COVER PAGE

Official Title:	A Randomized, Double-Blind, Parallel-Group, Phase I Study to Evaluate the Pharmacokinetics, Safety and Immunogenicity of BIIB800 s.c. Compared to Actemra® in Healthy Male Participants
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Statistical Analysis Plan

A Randomized, Double-Blind, Parallel-Group, Phase I Study to Evaluate the Pharmacokinetics, Safety and Immunogenicity of BIIB800 s.c. compared to Actemra® in Healthy Male Participants

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LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

$\%AUC_{extrap}$	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
ADA	anti-drug antibody
ADaM	Analysis Data Model
AE	adverse event
ANCOVA	analysis of covariance
APAS	all participants analysis set
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUE	area under the effect-time curve
BLQ	below the limit of quantification
BSSR	blinded sample size reassessment
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
CSR	clinical study report
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
E_{max}	maximum observed effect
E_{min}	minimum observed effect
EoS	end of study
FDA	Food and Drug Administration
GLSM	geometric least squares mean
hsCRP	high sensitivity C-reactive protein
ICH	International Council for/Conference on Harmonisation
ISR	injection site reaction
LLOQ	lower limit of quantification

ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralizing antibody
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PKCS	pharmacokinetic concentration analysis set
QTcF	QT interval corrected for heart rate using Fridericia's formula
R^2-adj	adjusted coefficient for determination of exponential fit
s.c.	subcutaneous
SAE	serious adverse event
SAFS	safety analysis full set
SAP	statistical analysis plan
SD	standard deviation
SDV	source document verification
sIL-6R	soluble interleukin-6-receptor
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
tE_{max}	time of maximum observed effect
tE_{min}	time of minimum observed effect
TFL	table, figure, and listing
t_{last}	time of the last quantifiable concentration
t_{max}	time of the maximum observed concentration
V_z/F	apparent volume of distribution during the terminal phase
WHODrug	World Health Organization Drug Dictionary
λ_z	apparent terminal elimination rate constant
λ_z Lower	start of exponential fit
λ_z N	number of data points included in the log-linear regression
λ_z Span Ratio	time period over which λ_z was determined as a ratio of $t_{1/2}$
λ_z Upper	end of exponential fit

1. INTRODUCTION

This SAP was developed after a review of the clinical study protocol (Final Version 2.0 dated 06 December 2023) and the corresponding electronic case report form (eCRF).

This SAP describes the planned statistical analysis of the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability data from this study. A detailed description of the planned tables, figures, and listings (TFLs) to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on pre-specifications from the protocol, unless modified by agreement with Biogen. A limited amount of background information about this study (e.g., objectives, study design) is provided to help the reader's understanding.

This SAP must be finalized prior to any unblinding of study data for analysis purposes (interim or final).

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified and detailed in Section 9 of this SAP. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed upon between Biogen and Fortrea prior to execution and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trials* and ICH E9 (R1) guideline *Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials*[1,2,3,4] along with the FDA and EMA guidelines for bioequivalence studies[5,6].

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 1.

Table 1: Study Objectives and Endpoints

Primary Objective	**Co-Primary Endpoints**
To show PK equivalence of BIIB800 and Actemra following a single dose s.c. administration to healthy male participants (volunteers)	For EMA, PK parameters derived from tocilizumab serum concentrations: • C_{max} • $AUC_{0\text{-}inf}$ For FDA, PK parameters derived from tocilizumab serum concentrations: • C_{max} • $AUC_{0\text{-}t}$
Secondary Objectives	**Secondary Endpoints**
To evaluate PK of BIIB800 s.c. and Actemra over time	Other PK parameters derived from tocilizumab serum concentrations, including: • t_{max} • CL/F • $t_{1/2}$
To evaluate the clinical safety of BIIB800 s.c. and Actemra	Incidence of AEs and SAEs from the time of administration to EoS
To evaluate PD profiles BIIB800 s.c. and Actemra	The PD parameters derived from sIL-6R concentrations, including: • AUE • E_{max} • tE_{max} The PD parameters derived from hsCRP concentrations, including: • AUE • E_{min} • tE_{min}
To evaluate the immunogenicity of BIIB800 s.c. and Actemra	• ADA and nAbs • ADA titers

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; AUE = area under the effect-time curve; CL/F = apparent total clearance; C_{max} = maximum observed concentration; EMA = European Medicines Agency; E_{max} = maximum observed effect; E_{min} = minimum observed

effect; EoS = end of study; FDA = Food and Drug Administration; hsCRP = high sensitivity C-reactive protein; nAbs = neutralizing antibodies; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; s.c. = subcutaneous; sIL-6R = soluble interleukin-6-receptor; $t_{1/2}$ = apparent terminal elimination half-life; tE_{max} = time of maximum observed effect; tE_{min} = time of minimum observed effect; t_{max} = time of the maximum observed concentration

3. STUDY DESIGN

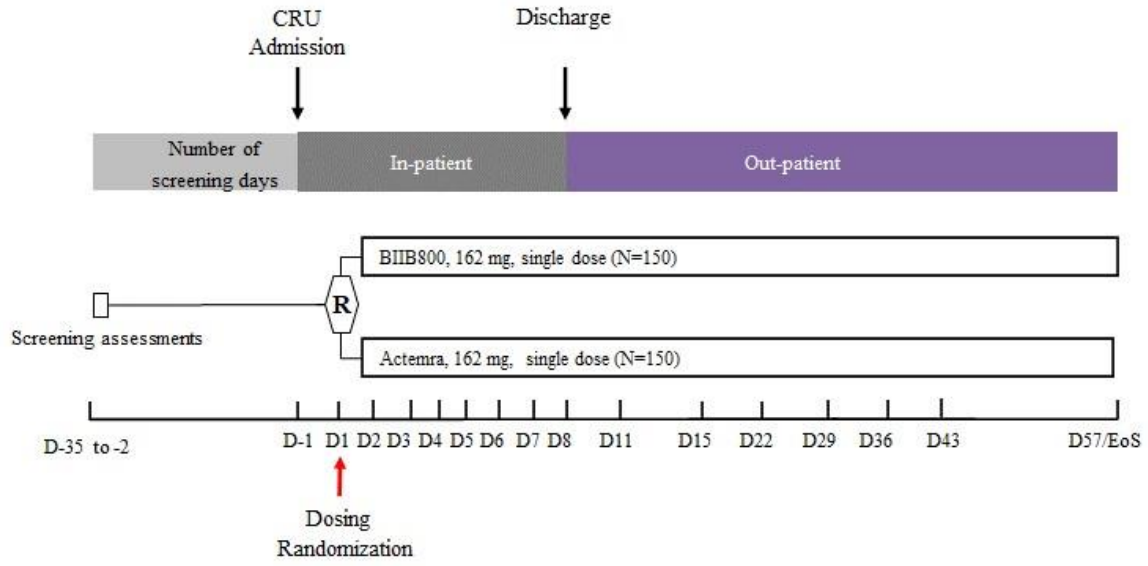
This is a randomized, active-controlled, double-blind, single-dose, 2-treatment arm, parallel-group study to compare the PK, PD, safety, and immunogenicity of BIIB800 s.c. with Actemra in healthy male participants.

A total of (approximately) 300 participants were planned to be enrolled and randomized 1:1 to receive a single 162 mg dose of BIIB800 or Actemra, administered as a subcutaneous (s.c.) injection in the outer upper arm. A blinded sample size reassessment (BSSR) during the study was prespecified to be conducted during the study, to assess the actual coefficient of variation (CV) and to inform whether an adjustment needed to be made to the sample size.

Informed consent was be obtained before performing any study-related procedures. Participants were be screened for eligibility between Day -35 and Day -2. On Day -1, eligible participants were admitted to the Phase I unit and planned to remain resident until after completion of the Day 8 assessments. On Day 1 participants were randomized 1:1, stratified according to body weight (<75kg, ≥ 75 kg), to 1 of the 2 treatment arms. Outpatient visits occured on Days 11, 15, 22, 29, 36, 43, and 57. Safety, PK, PD, and immunogenicity assessments were performed at specified time points throughout the study up to Day 57.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



4. SAMPLE SIZE JUSTIFICATION

Please see Blinded Sample Size Reassessment (BSSR) SAP (Final Version 1.0 dated 02JUL2024) for details.

5. STUDY TREATMENTS

The study treatment names and ordering to be used in the TFLs are presented in Table 2.

Table 2: Presentation of Study Treatments in TFLs

Study Treatment	Order in TFLs
162 mg BIIB800 (s.c.)	1
162 mg Actemra (s.c.)	2

Abbreviations: s.c. = subcutaneous

6. DEFINITIONS OF ANALYSIS SETS

Important protocol deviations will be specified in the study protocol deviation list. Any protocol deviations will be considered prior to database lock for their ethical/clinical relevance and taken into consideration when assigning participants to analysis sets.

For all analysis sets, statistical analyses and TFLs will be based on actual treatment received. Any deviation between the randomized treatment and the actual received treatment will be listed.

6.1. All Participants Analysis Set

The 'all participants analysis set' (APAS) will include all participants who signed the informed consent form and had any study assessment recorded in the database per the protocol. The APAS will be used for the disposition and demographics tables and for listings of all individual data.

6.2. Safety Analysis Full Set

The safety analysis full set (SAFS) will include all randomized study participants who received the study treatment. The SAFS will be used for the analysis of safety and immunogenicity data.

6.3. Pharmacokinetic Concentration Analysis Set

The PK concentration analysis set (PKCS) will include all study participants with at least 1 post-dose serum PK concentration available. The serum concentration of tocilizumab will be summarized based on the PKCS.

6.4. Pharmacokinetic Analysis Set

The PK Analysis Set (PKAS) will include all randomized study participants with at least 1 calculable PK parameter. Participants with an important protocol violation that would affect all PK co-primary endpoints evaluation will be excluded from the PKAS. Determination of exclusion, with a list of excluded participants, will be made prior to the unblinding in the blinded data review meeting (BDRM). The PKAS will be used to evaluate the PK equivalence between study treatments.

6.5. Pharmacodynamic Concentration Analysis Set

The PD concentration analysis set (PDCS) will include all study participants with at least 1 post-dose PD measurement. The concentrations of soluble interleukin-6-receptor (sIL-6R) and high sensitivity C-reactive protein (hsCRP) will be summarized based on the PDCS.

6.6. Pharmacodynamic Analysis Set

The PD Analysis Set (PDAS) will include all randomized study participants with at least 1 calculable PD parameter. Participants with an important protocol violation that would affect PD evaluation will be excluded from the PDAS. Determination of exclusion, with a list of excluded participants, will be made prior to the unblinding in the blinded data review meeting (BDRM).

7. STATISTICAL METHODOLOGY

7.1. General

Listings will be provided for all data captured during the study. Listings will include all participants assigned to the all-participants analysis set (APAS) and include data up to the point of study completion or discontinuation. Participants are considered to have completed the study if they complete the scheduled Day 57 end-of-study visit. Any participant who withdraws from the study prior to Day 57 will be identified accordingly in the listings. Summaries and statistical analyses will include the participants assigned to the relevant analysis set based on the data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if a new version is issued during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if a new version is issued during the study). Pinnacle 21 Community Validator Version 4.0.2 (or higher if a new version is issued during the study) will be used to ensure compliance with CDISC standards.

Where reference is made to ‘valid’ data, this refers to non-missing data that meet the predetermined criteria (i.e., are not flagged for exclusion).

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, and changes from baseline.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

7.1.1. Calculation of the Summary Statistics

For continuous data, the following rules will be applied:

- Missing values will not be imputed unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of participants with valid observations (n) <3, summary statistics will not be calculated, except n, minimum, and maximum.
- In general, as early termination data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics and statistical analyses. Exceptions may be made where justified. Reasons for any early terminations will be presented.

For categorical data, the following rules will be applied:

- For ordered categorical data (e.g., adverse event [AE] severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.
- For non-ordered categorical data (e.g., race), only those categories for which there is at least 1 participant represented will be included, unless specifically stated otherwise.
- Missing values will not be imputed unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the analysis set size totals are consistent across different parameters.

7.1.2. Repeat and Unscheduled Readings

For vital signs and 12-lead ECG data only, any pre-dose value recorded in addition to the original value, or a post-dose value recorded within 15 minutes of the original value will be defined as a repeat value; any post-dose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (e.g., laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations, with the exception of the 12-lead ECG outlier analysis (see Section 7.8.4).

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, except the baseline derivation (see Section 7.1.3) and 12 lead ECG outlier analysis (see Section 7.8.4).

7.1.3. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last value recorded during the screening period, prior to dosing. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing.

Individual changes from baseline will be calculated by subtracting the individual participant's baseline value from the value at the post-dose timepoint.

The summary statistics for change from baseline will be derived from individual participants' values (e.g., mean change from baseline will be the mean of the individual changes from baseline for all participants, rather than the difference between the mean value at the post-dose timepoint and mean value at baseline).

See Section 7.1.2 for more detail on handling repeat and unscheduled readings in the calculations.

7.2. Participant Disposition and Population Assignment

Participant disposition (including country of enrollment) and analysis set assignment will be listed.

A summary table by treatment will be provided, based on the APAS.

7.3. Screening Demographics

The screening demographics reported during the screening period including age, sex, race, ethnicity, height, body weight, and body mass index will be listed. In case of multiple results, the value obtained closest and prior to dosing will be used.

A summary table by treatment will be provided, based on the APAS.

7.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 (or higher if a new version is issued during the study; see the DMP for more details).

A summary table by system organ class, preferred term, and treatment will be provided, based on the SAFS.

7.5. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to dosing. Concomitant medication will be defined as medication that is administered at any time during and/or after study drug dosing.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version September 2023 (see the data management plan [DMP] for more details).

Prior and concomitant medications will be listed.

A summary table by preferred term and treatment will be provided, based on the SAFS.

7.6. Pharmacokinetic Assessments

7.6.1. Pharmacokinetic Analysis

The following PK parameters will be determined, where possible, from the serum concentrations of tocilizumab using noncompartmental methods in validated software program Phoenix WinNonlin Certara, Version 8.3.5 (or later if a new version is issued during the study):

Parameter	Units[a]	Definition
AUC_{0-t}	h*µg/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last}), The AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
AUC_{0-inf}	h*µg/mL	area under the concentration-time curve from time 0 extrapolated to infinity, based on the last observed quantifiable concentration
C_{max}	µg/mL	maximum observed concentration
t_{max}	h	time of the maximum observed concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance
V_z/F	L	apparent volume of distribution during the terminal phase

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (mg) and actual post-dose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

7.6.1.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each participant will be defined by visual inspection. Generally, the first point at which there is no systematic deviation from the log-linear decline in concentrations will be selected as the start time to include only the apparent terminal elimination phase in the slope selection.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points, not including C_{max}, and the adjusted coefficient for determination of exponential fit (R^2-adj) of the regression line is ≥0.8. Parameters requiring λ_z for their calculation ($AUC_{0\text{-}inf}$, $t_{1/2}$, CL/F, and V_z/F) will only be calculated if the R^2-adj value of the regression line is ≥0.8.

The following regression-related diagnostic PK parameters will be determined, when possible:

Parameter	Units	Definition
t_{last}	h	time of the last quantifiable concentration
$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2-adj	NA	adjusted coefficient for determination of exponential fit

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be ≥2 half-lives. If the λ_z Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the CSR.

7.6.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of area under the concentration-time curve (AUC) will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification (LLOQ). If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

7.6.1.3. Criteria for Handling Concentration Below the Limit of Quantification or Missing Concentrations for Derivation of Pharmacokinetic Parameters

Serum concentrations below the limit of quantification (BLQ) will be assigned a value of '0' before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If the actual sample time is missing but a valid concentration is available, the nominal time can be used for PK parameter calculation.
- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a pre-dose serum concentration is missing, it will be set to 0 by default within Phoenix WinNonlin.

7.6.1.4. Treatment of Outliers in Pharmacokinetic Analysis

Each outlier will be investigated and assessed in terms of being deemed as normal, abnormal, or errant. In principle, exclusions of abnormal values will be avoided unless there is strong justification (documentation of important protocol deviation during clinical or analytical procedures), which will be decided by the study team in a Blinded Data Review Meeting (BDRM) prior to unblinding, and documented in the CSR.

Any quantifiable pre-dose concentration value will be considered anomalous and set to missing for the PK analysis. This will be set to '0' by default in Phoenix WinNonlin.

7.6.1.5. Treatment of Samples affected by Non-compliant Laboratory Processes for the Pharmacokinetic Analysis

Any data from samples handled through non-compliant laboratory processes (as defined in the following table) will be excluded from any analysis, due to insufficient quality.

Table 3: Guidance for Lab-Related Protocol Deviations

Parameter	IL-6R	PK	ADA	hsCRP
Clotting time:				
<30 minutes	Include sample	Important deviation; exclude sample	Important deviation; exclude sample	Important deviation; exclude sample
30 - 120 minutes	Include sample	Include sample	Include sample	Include sample
> 120 minutes	Important deviation; exclude sample	Important deviation; exclude sample	Important deviation; exclude sample	Important deviation; exclude sample
Centrifugation time:				
< 15 minutes	Include sample	**<10 minutes** important deviation; exclude sample	**<10 minutes** important deviation; exclude sample	**<10 minutes** important deviation; exclude sample
> 15 minutes	**> 120 minutes** Important deviation; exclude sample	**> 120 minutes** important deviation; exclude sample	**> 120 minutes** important deviation; exclude sample	**> 20 minutes** important deviation; exclude sample
Time from centrifugation to freezing:				
> 120 minutes	Important deviation; exclude sample	Important deviation; exclude sample	Important deviation; exclude sample	N/A (ambient storage)

7.6.2. Presentation of Pharmacokinetic Data

All PK concentrations and parameters will be listed.

Summary tables, arithmetic mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by treatment and time post-dose will be provided for serum PK concentrations. All figures will be produced on both linear-linear and linear-logarithmic scales. The +SD bars will only be displayed on the linear-linear scale.

Summary tables by treatment will be provided for all PK parameters, except for diagnostic regression-related PK parameters.

If the actual time of sample collection falls outside the allowable window of the nominal time (details are provided below), the serum concentration will be excluded from the summary statistics and flagged in the concentration listings, the same approach will be followed for concentrations deemed to be anomalous.

PK sampling times and windows are as follows: Predose, 4 h (±10 minutes), 8 h (±10 minutes), 12 h (±10 minutes), 24 h (±1 hour), 48 h (±1 hour), 60 h (±1 hour), 72 h (±1 hour), 84 h (±1 hour), 96 h (±1 hour), 108 h (±1 hour), 120 h (±1 hour), 144 h (±3 hour), 168 h (±3 hour), 240 h (±1 day), 336 h (±1 day), 504 h (±1 day), 672 h (±1 day), 840 h (±1 day), 1008 h (±1 day), 1344 h (±1 day).

For serum concentration data the following rule will apply:

- Values that are BLQ will be set to half of LLOQ for the calculation of summary statistics.

For PK parameters the following rule will apply:

- Geometric mean and CV will not be calculated for t_{max}.

7.6.3. Primary Estimands for FDA and EMA

Population: PKAS including all randomized study participants who receive the study treatment and with at least one calculable PK parameter.

Endpoint: for EMA: C_{max} and $AUC_{0\text{-}inf}$ calculated on samples collected from Day 1 post-dose to EoS;

for FDA: C_{max} and $AUC_{0\text{-}t}$ calculated on samples collected from Day 1 post-dose to EoS.

Treatment condition: Randomized Actemra s.c. (reference product) and BIIB800 s.c. (test product).

- *Handling intercurrent events:* Premature discontinuation of study for any reason with available PK parameters

- Incomplete or partial dose delivery for any reason

An intercurrent event listed above will be considered relevant for C_{max} if it occurs at or before t_{max}, which is the time at which C_{max} is observed. If the event occurs after t_{max}, it will be considered an intercurrent event for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$, but not for C_{max}.

All the intercurrent events will be handled with the Treatment policy strategy for all co-primary endpoint pairs.

Contingency measures and missing data handling:

For fatal events whether related or unrelated to the treatments administered, and/or any other disruptive events such as a pandemic occur during the study conduct period, all available data to time of death or disruptive event will be used. Missing data will be handled through estimation (under estimator assumption), no imputation for missing data will be implemented.

Population-level summary: the ratio of the averages (population geometric means) of the PK parameters for the test and reference products.

7.6.3.1. Pharmacokinetic Statistical Methodology

A statistical analysis will be conducted to investigate the bioequivalence of 162 mg BIIB800 (test treatment) to 162 mg Actemra (reference treatment).

The natural log (ln)-transformed[7] $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} will be analyzed using an analysis of covariance (ANCOVA) model.[8] The model will include actual treatment, site, and body weight category (<75 kg, ≥75 kg) as factors. Site will be removed as a factor from the model if 1 site recruits fewer than 30 participants.

To effectively control the potential Type I error inflation from the BSSR process and ensure the actual Type I error rate remains strictly below 5%, we will conduct the two one-sided tests at a reduced significance level of 4.85%. Comprehensive studies[9] have shown that using an adjusted nominal level of 4.85% ensures the Type I error rate is strictly controlled below 5% across a wide range of possible coefficients of variation (CVs) from 30% to 80%. For each PK parameter separately, the least squares mean (LSM) for each treatment, the difference in LSMs between the test and reference treatments, and the corresponding 90.3% confidence interval (CI) will be estimated; these values will then be back-transformed to derive the geometric least square mean (GLSM), the ratio of GLSMs, and corresponding 90.3% CI.

For EMA, it will be concluded that the test treatment is bioequivalent to the reference treatment if the 90.3% CIs for the ratio of GLSMs are completely contained within the predefined interval of (0.8000, 1.2500) for $AUC_{0\text{-}inf}$, and C_{max}.

For FDA, bioequivalence will be concluded if the 90.3% CIs for the ratio of GLSMs are completely contained within the predefined interval of (0.8000, 1.2500) for $AUC_{0\text{-}t}$, and C_{max}.

This procedure is equivalent to Schuirmann's[10] two 1-sided tests at the 4.85% level of significance. According to the intersection-union principle[11], the related multiple testing procedure controls the experiment-wise type 1 error rate at 4.85% for each pair of co-primary PK endpoints.

Additionally, the pooled estimate (across the two treatments) of the CV will be derived, and residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

ANCOVA Analysis

```
proc mixed data = <data in>;
  by parcat1n parcat1 paramn param;
  class trtan weight site;
  model lpk = trtan weight site / cl residual;
  lsmeans trtan / cl pdiff = control('1') alpha = 0.097;
  ods output lsmeans = <data out>;
  ods output diffs = <data out>;
  ods output covparms = <data out>;
run;

Note: Remove site from the model if 1 site recruits fewer than 30
participants.
```

7.7. Pharmacodynamic Assessments

7.7.1. Pharmacodynamic Analysis

Serum concentrations of sIL-6R and hsCRP and their units will be used as supplied by the analytical laboratory for PD analysis.

The following PD parameters will be determined where possible from the serum concentrations of sIL-6R and hsCRP using noncompartmental methods in validated software program Phoenix WinNonlin Certara, Version 8.3.5 (or later if a new version is issued during the study):

Parameter	Units[a]	Definition
AUE	h*xg/mL	area under the effect-time curve from time 0 to the time of the last quantifiable concentration (t_{last}), the AUE will be calculated using the linear trapezoidal linear interpolation rule
E_{max}	xg/mL	maximum observed effect (sIL-6R only)
E_{min}	xg/mL	minimum observed effect (hsCRP)
tE_{max}	h	time of maximum observed effect (sIL-6R only)
tE_{min}	h	time of minimum observed effect (hsCRP)

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PD parameters)

PD parameters will be calculated from individual concentration-time profiles using actual times of blood draws. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time. When tE_{max} or tE_{min} occurs at more than 1 timepoint, tE_{max} will be assigned to the first occurrence of E_{max} and tE_{min} will be assigned to the first occurrence of E_{min}.

The PD parameters above will also be determined from baseline-corrected concentrations of sIL-6R and hsCRP. Baseline-corrected concentrations will be determined by subtracting the pre-dose concentration value from subsequent post-dose concentrations. Additional PD parameters may be determined where appropriate. Baseline-corrected concentrations may be

negative and hence leading to negative areas between the curve and the horizontal axis. AUE calculation will sum up negative and positive areas according to their sign.

Concentrations will be used as supplied by the analytical laboratory for PD analysis. The units of concentration and resulting PD parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

7.7.1.1. Criteria for Handling Concentration Below the Limit of Quantification or Missing Concentrations for Derivation of Pharmacodynamic Parameters

The serum sIL-6R and hsCRP concentrations that are BLQ will be set to half the LLOQ with the following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PD analysis.
- If a pre-dose concentration is missing, the baseline-corrected concentrations will not be derived.
- Other missing concentration values will not be imputed.

7.7.1.2. Treatment of Outliers in Pharmacodynamic Analysis

Each outlier will be investigated and assessed in terms of being deemed as normal, abnormal, or errant. If a value is considered to be anomalous due to being inconsistent with the expected PD profile, it may be appropriate to exclude the value from the PD parameter derivation. If the value impacts all derived PD parameters, all PD data from the entire participant may be listed only and excluded from the summary and inferential statistics. However, the exclusion of any data must have strong justification (documentation of important protocol deviation during clinical or analytical procedures), will be decided in a blinded Data Review Meeting prior to unblinding, and will be documented in the CSR.

7.7.1.3. Treatment of Samples affected by Non-compliant Laboratory Processes for the Pharmacodynamic Analysis

Any data from samples handled through non-compliant laboratory processes (see Table 3) will be excluded from any analysis, due to insufficient quality.

7.7.2. Presentation of Pharmacodynamic Data

All PD concentrations and their changes from baseline will be listed. Summary tables and mean figures by treatment and time post-dose will be provided for all PD concentrations and their changes from baseline.

If the actual time of sample collection falls outside the allowable window of the nominal time (details are provided in the protocol), the serum concentration will be excluded from the summary statistics and flagged in the concentration listings, the same approach will be followed for concentrations deemed to be anomalous.

All PD parameters (based on absolute and baseline-corrected concentrations) will be listed. Summary tables by treatment will be provided for all PD parameters.

Values BLQ will be set to half the LLOQ for the calculation of summary statistics.

7.7.3. Pharmacodynamic Statistical Methodology

No inferential statistical analyses are planned.

7.8. Safety and Tolerability Assessments

7.8.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 (or higher if a new version is issued during the study; see the DMP for more details).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after dosing or starts prior to dosing and increases in severity after dosing.

A treatment-related TEAE will be defined as a TEAE with a causal relationship with the study treatment , as determined by the investigator, and specified in the database as related.

All AEs will be listed. In addition to the data recorded in the database, the listing will include AE duration (AE stop date/time minus AE start date/time) and, only for TEAEs, the AE onset day/time relative to the date/time of study drug administration (AE start date/time minus date/time of dosing). Handling of missing dates/times are described further below.

Listings of serious TEAEs and TEAEs leading to discontinuation will be provided separately.

The frequency of participants with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of participants will be summarized by system organ class, preferred term, and treatment for the following:

- TEAEs

- treatment-related TEAEs
- serious TEAEs
- serious treatment-related TEAEs
- TEAEs leading to discontinuation
- treatment-related TEAEs leading to discontinuation

The frequency of participants will be summarized by preferred term and treatment for the following:

- TEAEs
- treatment-related TEAEs

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to dosing.
- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the derivation of onset day/time relative to study drug administration (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset day/time will not be calculated. If the start date/time of a TEAE is incomplete, where possible, the minimum possible onset day/time will be calculated and presented in '≥DD:HH:MM' format (e.g., if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset day/time will be calculated by assuming a TEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset day/time ≥01:16:00 in the listing). If the start date of a TEAE is the same as the date of dosing but the start time of a TEAE is missing, an onset day/time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.
- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (e.g., if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as

duration ≤02:15:59 in the listing). Any clock changes will be accounted for in the derivation.

- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category for severity.
- For the calculation of TEAE summary statistics: If a participant experienced multiple TEAEs with the same preferred term, these will be counted as separate TEAEs .

7.8.2. Clinical Laboratory Parameters

All clinical laboratory parameters and their changes from baseline will be listed, as applicable; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual participant value outside the respective clinical reference range.

Summary tables and boxplots by treatment and timepoint will be provided for biochemistry and hematology parameters, and their changes from baseline, as applicable.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, and presentation in the figures, <x and ≤x values will be set to half of x, whereas >x and ≥x values will be set to x.

7.8.3. Vital Signs Parameters

All vital signs parameters and their changes from baseline will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided for all vital signs parameters and their changes from baseline.

7.8.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters and their changes from baseline will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided for all 12-lead ECG parameters and their changes from baseline.

An outlier analysis will be performed for QT interval corrected for heart rate using Fridericia's formula (QTcF). The analysis will include all individual original, repeat, and unscheduled post-dose values.

The maximum post-dose values will be summarized by treatment according to the following categories:

- ≤450 ms

- >450 and ≤480 ms (all instances flagged in the listing)
- >480 and ≤500 ms (all instances flagged in the listing)
- >500 ms (all instances flagged in the listing)

The maximum increases from baseline will be summarized by treatment according to the following categories:

- ≤30 ms
- >30 and ≤60 ms (all instances flagged in the listing)
- >60 ms (all instances flagged in the listing)

7.8.5. Injection Site Reactions

All components of injection site reactions (ISRs) will be assigned a severity grade as outlined below

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially life threatening (Grade 4)**
Local				
Pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/ Redness	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/ Swelling[a]	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Systemic				
Fever[b]	38.0 - 38.4 °C	38.5 - 38.9 °C	39.0 - 40.0 °C	> 40.0 °C
Nausea/ vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools in 24 hours	4 - 5 loose stools in 24 hours	6 or more loose stools in 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization

Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

[a] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.
[b] Oral temperature; no recent hot or cold beverages or smoking. ER=emergency room.

All ISRs will be listed. Summary table by treatment and timepoint will be provided for severity grades of the ISRs.

7.8.6. Other Assessments

All safety and tolerability assessments not detailed in the above sections will be listed only.

7.8.7. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

7.9. Immunogenicity Assessment

7.9.1. Immunogenicity Analysis

The ADA/NAb status of each participant is determined using the following definitions:

- **ADA-positive status:** A participant with either pre-existing ADA-positive or treatment-induced ADA-positive
    - **Pre-existing ADA-positive status:** A participant with an ADA-positive sample at baseline (prior to administration of study treatment)
    - **Treatment-induced ADA-positive status**: A participant with a negative ADA sample at baseline (pre-dose) and at least one ADA-positive sample after the administration of the study treatment
- **ADA-negative status:** A participant without ADA-positive sample at baseline and only ADA-negative samples after administration of study treatment.

The **NAb-positive/ Nab-negative participant status** will be defined in the same manner as outlined above for ADA data.

7.9.2. Treatment of Samples affected by Non-compliant Laboratory Processes for the Immunogenicity Analysis

Any data from samples handled through non-compliant laboratory processes (see Table 3) will be excluded from any analysis, due to insufficient quality.

7.9.3. Presentation of Immunogenicity Data

7.9.3.1. Analysis per sampling timepoint

The number and percentage of participants by ADA/NAb status at each sampling timepoint will be presented by treatment on SAFS.

The denominator for the ADA and NAb positive calculation is the number of participants having a sample at the predefined sampling timepoints. Furthermore, the 'NAb to ADA positive ratio' per sampling timepoint will be presented.

The ADA titre (from positive ADA samples) will also be summarized over time using descriptive statistics, including geometric mean and CV.

7.9.3.2. Cumulative Analysis Across All Sampling Timepoints

The cumulative ADA/NAb analysis will summarize the **participant's ADA/NAb status**: ADA-positive, pre-existing ADA-positive, treatment-induced ADA-positive, ADA-negative and NAb-positive.

The number and the percentage of each ADA and NAb participant status will be presented. The denominator for the ADA and NAb positive calculation is the number of participants within the respective SAFS. Furthermore the 'Nab to ADA positive ratio' will be presented.

The maximal ADA titre in ADA-positive samples per participant will also be summarized using descriptive statistics, including geometric mean and CV, by different participant ADA status (pre-existing ADA , treatment induced ADA and overall ADA positive) . The ADA titre distribution at each ADA sampling time point will also be presented.

Any titre reported as <160 will be imputed as 160 for the descriptive statistics.

7.9.3.3. Subgroup Analysis

The following subgroup analyses performed by ADA status (positive or negative) are considered as an exploratory analysis.

Subgroup analysis results will be summarized and/or displayed by ADA participant status and treatment group:

- summary table of screening demographics
- summary table of PK concentrations
- summary table of PK parameters
- arithmetic mean (+ standard deviation [SD]) figure of PK concentrations
- overlaying individual figures of PK concentrations

- summary table of TEAEs and treatment-related TEAEs
- summary table of baseline-adjusted PD concentrations
- summary table of baseline-adjusted PD parameters

8. INTERIM ANALYSES

No unblinded interim analysis is planned to be performed.

A blinded sample size review was conducted; see BSSR SAP (Final Version 1.0 dated 02JUL2024) for details.

9. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

The PDCS and PDAS were added as these analysis sets will be required for summaries of the PD data.

For the analysis of co-primary endpoints, the nominal significance level has been reduced to 4.85% from 5% to ensure strict control of the actual Type I error below 5%.

In the immunogenicity analysis, additional ADA status categories have been introduced, including pre-existing ADA positive and treatment-induced ADA positive status.

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11. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	24FEB2025	Remove the requirement for there to be more than 20 participants with positive ADA in each treatment for the exploratory subgroup analyses detailed in Section 7.9.3.3 to be performed.

NA = not applicable