects who withdraw from the study for reasons other than safety may be replaced at the discretion of Biogen.

See Figure 1 for a schematic of the study design. Refer to Table 1 and Table 2 for the timing of all study assessments.

Figure 1: Study Design



BID = twice daily; LLN = lower limit of normal.
*Subjects will receive oral BG00012 at a dose of 120 mg BID for the first 7 days and at a maintenance dose of 240 mg BID thereafter. Temporary dose reductions to 120 mg BID may be considered.
**Subjects with a lymphocyte count <LLN will continue protocol-required visits and assessments and will have additional lymphocyte and subset analysis.

Schedule of Activities

Table 1: Study Activities for Study 109MS310 - Table 1 of 2

Tests and Assessments	**Screening**	**Treatment Period**											**Final Follow-Up Visit**[i]
	Within 28 days before Baseline	**Baseline (Day 1)**	**Week 4 (Day 28 ±3 days)**	**Week 8 (Day 56 ±3 days)**	**Week 12 (Day 84 ±3 days)**	**Week 24 (Day 168 ±5 days)**	**Week 36 (Day 252 ±5 days)**	**Week 48 (Day 336 ±5 days)**	**Week 60 (Day 420 ±5 days)**	**Week 72 (Day 504 ±5 days)**	**Week 84 (Day 588 ±5 days)**	**Week 96 (Day 672 ±5 days)**	**4 weeks ±5 days after final dose**
Informed Consent [ii]	X												
Medical History[iii]	X												
Hepatitis B and C Screen	X												
HIV Testing (As Per Local Guidelines) [iv]	X												
Physical Examination[v]	X							X				X	
Vital Signs[vi]	X	X	X	X	X	X	X	X		X		X	X
12-Lead ECG		X						X				X	
Hematology (CBC With Differential) [vii]	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X		X		X				X	X

Tests and Assessments	**Screening**	**Treatment Period**											**Final Follow-Up Visit**[i)]
	Within 28 days before Baseline	**Baseline (Day 1)**	**Week 4 (Day 28 ±3 days)**	**Week 8 (Day 56 ±3 days)**	**Week 12 (Day 84 ±3 days)**	**Week 24 (Day 168 ±5 days)**	**Week 36 (Day 252 ±5 days)**	**Week 48 (Day 336 ±5 days)**	**Week 60 (Day 420 ±5 days)**	**Week 72 (Day 504 ±5 days)**	**Week 84 (Day 588 ±5 days)**	**Week 96 (Day 672 ±5 days)**	**4 weeks ±5 days after final dose**
[redacted]													
Lymphocyte Subset Analysis[7]	X	X	X	X	X	X	X	X		X		X	X
Serum Pregnancy Test[viii)]	X												
Urine Pregnancy Test[8, 9]		X			X	X	X	X	X	X	X	X	
[redacted]													
Dispense BG00012		X			X	X	X	X	X	X	X		

Tests and Assessments	**Screening**	**Treatment Period**											**Final Follow-Up Visit**[i)]
	Within 28 days before Baseline	**Baseline (Day 1)**	**Week 4 (Day 28 ±3 days)**	**Week 8 (Day 56 ±3 days)**	**Week 12 (Day 84 ±3 days)**	**Week 24 (Day 168 ±5 days)**	**Week 36 (Day 252 ±5 days)**	**Week 48 (Day 336 ±5 days)**	**Week 60 (Day 420 ±5 days)**	**Week 72 (Day 504 ±5 days)**	**Week 84 (Day 588 ±5 days)**	**Week 96 (Day 672 ±5 days)**	**4 weeks ±5 days after final dose**
BG00012 Administration		X											
Concomitant Therapy and Procedures		X											
AE Recording		X											
SAE Recording	Monitor and record throughout the study.												

AE = adverse event; CBC = complete blood count; DNA = deoxyribonucleic acid; ECG = electrocardiogram; [redacted]: HIV = human immunodeficiency virus; Ig = immunoglobulin; LLN = lower limit of normal; MRI = magnetic resonance imaging; MS = multiple sclerosis; [redacted]; SAE = serious adverse event.

[1] Subjects will have a final Follow-Up Visit 4 weeks after taking their final dose, regardless of whether they complete the treatment period or discontinue prematurely, unless they have a lymphocyte count <LLN. Subjects who have a lymphocyte count <LLN will continue protocol-required visits and assessments.

[2] Written informed consent must be obtained prior to performing any study-related procedures.

[3] Medical history will include gastrointestinal abnormalities within the previous 6 months, as well as duration of MS (time since diagnosis), relapse history, and treatments for MS.

[4] HIV testing will be done locally at Screening only if required, per local guidelines.

[5] Physical examination includes height and weight measurements, as well as a neurological examination.

[6] Vital signs will include diastolic and systolic blood pressure, heart rate, and temperature. Subjects must be seated for 5 minutes prior to having their pulse and blood pressure measured.

[7] Whole blood may also be collected for lymphocyte functional tests. Lymphocyte subset analysis will include total Ig and IgG subclasses, and may also include assays for [redacted] and VLA-4 expression. In subjects with a confirmed lymphocyte count <500/mm^3 lymphocyte testing must be performed every 4 weeks; if the lymphocyte count remains <500/mm^3 for 24 weeks, study treatment will be temporarily withheld for 24 weeks or until the lymphocyte count recovers to LLN, whichever is sooner, and testing continues to be every 4 weeks; if the lymphocyte count does not recover to LLN within 24 weeks while study treatment is temporarily withheld, study treatment will be withheld permanently, and testing will be performed every 12 weeks for an additional 24 weeks or until the lymphocyte count recovers to LLN, or until the end of the study, whichever is sooner.

[8] Females of childbearing potential only. Results must be known to be negative prior to dispensing BG00012.

[9] Pregnancy test may be repeated locally at additional timepoints if needed, per local guidelines.

[redacted]

Table 2: Study Activities for Study 109MS310 - Table 2 of 2

Tests and Assessments	[redacted]	**Discontinuation and/or Withdrawal Visit**[ii)]	**Lymphocyte Follow-Up Visit**[iii)]	**Unscheduled Visit for Abnormal Laboratory Results (Other Than Lymphocytes)**
	These visits can be combined. If these visits are not combined, any assessment that was performed within the past 2 weeks (or the interval noted in the footnotes) does not need to be repeated unless clinically indicated.			
Physical Examination[iv)]	X		X	
Vital Signs[v)]	X	X	X	
Hematology (CBC With Differential)	X	X	X	X[vi)]
Blood Chemistry	X	X		X[vii)]
[redacted]				
Lymphocyte Subset Analysis		X	X	
[redacted]				
Concomitant Therapy and Procedures	X			
AE Recording	X			
SAE Recording	Monitor and record throughout the study.			

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; CBC = complete blood count; [redacted]; LLN = lower limit of normal; [redacted]; SAE = serious adverse event; ULN = upper limit of normal; WBC = white blood cell.

[redacted]

ii) Discontinuation refers to discontinuation of study treatment. Withdrawal refers to withdrawal of subjects from study. The Discontinuation and/or Withdrawal Visit should be conducted as soon as possible and no later than 2 weeks after their last dose of study treatment.

iii) Subjects who temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will continue protocol-required visits and assessments and will also be followed up every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for up to 48 weeks following drug discontinuation, whichever occurs sooner.

iv) Physical examination includes height and weight measurements, as well as a neurological examination.

v) Vital signs will include diastolic and systolic blood pressure, heart rate, and temperature. Subjects must be seated for 5 minutes prior to having their pulse and blood pressure measured.

vi) The Investigator should repeat the test as soon as possible. If retest value confirms that WBC count is <2000/mm^3, study treatment must be withheld. If the value remains <2000/mm^3 for ≥4 weeks after discontinuation of study treatment, then the subject must permanently discontinue study treatment, and the event must be recorded as an AE.

vii) The Investigator should repeat the test as soon as possible. If the retest value confirms AST or ALT >3 × ULN or creatinine >1.2 × ULN, the study treatment must be withheld. If the ALT/AST value remains >3 × ULN or creatinine is >1.2 × ULN for ≥4 weeks after discontinuation of study treatment, then the subject must permanently discontinue study treatment, and the event must be recorded as an AE.

[redacted]

2.2 Overall Study Duration and Follow-Up

The study period will consist of a Screening Visit within 4 weeks of Baseline, a Treatment Period of 96 weeks and a final Follow-Up Visit. Subjects will receive treatment for 96 weeks. The total duration of subject participation will be up to 104 weeks.

2.2.1 Screening

Subject eligibility for the study will be determined within 28 days prior to study entry. If required per local guidelines and if not already available within the previous 3 months, an MRI scan should be performed locally before starting therapy with BG00012.

2.2.2 Treatment Period

Eligible subjects will report to the study site every 4 weeks for the first 12 weeks and every 12 weeks thereafter for 96 weeks.

Discontinuation and/or Withdrawal Visits [redacted] Visits will be performed as necessary. Subjects who withdraw from the study early will be asked to return to complete a Discontinuation and/or Withdrawal Visit within 2 weeks of their last study treatment dose.

2.2.3 Follow-Up

Subjects are to return to the study site for a Follow-Up Visit 4 weeks after their last dose of study treatment. The final study visit will be Week 100.

Subjects who temporarily withhold or permanently discontinue BG00012 for any reason and have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for up to 48 weeks following drug discontinuation, whichever occurs sooner). Subjects whose lymphocyte count remains <LLN at the end of the study (Week 96) will complete the final Follow-Up Visit and will then be followed up outside of this protocol at the Investigator's discretion.

[redacted]

[redacted]

[redacted]

2.2.7 Additional Assessments if Required by Local Tecfidera Prescribing Information

Any additional assessments that are needed to comply with the local prescribing information for Tecfidera should also be performed and will be reimbursed by Biogen while a subject is participating in this study.

2.3 Study Stopping Rules

There are no study-specific stopping rules. Biogen may terminate this study at any time after informing Investigators. Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

2.4 End of Study

The end of study is last subject, last visit for final collection of data.

3 INTERIM ANALYSIS

In general, since this is an ongoing phase 3b study, interim analyses will be performed as needed for regulatory reporting, safety updates, publications, or as otherwise required by the Sponsor.

4 SAMPLE SIZE JUSTIFICATION

The sample size for this study is not based on formal hypothesis testing but on the precision of the estimation of the primary endpoints and the ratios between various ALC subgroups.

For example, the Phase 2 and 3 controlled and uncontrolled efficacy and safety studies in MS, based on data available as of May 2014 from 2470 subjects with at least 1 post-Baseline value from the interim analysis of the Integrated Summary of Safety of Tecfidera, showed that 76% of subjects had all ALC values ≥LLN and 24% had at least 1 ALC value <LLN up to Week 48. Assuming the same proportion of subjects in this study will have 1 or more ALC values <LLN, it is expected that approximately 137 subjects will have all ALC values ≥LLN and approximately 43 subjects will have at least 1 ALC value <LLN at Week 48, based on a total of 180 evaluable subjects at Week 48. With this sample size, the 90% CIs for the ratio of the 2 subgroups for the change from Baseline at Week 48 in lymphocyte subsets are illustrated below using the scenario of a true ratio of 0.8 (20% decrease) and 0.7 (30% decrease), respectively. When assessing lymphocyte subsets between subjects with at least 2 ALC values <LLN up to the first 48 weeks of treatment versus subjects who have all ALC values ≥LLN throughout the study, the 90% CIs of the ratio would be wider, as historical data suggest that 16% of the patients treated with Tecfidera may have 2 or more ALC values <LLN during the first 48 weeks of treatment.

To allow for a 10% discontinuation rate, a total of 200 subjects are planned for enrollment.

Table 3: Sample Size Calculations

Primary Endpoints	**SD** [a]	**Ratio**	**90% CI for the Ratio Based on N = 180**	
			Subjects With At Least 1 ALC <LLN[b] vs. Subjects With All ALC ≥LLN[b]	**Subjects With At Least 2 ALC <LLN[b] vs. Subjects With All ALC ≥LLN[b]**
	0.32	0.8	0.73, 0.88	0.71, 0.90

Primary Endpoints	SD [a]	Ratio	90% CI for the Ratio Based on N = 180	
			Subjects With At Least 1 ALC <LLN[b] vs. Subjects With All ALC ≥LLN[b]	Subjects With At Least 2 ALC <LLN[b] vs. Subjects With All ALC ≥LLN[b]
CD4 T cell count		0.7	0.63, 0.77	0.63, 0.78
CD8 T cell count	0.35	0.8	0.72, 0.89	0.71, 0.91
		0.7	0.63, 0.78	0.62, 0.79
$CD56^{bright}$ NK cell count	0.57	0.8	0.68, 0.95	0.65, 0.98
		0.7	0.59, 0.83	0.57, 0.86
T_{reg} count	0.95	0.8	0.60, 1.07	0.57, 1.12
		0.7	0.52, 0.93	0.50, 0.98

ALC = absolute lymphocyte count; CD = cluster of differentiation; CI = confidence interval; LLN = lower limit of normal; NK = natural killer; SD = standard deviation; T_{reg} = T regulatory; vs. = versus.

[a] Common standard deviation for the log-transformed change from Baseline.

[b] Up to Week 48.

5 STATISTICAL ANALYSIS METHODS

5.1 General consideration

The statistical software, SAS® ,will be used for all summaries and statistical analyses.

This study only includes a single arm. In general, statistical analyses will be descriptive in nature with appropriate measures of variation provided where applicable. For continuous endpoints, number of subjects in the analysis population, number of subjects with non-missing observations, mean, standard deviation (SD), median, minimum and maximum will be reported. For categorical endpoints, number of subjects in the analysis population, number with non-missing observations, and the percent of those with data in each category will be summarized.

Several analysis populations are defined for different analysis purposes in this study. An overview of these analysis populations will be summarized.

- Pharmacodynamic Population - it is defined as all subjects who receive at least 1 dose of study treatment and have at least 1 pharmacodynamic measurement after Baseline.

- Safety Population – it is defined as all subjects who receive at least 1 dose of study treatment.
- [redacted]

In general, for data that are summarized by visit, any early withdrawal, unscheduled or scheduled visits will be assigned to an appropriate scheduled visit by using a mid-point of the two visits windowing scheme. The date of first dose will be the reference point. The detailed windowing rules for lymphocyte subsets, hematology, blood chemistry and vital signs are available in Appendix 2. After windowing, if there is only 1 record in the visit window, then this recored will be selected; if there are multiple records falling into the same visit window with different distance from the target day then select the one cloest to the target day; if there are 2 visits with the same distance from the target day, but one is before the target day and the other is after the target day, then select the later one; for laboratory test, if more than one observation falls in the same distance from the target regular scheduled visit day, the mean observation will be calculated and used in the summary statistics and analyses.

No imputation will be used for missing data in this study. The observed data will be used for all analyses.

5.2 Analysis of Baseline Data and Exposure to Study Drug

The baseline data and exposure to study drug will be summarized for pharmacodynamic population. Descriptive statistics will be presented for both continuous endpoints and categorical endpoints.

5.2.1 Accounting of Subjects

Numbers and percentages of subjects enrolled, completed the treatment, and completed the study, along with reasons for discontinuing treatment and withdrawing from the study, will be presented.

5.2.2 Demographics and Baseline Disease Characteristics

Demographic data, including age (years), age category (18-19, 20-29, 30-39, 40-49, 50-55, and > 55), gender, country, race and ethnicity will be summarized. In addition, summary of height (cm), weight (kg), and BMI will be presented. A listing of demography will also be presented.

Baseline disease characteristics will also be summarized descriptively. Disease characteristics will include number of years since MS onset and diagnosis, [redacted]

[redacted].

5.2.3 Medical History and Previous MS Therapy

Medical history will be coded by MedDRA Version 19.1 or later and summarized, as number and percent of subjects, by system organ class (SOC) and preferred term (PT). Prior MS treatment history and baseline cardiac risk factors will also be summarized.

5.2.4 Protocol Deviations

Protocol deviations identified in the study will be listed.

5.2.5 Time on Study and Treatment

The total number of days/weeks patients on study will be summarized. Number of weeks the subject on the study will also be categorized into 12 week intervals and summarized. The total number of days subjects on study is calculated as

Date of study end – date of first dose + 1.

The total number of days/weeks patients on treatment will be summarized. Number of weeks the subject on treatment will also be categorized into 12 week intervals and summarized. The time patients on temporary drug interruption will be excluded from the time on treatment calculation. Therefore, the total number of days subjects on treatment is calculated as

(Date of last dose – date of first dose + 1) - total days of temporary dose interruption if any.

For partial study or study treatment end date, if day is missing then impute the day to 30/31/28/29 depending on the month; if day and month are missing then impute the month and day to December 31st.

5.2.6 Treatment Compliance

The total number of study drug capsules taken by the subject will be summarized. The compliance through the date of last dose of study drug and the overall 96-week compliance who complete the study will be summarized. The percent compliance is defined as follows for each subject:

Percent Compliance = [(total number of capsules taken) / (total number of capsules subject is expected to take)] *100

The total number of capsules that the subject expected to take is defined as the number of days the subject on the study drug multiplied by 4 (4 capsules is the expected number per day), except for the first week where 2 capsules a day is expected. The total number of capsules actually taken is calculated using total number of doses expected minus the missed doses.

5.2.7 Concomitant Medications and Non-drug Therapies

Concomitant medication is defined as prescribed or over-the-counter medications used during the study (e.g., either started prior to the study and continued on the study or started on or after the first dose of study drug). If a medication had a missing start date and a missing end date, or had a missing start date and an end date which was after the first day the subject was on study drug, or a start date which was after the date of the first day the subject was on study drug, the medication is considered concomitant. When partial concomitant medication start or end date exists, before determining whether concomitant or not, the following imputation rules are applied.

Partial start dates:

If day is missing (only month and year are present)

- If year and month are same as treatment start date then assign the day of treatment start date to the partial date
- Otherwise assign the day to '01'

If only year is present

- If year is same as treatment start date then assign the month and day of the treatment start date to the partial date
- Otherwise assign the month and day to 'January-01'

Partial end dates:

If day is missing (only month and year are present)

- If year and month are same as the year and month of study end date then assign the day of the study end date to the partial date
- If year and month are prior to the year and month of study end date then assign the last day of the month (28, 29, 30 or 31)

If only year is present

- If year is same as the year of study end date then assign the month and day of the study end date to the partial date
- If year is prior to the year of study end date then assign 'December-31' to the partial date.

If the study is ongoing and study end date is not available then the cut-off date will be used in the place of study end date

The WHO dictionary will be used for coding concomitant medication. MedDRA is used for coding concomitant non-drug therapies.

The number and percentage of subjects taking concomitant medication, concomitant MS medication, and receiving non-drug treatments will be summarized. Concomitant medication and non-drug concomitant medication will be listed.

5.3 Pharmacodynamics

The pharmacodynamic analysis will be based on data from the pharmacodynamic population as defined in Section 5.1. The pharmacodynamic data includes the lymphocyte subsets, ALC, and isotypes (including IgA, IgM, IgG and IgG subclasses). A listing of reportable lymphocyte subset parameters are available in Appendix 1. The lymphocyte subsets are categorized into the following eight groups:

- TBNK lymphocyte subsets
- T cell subsets
- B cell subsets
- Myeloid and NK cell subsets
- Intracellular T cell cytokines
- VLA-4/LFA-1 expression
- [redacted]
- [redacted]

Statistical analyses will be [redacted] and descriptive in nature, with appropriate measures of precision provided where applicable.

5.3.1 Analysis of the Primary Endpoint

The primary endpoints are the changes in lymphocyte subset counts for up to 48 weeks.The actual value, change and percent change from baseline in count and percent for each lymphocyte subset will be descriptively summarized at each applicable visit. Graphical display of median (Q1-25 percentile/Q3-75 percentile) of actual value and percent change from baseline in count and percent for each lymphocyte subset over time will also be presented. The Wilcoxon signed rank test will be used to test if thechange and percent change from baseline in count and percent for each lymphocyte subset is different from zero. Listings of lymphocyte subsets will also be presented.

Furthermore, the primary endpoints will be summarized in various ALC subgroups to evaluate the nature of change in each subset in relation to the change in ALC.

ALC subgroups of interest include (1) subjects who have all ALC values $\geqslant$LLN (0.91×10^9/L) up to Week 48, and (2) subjects who have at least 1 ALC value <LLN over 48 weeks. A mixed model for repeated measures (MMRM) will be used to estimate the difference between ALC subgroups at each post-baseline visit up to Week 48. The model will be fitted with the change from baseline in count up to Week 48 for each of the TBNK lymphocyte subset as the dependent variable and will include ALC subgroup (all ALC values

≥LLN up to Week 48; at least 1 ALC value <LLN over 48 weeks), visit, corresponding Baseline counts, age, gender, and ALC subgroup-by-visit interaction as fixed effects. An unstructured variance-covariance matrix structure will be used in the MMRM model. Least squares (LS) mean, standard error, LS mean difference, 2-sided 95% confidence intervals (CIs) and p-values will be reported. Before the MMRM analysis, appropriate transformation may be performed based on the distribution of each TBNK lymphocyte subset parameter. The same analysis may be applied to other subsets.

Additional subgroups based on ALC values over time are defined:

1) ALC < 0.5×10^9/L for ≥ 6 months (24 weeks);
2) 0.5×10^9/L ≤ALC <0.8×10^9/L for ≥6 months (excluding < 0.5×10^9/L for ≥ 6 months);
3) <LLN any time (excluding < 0.8×10^9/L for ≥ 6 months);
4) ALC always ≥LLN.

Summary of actual value, change and percent change from baseline in count and percent for each lymphocyte subset will be presented by the ALC subgroups defined above.

The following subgroups analyses based on ALC during the first 48 weeks will be peformed:

1) At least 2 ALC values <LLN in the first 48 weeks;
2) Always >= LLN or with one ALC < LLN in the first 48 weeks

Additionally subgroups analyses based on baseline ALC quartiles will also be explored. The same descriptive summary on these subgroups will be applied to the count and percent for the TBNK lymphocyte subsets and may be applied to other subsets. Additional subgroups of interest may also be explored.

The correlation between TBNK actual value and ALC will be summarized by visit and also presented as plots.

5.3.2 Analysis of the Secondary Endpoints

The secondary endpoints are the changes from baseline in Ig isotypes (including IgA, IgM, IgG and IgG subclasses) and ALCs for up to 48 weeks. The actual values, change and percent change from baseline for Ig isotypes and ALCs at each applicable visit will be descriptively summarized. Graphical display of mean (+/- SE) of actual values and percent change from baseline over time in Ig isotypes will be presented as well. Individual patient's Ig isotypes will also be listed.

In addition, MMRM analysis will be conducted for each Ig isotype and for ALC with the change from baseline up to Week 96 as the dependent variable. The model will include visit, corresponding baseline value, age, and gender as fixed effects and an unstructured variance-covariance matrix structure. LS mean, standard error and 95% CIs will be reported for each visit.

5.3.3 Lymphocyte analysis during lymphocyte follow-up period

Subjects who temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will continue protocol-required visits and assessments and will also be followed up every 4 weeks for 24 weeks, then every 12 weeks (unless clinically indicated more often or at the Investigator's discretion) until the lymphocyte count is ≥LLN or for up to 48 weeks following drug discontinuation, whichever occurs sooner. [redacted]

In general, the lymphocyte follow-up analysis will include subjects who have at least one ALC < LLN during the treatment period and have at least one ALC value during the lymphocyte follow-up period. The lymphocyte follow-up period is defined as the time starting from the date of temporary dose interruption or study drug discontinuation. The start date of the lymphocyte follow-up period is defined as the start date of temporary dose interruption or the treatment end date. The last observed value collected on or prior to the date of temporary dose interruption or study drug discontinuation will be the reference point (lymphocyte follow-up baseline). Data that are collected during the lymphocyte follow-up period will be assigned to an appropriate visit by using the mid-point of the two visits windowing scheme. Visits will be mapped every 4 weeks for 24 weeks and then every 12 weeks afterward. The detailed windowing rule is available in Appendix 2. Patients who have any post lymphocyte follow-up baseline values will be included in the analysis. ALCs collected during the lymphocyte follow-up period will be analyzed. The lymphocyte subsets and Ig isotypes observed obvious decline over time in the treatment period will also be explored.

The by-visit summary of actual value, change and percent change from the lymphocyte follow-up baseline in ALC during the lymphocyte follow-up period will be presented. The by-visit summary of actual value, change and percent change from the study baseline in ALC during the whole study period will also be presented. In addition, graphical display of median (Q1/Q3) of actual value in ALC in the whole study period will be presented; graphical display of median (Q1/Q3) of percent change from study baseline and lymphocyte follow-up baseline will be presented. The same analyses will be applied to selected lymphocyte subsets and Ig isotypes of interest.

The concomitant medication, AEs, hematology, vital signs and physical examination data collected during the lymphocyte follow-up visits will be discussed in Section 5.4.6.

Additional analyses exploring lymphocyte subsets and ALCs collected during the lymphocyte follow-up period may be conducted.

5.4 Safety

All AEs, clinical laboratory results, physical examinations, vital signs, and 12-lead ECG readings data will be evaluated for safety. The data from safety population defined in Section 5.1 will be used for safety analysis. Statistical analyses will be [redacted] and descriptive in nature.

5.4.1 Adverse Events

AEs will be coded using MedDRA version of 19.1 or later. Only treatment-emergent AEs will be analyzed. A treatment-emergent AE is defined as any AE that has an *onset* date and time that is *on or after* the date of the first dose of study treatment, or that has *worsened after* the date of the first dose of study treatment. In the case of a worsening AE, the AE is supposed to be recorded as a new event with an onset date after first dose of study drug. Therefore, all treatment emergent AEs will be captured as AEs that have an onset date that is on or after date of first dose of study drug.

If an AE had a missing onset date and a missing resolution date, or had a missing onset date and a resolution date which was after the first day the subject was on study drug, or an onset date which was after the date of the first day the subject was on study drug, the event is considered treatment emergent. If the onset date of the AE was the same as date of the first day the subject took study drug the event is considered treatment-emergent. When partial AE start or end date exists, before determining whether treatment-emergent or not, the following imputation rules are applied.

Partial start dates:

If day is missing (only month and year are present)

- If year and month are same as treatment start date then assign the day of treatment start date to the partial date
- Otherwise assign the day to '01'

If only year is present

- If year is same as treatment start date then assign the month and day of the treatment start date to the partial date
- Otherwise assign the month and day to 'January-01'

Partial end dates:

If day is missing (only month and year are present)

- If year and month are same as the year and month of study end date then assign the day of the study end date to the partial date
- If year and month are prior to the year and month of study end date then assign the last day of the month (28, 29, 30 or 31)

If only year is present

- If year is same as the year of study end date then assign the month and day of the study end date to the partial date
- If year is prior to the year of study end date then assign 'December-31' to the partial date.

If the study is ongoing and study end date is not available then the cut-off date will be used in the place of study end date

AE overview

The summary of treatment-emergent AEs will include the number of subjects and percentage for the following categories: at least one treatment-emergent AE, at least one moderate or severe treatment-emergent AE, at least one severe treatment-emergent AE, at least one related treatment-emergent AE, at least one treatment-emergent SAE, discontinuing treatment due to an event and withdrawing from study due to an event. A listing of all AEs will be presented for all subjects.

AEs

- The incidence of treatment-emergent AEs classified by the appropriate system organ class (SOC) and preferred term (PT) will be summarized.
- The incidence of treatment-emergent AEs classified by PT will be summarized.
- The incidence of treatment-emergent AEs considered as related to study drug classified by the appropriate SOC and PT will be summarized. Treatment-related is defined as events with a "possibly" or "related" relationship to study drug.
- Incidence of treatment-emergent AEs by relationship to study drug will be summarized. In the relationship to study drug column within each SOC and PT, a subject was counted only once and only in the category of strongest relationship to study drug.
- Incidence of treatment-emergent AEs by severity will be summarized. If a patient experiences an event more than once with varying severity during a study phase, he/she will be counted only once with the maximum severity within each SOC and PT.
- The incidence of treatment-emergent AEs that led to the discontinuation of study drug will be presented by SOC and PT. A listing of these AEs will also be presented.
- The incidence of treatment-emergent AEs that led to premature withdrawal from the study will be presented by SOC and PT. A listing of these AEs will also be presented.
- The incidence of treatment-emergent AEs that led to temporary dose interruption will be presented by SOC and PT.

- The incidence of treatment-emergent AEs that led to dose reduction will be presented by SOC and PT.

SAEs and severe AEs

- The incidence of treatment-emergent SAEs will be presented by SOC and PT. Individual SAEs will be listed. The information presented will include subject ID, treatment, SOC and PT, date of onset, severity, and relationship to and action taken with the study drug.
- The incidence of treatment-emergent severe AEs classified by SOC and PT will be summarized.

Infections

The incidence of treatment-emergent infections, serious infections, and potential opportunistic infections by system organ class and preferred term will be summarized by subgroups based on the ALC values over time.

PML

Given that PML has been observed very rarely in patients who receive BG00012, any PML cases in this study will be listed.

Pancreatitis

Listing of events associated to pancreatitis will be presented.

Death

Death is classified as an outcome, not as an AE. Therefore, cause of death will be listed as the AE. Death will only be listed as an AE when the cause of death is unknown (e.g., in the case of sudden death). . The information presented will include subject ID, treatment group, SOC and PT, date of death, cause of death, and relationship to the study drug.

5.4.2 Clinical Laboratory Results

The following laboratory parameters will be analyzed:

- Hematology: WBC, lymphocytes, neutrophils, monocytes, eosinophils, basophils, RBC, hemoglobin, hematocrit, platelets.
- Blood chemistry: ALT/SGPT, AST/SGOT, alkaline phosphatase (ALP), total bilirubin, BUN/urea, creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, glucose, uric acid.

Shift analyses

Laboratory data will be summarized using shift tables. Each subject's hematology and blood chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory or as "unknown" if no result is available. Shifts from baseline to

high/low status for hematology and blood chemistry parameters will be presented. Subjects need to have at least one-post baseline evaluation in order to be included in the analysis. In addition, the shift from baseline to the maximum post-baseline value will be presented for selected blood chemistry parameters (ALT, AST, alkaline phosphatase and total bilirubin). The rationale for using the maximum values or worst values is that should a treatment affect a laboratory value, that value could be affected at different times for different subjects. Therefore, the analyses present the most extreme values for each subject over time.

In addition, summary of maximum post-baseline values for selected blood chemistry parameters (ALT, AST, and total bilirubin) will be presented. For liver function tests ALT, AST, the number and percentage of subjects with post-baseline values classified by categories will be summarized. The categories are defined as: <= 1xULN, >1 x ULN, >= 3xULN, >5xULN, >10xULN, and >20xULN, where ULN is the Upper Limit of the Normal value. For total bilirubin, the categories are: <= 1xULN, >1 x ULN, >= 1.5xULN, and > 2.0xULN. A graphical summary of baseline and worst post-baseline values for selected laboratory parameters (WBC and lymphocyte) will also be presented.

Change from baseline analyses

Summary of hematology and blood chemistry values and change from Baseline by visit up to Week 96 will be presented. Graphical display of mean (+/- SE) of change from Baseline for hematology and blood chemistry parameters over time will be presented. Subject listings of hematology and blood chemistry will also be presented.

Abnormality analyses

Additional summary statistics will be presented for potentially clinically significant abnormalities for selected laboratory parameters. For example, the worst post-baseline values for WBC, lymphocyte, platelet, RBC, neutrophils, hemoglobin, classified based on clinically meaningful cut-off values, will be summarized.

Table 4: Definition for potentially clinically significant abnormalities for selected laboratory parameters

Parameter (unit)	Definition of potentially clinically significant abnormalities (each defined separately)
WBC (x 10^9/L)	<3.0 >=16
Lymphocyte (x 10^9/L)	<0.8 <0.5 >12
Neutrophil (x 10^9/L)	<=1.0

	<1.5 >=12
RBC (x 10^{12}/L)	<=3.3 >=6.8
Hemoglobin (g/L)	<=100
Platelet count (x 10^{9}/L)	<=100 >=600

5.4.3 Physical Examinations

The analyses of physical examinations will include summary statistics (actual value and change from Baseline for body weight and height) over time by visit.

5.4.4 Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. For each vital sign, the number of subjects evaluated and the number and percentage of subjects with the defined abnormality at any time post-baseline will be presented.

The definitions of these clinically relevant abnormalities are shown in Table 4.

Table 4: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C post baseline and an increase from Baseline of ≥1°C
Pulse	>120 bpm post baseline or an increase from Baseline of >20 bpm <50 post baseline bpm or a decrease from Baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg post baseline or an increase from Baseline of >40 mmHg <90 mmHg post baseline or a decrease from Baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg post baseline or an increase from Baseline of >30 mmHg <50 mmHg post baseline or a decrease from Baseline of >20 mmHg

The analyses of vital signs will also include summary statistics (actual value and change from Baseline for temperature, pulse, and systolic and diastolic blood pressure) over time by visit.

5.4.5 ECG Data

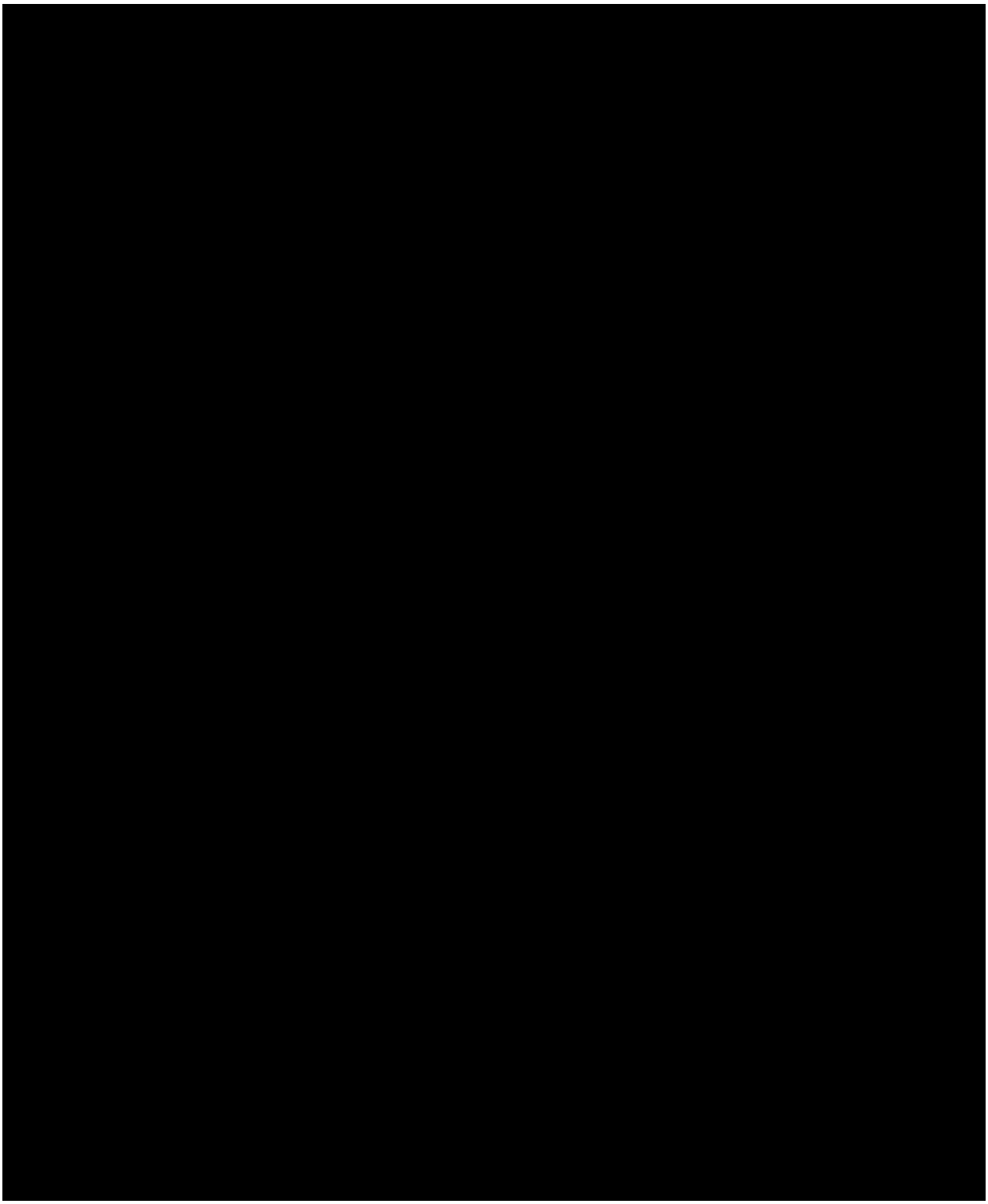
A listing of subjects with abnormal ECG status will be presented. The number and percentage of subjects with shifts from baseline to each of the categorical values denoting an abnormal scan (abnormal, not AE/abnormal, AE) will be summarized.

5.4.6 Safety analysis during lymphocyte follow-up period

The concomitant medication, AEs, hematology, vital signs and physical examination data collected during the lymphocyte follow-up period will be analyzed.

The concomitant medication and AEs, either started prior to the lymphocyte follow-up period and continued during the lymphocyte follow-up period, or started on or after the lymphocyte follow-up period will be listed.

Hematology, vital signs and physical examination data during the lymphocyte follow-up period will either be descriptively summarized or listed. The windowing rule defined in Section 5.3.3 will be used for visit mapping. Additional safety analyses during lymphocyte follow-up period may be conducted.



5.7 Changes in statistical analysis methods

5.7.1 Change in clinical assessment population definition

In protocol, the evaluable population for clinical assessments is defined as all subjects who receive at least 1 dose of study treatment and at least 1 measurement for each of the clinical assessments after Baseline.

Appendix 1 – List of reportable lymphocyte subset parameters

Lab test name (LabCorp)	Lab test code (LabCorp)	Lab label	Subset type
%CD24hi/CD38hi [CD19+/CD3-]	BCSB03	Transitional B-cells (% of B cells)	B Cell Subsets
%CD24hi/CD38hi/CD10+ [19+/3-]	BCSB08	CD10+ Transitional B cells (% of B cells)	B Cell Subsets
%CD27++/CD38++ [CD19+/CD3-]	BCSB09	Plasmablasts (% of B cells)	B Cell Subsets
%CD27++/CD38++/CD10- [19+/3-]	BCSB10	Plasma Cells [CD10-] (% of B cells)	B Cell Subsets
%CD27++/CD38++/CD138+ [19+/3-]	BCSB12	CD138+ Plasma Cells (% of B cells)	B Cell Subsets
%CD27+/IgD+ [CD19+/CD3-]	BCSB07	IgD+ Memory B cells [non-class switched] (% of B cells)	B Cell Subsets
%CD27+/IgD- [CD19+/CD3-]	BCSB06	IgD- Memory B cells [class switched] (% of B cells)	B Cell Subsets
%CD27-/IgD+ [CD19+/CD3-]	BCSB05	Naïve B cells (% of B cells)	B Cell Subsets
Absolute 27++/38++/10-[19+/3-]	BCSB22	Plasma Cells [CD10-] (cells/mm3)	B Cell Subsets
Absolute CD24hi/CD38hi[19+/3-]	BCSB15	Transitional B-cells (cells/mm3)	B Cell Subsets
Absolute CD27++/38++[19+/3-]	BCSB21	Plasmablasts (cells/mm3)	B Cell Subsets
Absolute CD27+/IgD+ [CD19+/3-]	BCSB19	IgD+ Memory B cells [non-class switched] (cells/mm3)	B Cell Subsets
Absolute CD27+/IgD- [CD19+/3-]	BCSB18	IgD- Memory B cells [class switched] (cells/mm3)	B Cell Subsets
Absolute CD27-/IgD+ [CD19+/3-]	BCSB17	Naïve B cells (cells/mm3)	B Cell Subsets
Absolute24hi/38hi/10+[19+/3-]	BCSB20	CD10+ Transitional B cells (cells/mm3)	B Cell Subsets
Absolute27++/38++/138+[19+MNC]	BCSB24	CD138+ Plasma Cells (cells/mm3)	B Cell Subsets
%CD11a+ [CD11c++]	A4S96	CD11a+ (% of dendritic cells [CD11c++])	VLA-4/LFA-1 Expression
%CD11a+ [CD19+]	A4S82	CD11a+ (% of B cells)	VLA-4/LFA-1 Expression
%CD11a+ [CD3+]	A4S68	CD11a+ (% of T cells)	VLA-4/LFA-1 Expression
%CD11a+ [Lymphs]	A4S26	CD11a+ (% of lymphocytes)	VLA-4/LFA-1 Expression
%CD11a+ [MNC]	A4S12	CD11a+ (% of MNC)	VLA-4/LFA-1 Expression
%CD11a+ [Monos]	A4S40	CD11a+ (% of monocytes)	VLA-4/LFA-1 Expression

%CD11a+ [Neut]	A4S54	CD11a+ (% of neutrophils)	VLA-4/LFA-1 Expression
%CD49d+ (9F10) [CD11c++]	A4S95	CD49d+ (% of dendritic cells [CD11c++])	VLA-4/LFA-1 Expression
%CD49d+ (9F10) [CD19+]	A4S81	CD49d+ (% of B cells)	VLA-4/LFA-1 Expression
%CD49d+ (9F10) [CD3+]	A4S67	CD49d+ (% of T cells)	VLA-4/LFA-1 Expression
%CD49d+ (9F10) [Lymphs]	A4S25	CD49d+ (% of lymphocytes)	VLA-4/LFA-1 Expression
%CD49d+ (9F10) [MNC]	A4S11	CD49d+ (% of MNC)	VLA-4/LFA-1 Expression
%CD49d+ (9F10) [Monos]	A4S39	CD49d+ (% of monocytes)	VLA-4/LFA-1 Expression
%CD49d+ (9F10) [Neut]	A4S53	CD49d+ (% of neutrophils)	VLA-4/LFA-1 Expression
MESF Total CD11a [CD11c++]	A4S92	CD11a+ dendritic cells [CD11c++] (MESF)	VLA-4/LFA-1 Expression
MESF Total CD11a [CD19+]	A4S78	CD11a+ B cells (MESF)	VLA-4/LFA-1 Expression
MESF Total CD11a [CD3+]	A4S64	CD11a+ T cells (MESF)	VLA-4/LFA-1 Expression
MESF Total CD11a [Lymphs]	A4S22	CD11a+ lymphocytes (MESF)	VLA-4/LFA-1 Expression
MESF Total CD11a [MNC]	A4S08	CD11a+ MNC (MESF)	VLA-4/LFA-1 Expression
MESF Total CD11a [Monos]	A4S36	CD11a+ monocytes (MESF)	VLA-4/LFA-1 Expression
MESF Total CD11a [Neut]	A4S50	CD11a+ neutrophils (MESF)	VLA-4/LFA-1 Expression
MESF Total CD49d (9F10) [CD3+]	A4S63	CD49d+ dendritic cells [CD11c++] (MESF)	VLA-4/LFA-1 Expression
MESF Total CD49d (9F10) [MNC]	A4S07	CD49d+ B cells (MESF)	VLA-4/LFA-1 Expression
MESF Total CD49d (9F10) [Neut]	A4S49	CD49d+ T cells (MESF)	VLA-4/LFA-1 Expression

MESF Total CD49d [CD11c++]	A4S91	CD49d+ lymphocytes (MESF)	VLA-4/LFA-1 Expression
MESF Total CD49d [CD19+]	A4S77	CD49d+ MNC (MESF)	VLA-4/LFA-1 Expression
MESF Total CD49d [Lymphs]	A4S21	CD49d+ monocytes (MESF)	VLA-4/LFA-1 Expression
MESF Total CD49d [Monos]	A4S35	CD49d+ neutrophils (MESF)	VLA-4/LFA-1 Expression
%CD14+ [CD45+]	DMNK02	Total monocytes [CD14+] (% of CD45+ leukocytes)	Myeloid and NK cell subsets
%CD16+/CD14+dim [CD45+]	DMNK04	Non-classical Monocytes (% of CD45+ leukocytes)	Myeloid and NK cell subsets
%CD16+/CD56hi/3-/19- [Lymphs]	DMNK10	$CD56^{Bright}$ NK cells (% of lymphocytes)	Myeloid and NK cell subsets
%CD16+/CD56low/3-/19- [Lymphs]	DMNK09	$CD56^{Dim}$ NK cells (% of lymphocytes)	Myeloid and NK cell subsets
%CD16-/CD14+ [CD45+]	DMNK03	Classical Monocytes (% of CD45+ leukocytes)	Myeloid and NK cell subsets
%HLA-DR+ [MNC]	DMNK06	Total dendritic cells (% of MNC)	Myeloid and NK cell subsets
%HLA-DR+/CD11c+ [MNC]	DMNK07	Myeloid dendritic cells (% of MNC)	Myeloid and NK cell subsets
%HLA-DR+/CD123+ [MNC]	DMNK08	Plasmacytoid dendritic cells (% of MNC)	Myeloid and NK cell subsets
Abs CD16+/CD56hi/3-/19- Lymphs	DMNK20	$CD56^{Bright}$ NK cells (cells/mm3)	Myeloid and NK cell subsets
AbsCD16+/CD56low/3-/19- Lymphs	DMNK19	$CD56^{Dim}$ NK cells (cells/mm3)	Myeloid and NK cell subsets
Absolute CD14+	DMNK12	Total monocytes [CD14+] (cells/mm3)	Myeloid and NK cell subsets
Absolute CD16+/CD14+dim	DMNK14	Non-classical Monocytes (cells/mm3)	Myeloid and NK cell subsets
Absolute CD16-/CD14+	DMNK13	Classical Monocytes (cells/mm3)	Myeloid and NK cell subsets
Absolute HLA-DR+ [MNC]	DMNK16	Total dendritic cells (cells/mm3)	Myeloid and NK cell subsets

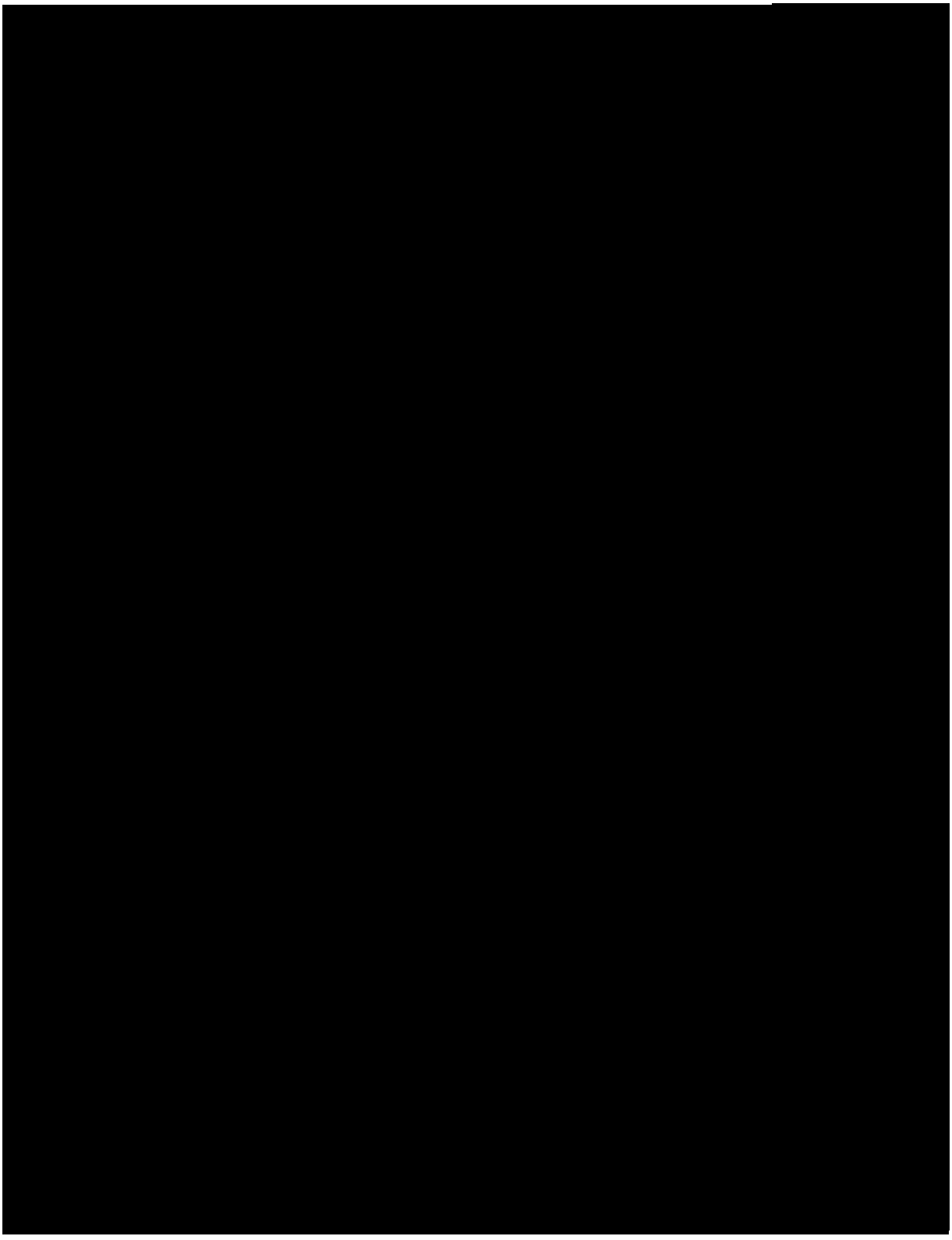
Absolute HLA-DR+/CD11c+ [MNC]	DMNK17	Myeloid dendritic cells (cells/mm3)	Myeloid and NK cell subsets
Absolute HLA-DR+/CD123+ [MNC]	DMNK18	Plasmacytoid dendritic cells (cells/mm3)	Myeloid and NK cell subsets
%45+/25+/127low/- [3+/4+]	TCTR22	Regulatory T-cells (% of CD4+ T cells)	T cell subsets
%45+/25+/127low/-/45RO-[3+/4+]	TCTR25	Naïve Regulatory T-cells (% of CD4+ T cells)	T cell subsets
%45+/25+/127low/45RO+ [3+/4+]	TCTR26	Effector Regulatory T-cells (% of CD4+ T cells)	T cell subsets
%45+25+127low45RO+DR+[3+4+]	TCTR075	Terminal Effector Regulatory T-cells (% of CD4+ T cells)	T cell subsets
%CD38+ [3+/4+/8-]	TCTR069	Activated [CD38+] (% of CD4+ T cells)	T cell subsets
%CD38+ [3+/4-/8+]	TCTR072	Activated [CD38+] (% of CD8+ T cells)	T cell subsets
%CD38+/HLA-DR+ [CD3+/CD4+]	TCTR14	Activated [CD38+HLA-DR+] (% of CD4+ T cells)	T cell subsets
%CD38+/HLA-DR+ [CD3+/CD8+]	TCTR21	Activated [CD38+HLA-DR+] (% of CD8+ T cells)	T cell subsets
%CD4+/CD45RA+ [CD3+]	TCTR08	Naïve CD4+ T-cell [CD45RA+] (% of T cells)	T cell subsets
%CD4+/CD45RA- [CD3+]	TCTR09	Memory CD4+ T-cell [CD45RA-] (% of T cells)	T cell subsets
%CD45RA+/CCR7+ [CD3+/CD4+]	TCTR10	Naïve CD4+ T-cell [CD45RA+CCR7+] (% of CD4+ T cells)	T cell subsets
%CD45RA+/CCR7+ [CD3+/CD8+]	TCTR17	Naïve CD8+ T-cell [CD45RA+CCR7+] (% of CD8+ T cells)	T cell subsets
%CD45RA+/CCR7- [CD3+/CD4+]	TCTR11	Effector CD4+ T-cell [CD45RA+CCR7-] (% of CD4+ T cells)	T cell subsets
%CD45RA+/CCR7- [CD3+/CD8+]	TCTR18	Effector CD8+ T-cell [CD45RA+CCR7-] (% of CD8+ T cells)	T cell subsets
%CD45RA-/CCR7+ [CD3+/CD4+]	TCTR12	Central Memory CD4+ T-cell [CD45RA-CCR7+] (% of CD4+ T cells)	T cell subsets
%CD45RA-/CCR7+ [CD3+/CD8+]	TCTR19	Central Memory CD8+ T-cell [CD45RA-CCR7+] (% of CD8+T cells)	T cell subsets
%CD45RA-/CCR7- [CD3+/CD4+]	TCTR13	Effector Memory CD4+ T-cell [CD45RA-CCR7-] (% of CD4+ T cells)	T cell subsets

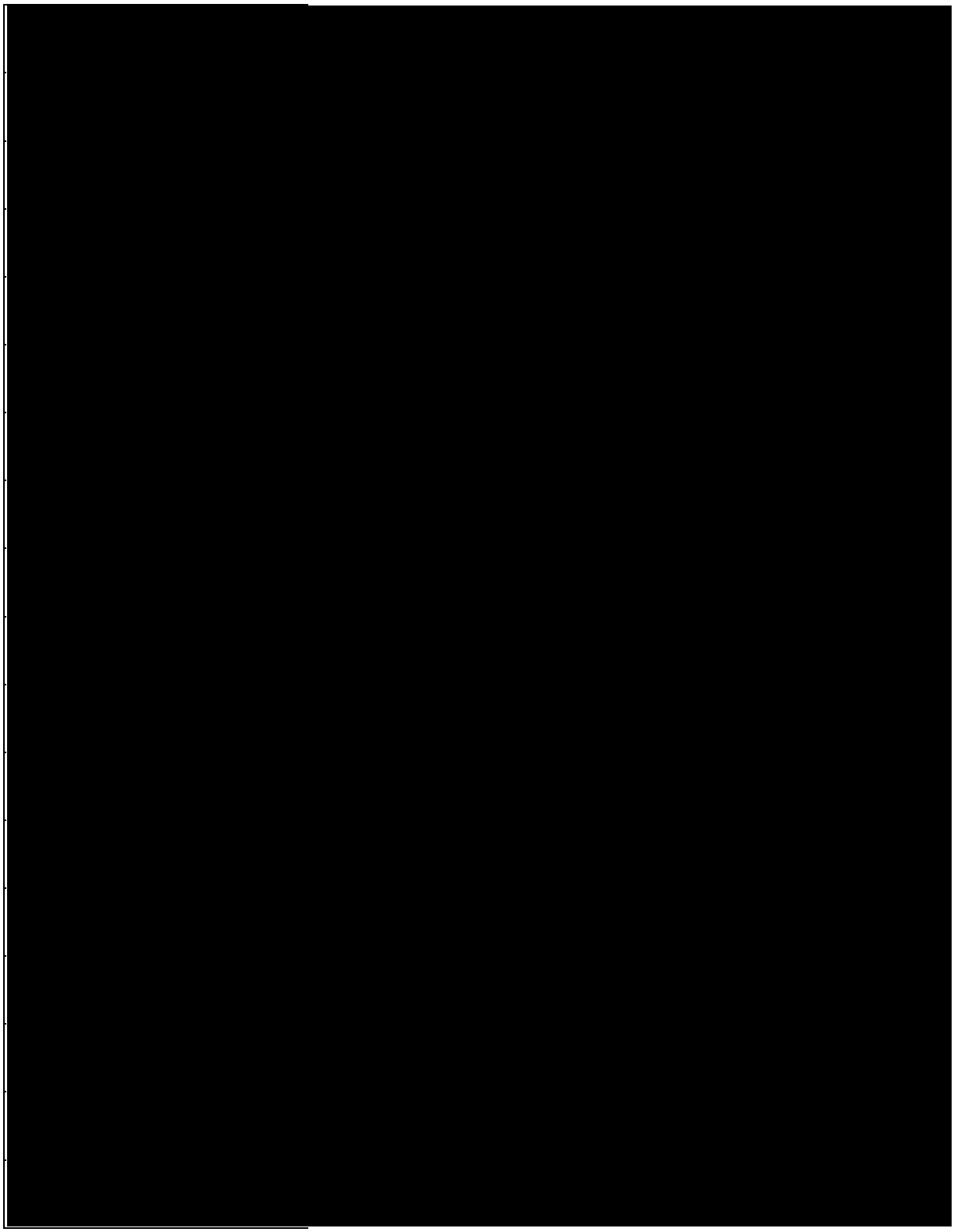
%CD45RA-/CCR7- [CD3+/CD8+]	TCTR20	Effector Memory CD8+ T-cell [CD45RA-CCR7-] (% of CD8+T cells)	T cell subsets
%CD8+/CD45RA+ [CD3+]	TCTR15	Naïve CD8+ T-cell [CD45RA+] (% of T cells)	T cell subsets
%CD8+/CD45RA- [CD3+]	TCTR16	Memory CD8+ T-cell [CD45RA-] (% of T cells)	T cell subsets
%CXCR3+/CCR6- [CD3+/CD4+]	TCTR29	Th1 phenotype (% of CD4+ T cells)	T cell subsets
%CXCR3+CCR6-38+HLA-DR+ [3+4+]	TCTR32	Activated Th1 phenotype (% of CD4+ T cells)	T cell subsets
%CXCR3-/CCR6+ [CD3+/CD4+]	TCTR31	Th17 phenotype (% of CD4+ T cells)	T cell subsets
%CXCR3-/CCR6- [CD3+/CD4+]	TCTR30	Th2-enriched phenotype (% of CD4+ T cells)	T cell subsets
%CXCR3-CCR6+38+HLA-DR+ [3+4+]	TCTR34	Activated Th17 phenotype (% of CD4+ T cells)	T cell subsets
%CXCR3-CCR6-38+HLA-DR+ [3+4+]	TCTR33	Activated Th2-enriched phenotype (% of CD4+ T cells)	T cell subsets
%HLA-DR+ [3+/4+/8-]	TCTR068	Activated [HLA-DR+] (% of CD4+ T cells)	T cell subsets
%HLA-DR+ [3+/4-/8+]	TCTR071	Activated [HLA-DR+] (% of CD8+ T cells)	T cell subsets
Abs 45+25+127low/-45RO-[3+4+]	TCTR56	Naïve Regulatory T-cells (cells/mm3)	T cell subsets
Abs 45+25+127low45RO+ [3+4+]	TCTR57	Effector Regulatory T-cells (cells/mm3)	T cell subsets
Abs 45+25+127low45RO+DR+[3+4+]	TCTR084	Terminal Effector Regulatory T-cells (cells/mm3)	T cell subsets
AbsCXCR3+CCR6-38+HLA-DR+[3+4+]	TCTR63	Activated Th1 phenotype (cells/mm3)	T cell subsets
AbsCXCR3-CCR6+38+HLA-DR+[3+4+]	TCTR65	Activated Th17 phenotype (cells/mm3)	T cell subsets
AbsCXCR3-CCR6-38+HLA-DR+[3+4+]	TCTR64	Activated Th2-enriched phenotype (cells/mm3)	T cell subsets
Absolute 38+/HLA-DR+ [3+/8+]	TCTR52	Activated CD8+ T-cell [CD38+HLA-DR+] (cells/mm3)	T cell subsets
Absolute 38+/HLA-DR+ [3+/4+]	TCTR45	Activated CD4+ T-cell [CD38+HLA-DR+] (cells/mm3)	T cell subsets
Absolute 45+25+127low/- [3+4+]	TCTR53	Regulatory T-cells (cells/mm3)	T cell subsets

Absolute 45RA+/CCR7+ [3+/4+]	TCTR41	Naïve CD4+ T-cell [CD45RA+CCR7+] (cells/mm3)	T cell subsets
Absolute 45RA+/CCR7+ [3+/8+]	TCTR48	Naïve CD8+ T-cell [CD45RA+CCR7+] (cells/mm3)	T cell subsets
Absolute 45RA+/CCR7- [3+/4+]	TCTR42	Effector CD4+ T-cell [CD45RA+CCR7-] (cells/mm3)	T cell subsets
Absolute 45RA+/CCR7- [3+/8+]	TCTR49	Effector CD8+ T-cell [CD45RA+CCR7-] (cells/mm3)	T cell subsets
Absolute 45RA-/CCR7+ [3+/4+]	TCTR43	Central Memory CD4+ T-cell [CD45RA-CCR7+] (cells/mm3)	T cell subsets
Absolute 45RA-/CCR7+ [3+/8+]	TCTR50	Central Memory CD8+ T-cell [CD45RA-CCR7+] (cells/mm3)	T cell subsets
Absolute 45RA-/CCR7- [3+/4+]	TCTR44	Effector Memory CD4+ T-cell [CD45RA-CCR7-] (cells/mm3)	T cell subsets
Absolute 45RA-/CCR7- [3+/8+]	TCTR51	Effector Memory CD8+ T-cell [CD45RA-CCR7-] (cells/mm3)	T cell subsets
Absolute CD38+ [3+/4+/8-]	TCTR078	Activated CD4+ T-cell [CD38+] (cells/mm3)	T cell subsets
Absolute CD38+ [3+/4-/8+]	TCTR081	Activated CD8+ T-cell [CD38+] (cells/mm3)	T cell subsets
Absolute CD4+/CD45RA+ [CD3+]	TCTR39	Naïve CD4+ T-cell [CD45RA+] (cells/mm3)	T cell subsets
Absolute CD4+/CD45RA- [CD3+]	TCTR40	Memory CD4+ T-cell [CD45RA-] (cells/mm3)	T cell subsets
Absolute CD8+/CD45RA+ [CD3+]	TCTR46	Naïve CD8+ T-cell [CD45RA+] (cells/mm3)	T cell subsets
Absolute CD8+/CD45RA- [CD3+]	TCTR47	Memory CD8+ T-cell [CD45RA-] (cells/mm3)	T cell subsets
Absolute CXCR3+/CCR6- [3+/4+]	TCTR60	Th1 phenotype (cells/mm3)	T cell subsets
Absolute CXCR3-/CCR6+ [3+/4+]	TCTR62	Th17 phenotype (cells/mm3)	T cell subsets
Absolute CXCR3-/CCR6- [3+/4+]	TCTR61	Th2-enriched phenotype(cells/mm3)	T cell subsets
Absolute HLA-DR+ [3+/4+/8-]	TCTR077	Activated CD4+ T-cell [HLA-DR+] (cells/mm3)	T cell subsets
Absolute HLA-DR+ [3+/4-/8+]	TCTR080	Activated CD8+ T-cell [HLA-DR+] (cells/mm3)	T cell subsets

%IFNg+/ IL-17A- [3+/8+] Stim	ICT56	IFNg+ (% of CD8+ T cells)	Intracellular T cell Cytokines
%IFNg+/IL-17A- [CD3+/CD4+]Stim	ICT30	IFNg+ (% of CD4+ T cells)	Intracellular T cell Cytokines
%IFNg+/IL-17A-[3+4+8-45RA-]St	ICT39	IFNg+ (% of memory CD4+ T cells)	Intracellular T cell Cytokines
%IFNg+/IL-17A-[3+8+4-45RA-]St	ICT61	IFNg+ (% of memory CD8+ T cells)	Intracellular T cell Cytokines
%IL-17A+/IFNg- [3+/8+] Stim	ICT58	IL-17A+/IFNg- (% of CD8+ T cells)	Intracellular T cell Cytokines
%IL-17A+/IFNg- [CD3+/CD4+]Stim	ICT32	IL-17A+/IFNg- (% of CD4+ T cells)	Intracellular T cell Cytokines
%IL-17A+/IFNg-[3+4+8-45RA-]St	ICT41	IL-17A+/IFNg- (% of memory CD4+ T cells)	Intracellular T cell Cytokines
%IL-17A+/IFNg-[3+8+4-45RA-]St	ICT63	IL-17A+/IFNg- (% of memory CD8+ T cells)	Intracellular T cell Cytokines
%IL-2+ [3+/4+/8-/45RA-] Stim	ICT42	IL-2+ (% of memory CD4+ T cells)	Intracellular T cell Cytokines
%IL-2+ [3+8+4-45RA-]St	ICT64	IL-2+ (% of memory CD8+ T cells)	Intracellular T cell Cytokines
%IL-2+ [CD3+/CD4+] Stim	ICT33	IL-2+ (% of CD4+ T cells)	Intracellular T cell Cytokines
%IL-2+ [CD3+/CD8+] Stim	ICT59	IL-2+ (% of CD8+ T cells)	Intracellular T cell Cytokines
%IL-4+ [3+/4+/8-/45RA-]Stim	ICT40	IL-4+ (% of memory CD4+ T cells)	Intracellular T cell Cytokines
%IL-4+ [3+8+4-45RA-] Stim	ICT62	IL-4+ (% of memory CD8+ T cells)	Intracellular T cell Cytokines
%IL-4+ [CD3+/CD4+] Stim	ICT31	IL-4+ (% of CD4+ T cells)	Intracellular T cell Cytokines
%IL-4+ [CD3+/CD8+] Stim	ICT57	IL-4+ (% of CD8+ T cells)	Intracellular T cell Cytokines
% Granulocytes	PGRANS	Granulocytes (% of leukocytes)	TBNK Lymphocyte Subsets
% Lymphocytes	PLYMPH	Lymphocytes(% of leukocytes)	TBNK Lymphocyte Subsets

% Monocytes	PMONOS	Monocytes (% of leukocytes)	TBNK Lymphocyte Subsets
%CD19+ (TBNK TruCount BD)	CD19P1	B cells (% of lymphocytes)	TBNK Lymphocyte Subsets
%CD3+ [Tube 1]	CD3P1	T cells (% of lymphocytes)	TBNK Lymphocyte Subsets
%CD3+/CD4+	CD4P1	CD4+ T cells (% of lymphocytes)	TBNK Lymphocyte Subsets
%CD3+/CD8+	CD8P1	CD8+ T cells (% of lymphocytes)	TBNK Lymphocyte Subsets
%CD3-/CD16+,CD56+	NK2P1	NK cells (% of lymphocytes)	TBNK Lymphocyte Subsets
Abs Granulocytes	AGRANS	Granulocytes (cells/mm3)	TBNK Lymphocyte Subsets
Abs Monocytes	AMONOS	Monocytes (cells/mm3)	TBNK Lymphocyte Subsets
Absolute CD3+ [Tube 1]	CD3A1	T Cells (cells/mm3)	TBNK Lymphocyte Subsets
Absolute Lymphocytes [Tube 1]	ALYMT1	Lymphocytes (cells/mm3)	TBNK Lymphocyte Subsets
CD16,56 Absolute	NK2A	NK cells (cells/mm3)	TBNK Lymphocyte Subsets
CD19 Absolute	CD19A	B cells (cells/mm3)	TBNK Lymphocyte Subsets
CD4 Absolute	CD4A	CD4+ T cells (cells/mm3)	TBNK Lymphocyte Subsets
CD8 Absolute	CD8A	CD8+ T cells (cells/mm3)	TBNK Lymphocyte Subsets
[redacted]			





Appendix 2 – Visit windowing rules

For Blood Chemistry, window to scheduled visits using the following windows:

Visit Name	Target Day	Study Day in Range Window
Baseline	first dose date	<= first dose date
Week 4	Day 29	(first dose date+1) to Day 42
Week 8	Day 57	Day 43 to Day 112
Week 24	Day 169	Day 113 to Day 252
Week 48	Day 337	Day 253 to Day 504
Week 96	Day 673	>=Day 505

For Hematology parameters, window to scheduled visits using the following windows:

Visit Name	Target Day	Study Day in Range Window
Baseline	first dose date	<= first dose date
Week 4	Day 29	(first dose date+1) to Day 42
Week 8	Day 57	Day 43 to Day 70
Week 12	Day 85	Day 71 to Day 126
Week 24	Day 169	Day 127 to Day 210
Week 36	Day 253	Day 211 to Day 294
Week 48	Day 337	Day 295 to Day 378
Week 60	Day 421	Day 379 to Day 462
Week 72	Day 505	Day 463 to Day 546
Week 84	Day 589	Day 547 to Day 630
Week 96	Day 673	>=Day 631

For the lymphocyte subsets, Igs and vital signs, window to scheduled visits using the following windows:

Visit Name	Target Day	Study Day in Range Window
Baseline	first dose date	<= first dose date
Week 4	Day 29	(first dose date+1) to Day 42
Week 8	Day 57	Day 43 to Day 70
Week 12	Day 85	Day 71 to Day 126
Week 24	Day 169	Day 127 to Day 210
Week 36	Day 253	Day 211 to Day 294
Week 48	Day 337	Day 295 to Day 420
Week 72	Day 505	Day 421 to Day 588
Week 96	Day 673	>=Day 589

For the physical exam (weight and height), window to scheduled visits using the following windows:

Visit Name	Target Day	Study Day in Range Window
Baseline	first dose date	<= first dose date
Week 48	Day 337	(first dose date+1) to Day 504
Week 96	Day 673	>=Day 505

For the lymphocyte subsets in the lymphocyte follow-up period, window to scheduled visits using the following windows:

Visit Name	**Target Day**	**Study Day in Range Window**
Lymphocyte FU Baseline	lymphocyte follow-up start date	<= lymphocyte follow-up start date
4 weeks from Lymphocyte FU baseline	Day 29	Day 2 to Day 42
8 weeks from Lymphocyte FU baseline	Day 57	Day 43 to Day 70
12 weeks from Lymphocyte FU baseline	Day 85	Day 71 to Day 98
16 weeks from Lymphocyte FU baseline	Day 113	Day 99 to Day 126
20 weeks from Lymphocyte FU baseline	Day 141	Day 127 to Day 154
24 weeks from Lymphocyte FU baseline	Day 169	Day 155 to Day 210
36 weeks from Lymphocyte FU baseline	Day 253	Day 211 to Day 294
48 weeks from Lymphocyte FU baseline	Day 337	>= Day 295