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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PROTOCOL NUMBER: **294BS101**

PHASE OF DEVELOPMENT: I

PROTOCOL 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

DATE: 06 December 2023
Version 2.0

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Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

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1. KEY STUDY ELEMENTS

1.1. Synopsis

Protocol 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	
Protocol Number	294BS101	
Version Number	2.0	
Name of Study Treatment	Research Name:	BIIB800 (prefilled autoinjector, 162 mg/0.9 mL, for subcutaneous [s.c.] injection) Actemra® (prefilled autoinjector, 162 mg/0.9 mL, for s.c. injection)
	INN:	Tocilizumab
Study Phase	1	
Project Indication	See Section 3.2.1 for a full list of indications approved for the reference	
Study Rationale	Tocilizumab (commercial name: RoActemra® in Europe, Actemra in the United States [US] and other countries) a biologic disease-modifying antirheumatic drug, is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody against the interleukin 6 receptor (IL-6R). BIIB800 (also referred as BAT1806) is being developed as a biosimilar tocilizumab product to the reference products RoActemra and Actemra. The aim of the current study is to demonstrate equivalence in pharmacokinetics (PK) between BIIB800 and Actemra and to compare the pharmacodynamics (PD), safety, and immunogenicity profiles of BIIB800 and Actemra, administered s.c. to healthy adult male participants.	
Rationale for Starting Dose and Maximum Exposure	In accordance with the approved dosing recommendation for the reference product, participants will receive 162 mg BIIB800 or 162 mg Actemra, administered s.c. A single dose will be administered at one injection location (outer upper arm); this is considered sufficient to establish PK equivalence and comparability of immunogenicity and safety parameters between BIIB800 and reference tocilizumab.	

Study Objectives and Endpoints

Primary Objective	Co-Primary Endpoints
To show equivalence in PK of BIIB800 and Actemra following s.c. administration of a single dose to healthy male participants	European Medicines Agency (EMA): • Maximum tocilizumab serum concentration (C_{max}) • Tocilizumab area under the concentration-time curve from time zero to infinity (AUC_{0-inf}) Food and Drug administration (FDA): • Tocilizumab C_{max} • Tocilizumab area under the concentration-time curve up to the last measurable concentration (AUC_{0-t})
Secondary Objectives	**Secondary Endpoints**
To evaluate PK of BIIB800 and Actemra over time	• Time to reach C_{max} (T_{max}) • Apparent total body clearance (CL/F) • Apparent terminal half-life ($t_{1/2}$)
To evaluate the clinical safety of BIIB800 and Actemra	• Incidence of treatment-emergent adverse events (TEAEs) and serious AEs from time of administration to end of study (EoS)
To evaluate PD profiles BIIB800 and Actemra	For soluble IL-6R: • Area under the effect–time curve (AUE) • Maximum observed effect (E_{max}) • Time to E_{max} (tE_{max}) For high sensitive C-reactive protein (hsCRP): • AUE • Minimum observed effect E_{min} • Time to E_{min} (tE_{min})
To evaluate the immunogenicity of BIIB800 and Actemra	• Anti-drug antibodies (ADA) and neutralizing antibodies (nAbs) • ADA titers

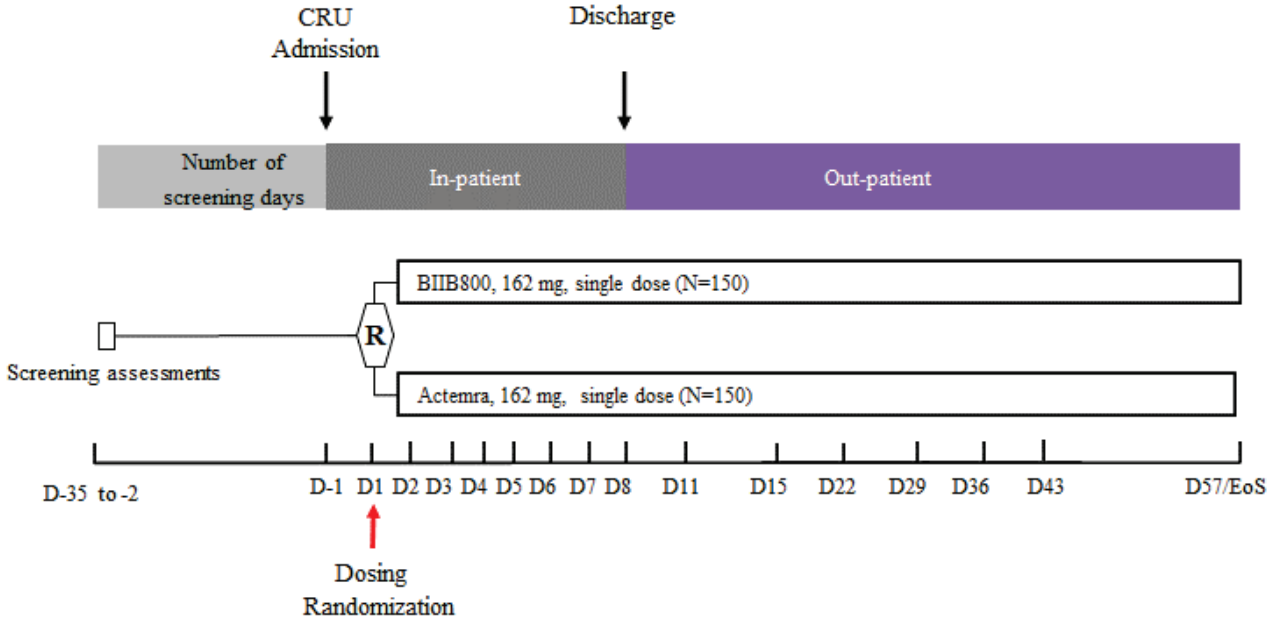
Study Design:	Randomized, double-blind, single-dose, 2-treatment arm, parallel-group study.
Study Location:	A maximum of 4 sites across the United Kingdom (1) and the US (3) are planned.
Study Population:	This study will be conducted in participants who meet the following inclusion criteria: • Male, aged 18 to 55 years inclusive at the time of signing informed consent • Body weight between 60 kg and 90 kg and body mass index between 18.5 and 29.9 kg/m², inclusive • Good health as determined by the Investigator, based on medical history, screening assessments and physical examination Detailed criteria are described in Section 6.
Number of Planned participants:	Approximately 300 participants are planned to be randomized.
Treatment Groups:	Two treatment groups: • BIIB800 group, approximately 150 participants • Actemra group, approximately 150 participants Dosing regimen: a single dose of 162 mg BIIB800 or Actemra administered s.c. to the outer upper arm.
Sample Size Determination:	A sample size of 300 participants (150 per arm) will provide approximately 90% power for the bioequivalence testing of each pair of co-primary endpoints for each Regulatory Agency: C_{max} and AUC_{0-t} for FDA, and C_{max} and AUC_{0-inf} for EMA. Enrolled participants will be randomized 1:1 to receive either BIIB800 or Actemra. An inter-subject coefficient of variation (CV) of approximately 0.5 is initially assumed and a single injection site is specified. The geometric mean ratio is assumed to be 1.05. The PK endpoints are highly correlated; this correlation is initially assumed to be 1 and will be revisited during the pre-specified blinded sample size reassessment (BSSR), performed to recalculate the CV of PK endpoints. Based on the recalculated CV and evaluation of the correlation between the coprimary endpoints at the

	BSSR timepoint, the sample size will be recalculated, and enrolment may be adjusted accordingly to ensure that the targeted study power is approximately 90%. Details on the BSSR procedure are described in Section 13.5.2.
Statistical Methods:	**Co-primary endpoints and statistical analysis for bioequivalence assessment** The statistical analysis of the PK endpoints, AUC and C_{max}, is based upon the 90% confidence intervals for the ratio of the population geometric means for the parameters under consideration. This method is equivalent to two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance level. The 90% confidence interval (for the average bioequivalence) is derived for the ratio of the averages (population geometric means) of the outcomes for BIIB800 or Actemra. The data will be transformed prior to analysis using a logarithmic transformation and the corresponding confidence interval for the difference between products will be obtained from an analysis of variance (ANOVA) model (fixed effects for treatment and body weight). To establish bioequivalence, the derived 90% confidence intervals back-transformed on the original scale should fall within 80-125% limits.
Visit Schedule	Participants will undergo a screening visit and will be admitted to the clinical research unit (CRU) from Day -1 to Day 8. After discharge participants will attend the CRU for a further 7 scheduled outpatient visits. Study assessments conducted at each visit are listed in the Schedule of Activities (Table 1).
Duration of Study Participation:	Study duration for each participant will be up to 13 weeks: • Screening period up to 5 weeks • Treatment period: single dose at Day 1 • Post-dose period: 8 weeks
Benefit-Risk Analysis	The study participants (healthy volunteers) will not obtain any clinical benefit from the treatment. Possible risks include those associated with s.c. injection (e.g. injection site discomfort or reaction). In a Phase I study utilizing a single dose of i.v. tocilizumab (4 mg/kg BIIB800, RoActemra, or Actemra [1]) approximately 70% of participants experienced treatment-related AEs. The most common treatment-related AEs were neutrophil count decreased (44%), white blood cell count decreased (27%), hypertriglyceridemia (20%), alanine

aminotransferase (ALT) increased (18%), and aspartate aminotransferase (AST) increased (18%). AEs were transient and no serious AEs occurred.

1.2. Study Design Schematic

Figure 1: Study Design



CRU=Clinical Research Unit, D=day; EoS=end of study; N=number of participants; R=randomization.

1.3. Schedule of Activities

Table 1: Schedule of Activities

	Screening	Admission	Study period																				
			In-patient														Out-patient						
Study Day	**-35 to -2**	**-1**	**1**					**2**	**3**		**4**		**5**		**6**	**7**	**8**	**11**	**15**	**22**	**29**	**36**	**43**	**57/EoS[1]**
Hours Post Dose (Window)			**Predose**	**Dosing**	**4 (± 10min)**	**8 (± 10min)**	**12 (± 10min)**	**24 (± 1h)**	**48 (± 1h)**	**60 (± 1h)**	**72 (± 1h)**	**84 (± 1h)**	**96 (± 1h)**	**108 (± 1h)**	**120 (± 1h)**	**144 (± 3h)**	**168 (± 3h)**	**240 (± 1 day)**	**336 (±1 day)**	**504 (±1 day)**	**672 (± 1 day)**	**840 (± 1 day)**	**1008 (± 1 day)**	**1344 (± 1 day)**
Informed Consent	✓																							
Inclusion/Exclusion	✓	✓																						
Demographic Information, Medical and Medication History	✓	✓																						
Cotinine testing	✓	✓																						
Height, weight, BMI	✓	✓[5]																						
Physical Examination	✓	✓[2]	✓[2]					✓[2]	✓[2]		✓[2]		✓[2]		✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]
Vital Signs	✓	✓	✓		✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Biochemistry, Hematology, Urinalysis	✓	✓						✓								✓		✓	✓	✓	✓	✓	✓	✓
Coagulation	✓																							
12-Lead ECG	✓	✓						✓					✓					✓			✓			✓
Tuberculosis Test (QuantiFERON Gold)	✓																							
Alcohol Screen[3]	✓	✓																						
Urine Drug Test	✓	✓																						
HIV/Hepatitis[4]	✓																							
Randomization			✓																					
IMP Dose				✓																				

continued

Table 1: Schedule of Activities *(continued)*

	Screening	Admission	Study period																				
			In-patient														Out-patient						
Study Day	**-35 to -2**	**-1**	**1**					**2**	**3**		**4**		**5**		**6**	**7**	**8**	**11**	**15**	**22**	**29**	**36**	**43**	**57/EoS[1]**
Hours Post Dose (Window)			**Predose**	**Dosing**	**4 (± 10min)**	**8 (± 10min)**	**12 (± 10min)**	**24 (± 1h)**	**48 (± 1h)**	**60 (± 1h)**	**72 (± 1h)**	**84 (± 1h)**	**96 (± 1h)**	**108 (± 1h)**	**120 (± 1h)**	**144 (± 3h)**	**168 (± 3h)**	**240 (± 1 day)**	**336 (±1 day)**	**504 (±1 day)**	**672 (± 1 day)**	**840 (± 1 day)**	**1008 (± 1 day)**	**1344 (± 1 day)**
Blood Sample for PK			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood Sample for hsCRP and sIL-R6			✓		✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓	✓	✓	✓			✓
Blood Sample for ADA and nAbs			✓																✓		✓			✓
Injection Site Exam.					✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
(S)AE Recording[6]												✓												
Concomitant medication/procedure												✓												

ADA=anti-drug antibodies; AE=adverse event; BMI=body mass index; ECG=electrocardiogram; EoS=end of study; Exam.=examination; HIV=human immunodeficiency virus; hsCRP=high sensitive C-reactive protein; IMP=investigational medicinal product; nAbs=neutralizing antibodies; PK=pharmacokinetics, SAE=serious adverse event; sIL-R6=soluble interleukin-6-receptor.

[1] Participants who withdraw prior to Day 57 should undergo all assessments specified for the EoS visit.
[2] Full physical examination once during screening: symptom-directed physical examination at the Investigator's discretion at other study timings
[3] Blood, breath, or urine testing.
[4] Hepatitis includes: hepatitis C virus antibodies, hepatitis B surface antigen and total hepatitis B core antibody, hepatitis B surface antibody.
[5] Weight and BMI only.
[6] Any AE with onset between consenting and administration of the study treatment must be recorded if related to any study procedures. Between the time of administration of study treatment and EoS all AEs regardless of their relationship to study treatment or procedure must be reported.

Time of study drug administration and all blood draws will be recorded into participant notes and entered into the electronic case report form.

2. LIST OF ABBREVIATIONS

ACR20	American College of Rheumatology 20%
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantification
BMI	body mass index
BSSR	blinded sample size reassessment
CRO	contract research organization
CRU	Clinical Research Unit
CS	clinically significant
CV	coefficient of variation
D	day
DHA	Dose Handling and Administration
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EoS	end of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPSP	Global Patient Safety and Pharmacovigilance
HbsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
hsCRP	high sensitive C-reactive protein
ICH	International Council for Harmonisation
ICF	informed consent form
Ig	immunoglobulin
IL-6(R)	interleukin-6(-receptor)
INR	international normalized ratio
IRB	Institutional Review Board
i.v.	intravenous
LLN	lower limit of normal
N	number of participants
nAb	neutralizing antibody
NCS	abnormal not clinically significant
PD	pharmacodynamics

PK	pharmacokinetic
PKAS	PK analysis set
PKCS	PK concentration analysis set
PT	prothrombin time
PTT	partial thromboplastin time
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SAFS	safety analysis full set
s.c.	subcutaneous
SD	standard deviation
sIL-6R	soluble interleukin-6-receptor
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TMF	trial master file
ULN	upper limit of normal
US	United States
USPI	US prescribing information
WHO	World Health Organization
PK/PD Terms and Definition	
Abbreviation	**Definition**
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve up to the last measurable concentration
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity
AUE	area under the effect–time curve
C_{max}	maximum concentration
CL/F	apparent total body clearance
E_{max}	maximum observed effect
E_{min}	minimum observed effect
$t_{1/2}$	apparent terminal half-life
T_{max}	time to reach C_{max}
$tE_{max(min)}$	time to $E_{max(min)}$

3. INTRODUCTION

Tocilizumab (commercial name: RoActemra® in Europe, Actemra® in the United States [US] and other countries) a biologic disease-modifying antirheumatic drug, is a recombinant humanized monoclonal immunoglobulin (Ig) G1 antibody against the interleukin-6 receptor (IL-6R). Tocilizumab has been licensed first as an intravenous (i.v.) infusion (2009 in Europe) for the management of patients with rheumatoid arthritis (RA) refractory to conventional synthetic disease-modifying antirheumatic drugs and tumor necrosis factor inhibitors, followed by the approval of a subcutaneous (s.c.) formulation (2014 in Europe) [2]. Both presentations show similar effectiveness [2]. The s.c. formulation, however, offers a treatment option that may better suit patients' lifestyle, contributing to improved convenience. Administration time is short and the burden on patients due to clinic visits is reduced as the dose can be administered at home by self-injection, using a device that requires no pre-injection preparation.

3.1. Study Rationale

BIIB800 (also referred to BAT1806) is being developed as a biosimilar tocilizumab product to the reference product RoActemra (EU brand name)/Actemra (US brand name).

Bioequivalence of i.v. BIIB800 and the reference products RoActemra and Actemra administered to healthy Chinese males was established in a randomized, double-blind, Phase I pharmacokinetic (PK) study [1]. In a randomized, double-blind Phase III study in patients with moderate to severe RA despite methotrexate treatment, i.v. BIIB800 demonstrated equivalence to Actemra in terms of clinical efficacy, as assessed by the American College of Rheumatology 20% (ACR20) response at 12 and 24 weeks after randomization.

The aim of the current study is to demonstrate equivalence between BIIB800 and Actemra administered s.c. in terms of PK outcomes, and to compare the pharmacodynamics (PD), safety, and immunogenicity of BIIB800 and Actemra in healthy adult male participants.

3.1.1. Rationale for Study Population

This study will be conducted in healthy male volunteers. The study will provide an assessment of PK, PD, immunogenicity, and safety of s.c. BIIB800 in a sensitive population i.e., one without the confounding effects of comorbidities and concomitant medications which may be prevalent in patient populations.

Enrolling only male participants reduces the potential variability in PK parameters.

3.1.2. Rationale for Dose

In accordance with the approved dosing recommendation for the reference product, participants will receive 162 mg of BIIB800 or Actemra, administered s.c. A single dose will be administered at one injection location (outer upper arm). This is considered sufficient to establish PK equivalence and comparability of PD, immunogenicity, and safety parameters between BIIB800 and reference tocilizumab.

3.1.3. Study Design Rationale

Analytical studies demonstrated a high degree of similarity between BIIB800 and the reference product in terms of quality attributes potentially relevant for PK and immunogenicity (Biogen, data on file).

No clinically relevant immunogenicity has been observed for the reference product, regardless of administration route [3]. Furthermore, previous studies investigating BIIB800 administered via the i.v. route either as a single dose to healthy participants or by repeat dosing to patients with RA did not suggest any clinically relevant immunogenicity (Biogen, data on file).

The study duration (57 days post dose at the participant level) is considered to be adequate, based upon the half-life of tocilizumab s.c. in healthy participants (29-43 hours [1,4,5]) and immunogenicity data from the Phase I BIIB800 i.v. study, indicating an increased incidence of anti-drug antibodies (ADAs) across treatment groups over time up to Day 57 following a single i.v. administration of reference or biosimilar tocilizumab [1].

The final blood draw to measure serum tocilizumab is on Day 57 post dose. This corresponds to approximately 31 half-lives of tocilizumab administered s.c., based on calculations according to Schwabe et al. [4]. A 57-day follow-up is expected to cover the entirety of the quantifiable concentration-time plot for tocilizumab.

3.2. Background

3.2.1. Background on Tocilizumab

Tocilizumab (commercial name: RoActemra in Europe, Actemra in the US and other countries) is a humanized, anti-human monoclonal antibody of the IgG1 subclass that targets soluble and membrane-bound IL-6R. It is produced in Chinese hamster ovary cells by recombinant deoxyribonucleic acid technology. Tocilizumab was shown to specifically bind to soluble IL-6R (sIL-6R) and membrane-bound IL-6R thereby inhibiting both soluble and membrane-bound IL-6-mediated signaling. Interleukin 6 (IL-6) is a pleiotropic pro-inflammatory multifunctional cytokine produced by a variety of cell types. IL-6 has a local paracrine function and can regulate systemic physiological and pathological processes, such as inducing secretion of immunoglobulins, activating T cells, inducing secretion of hepatic acute-phase proteins, and stimulating erythropoiesis. Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders including RA, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, giant cell arteritis, and cytokine-release syndrome. Inhibition of the biological activity of IL-6 or IL-6R has been effective in the treatment of these diseases for which tocilizumab has been approved in many countries.

Tocilizumab has i.v. and s.c. formulations. In the US and European Union, both formulations of tocilizumab have been approved for many of the indications listed above (including RA, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, systemic sclerosis-associated interstitial lung disease, and giant cell arteritis).

3.2.2. Profile of Previous Experience with BIIB800

See the Investigator's Brochure for detailed information on relevant nonclinical and clinical studies. In addition, for the nonclinical and clinical profile of the reference products please refer to the Prescribing Information of Actemra [6] and the Summary of Product Characteristics for RoActemra [7].

3.2.2.1. Nonclinical Experience

The nonclinical studies for BIIB800 showed pharmacological effects similar to the reference products *in vitro* and *in vivo*.

BIIB800 and Actemra showed similar *in vitro* binding activity to IL-6R and cellular activity, preventing the binding of membrane-bound IL-6R and soluble IL-6R. BIIB800 did not produce antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity effects. *In vivo* PD studies showed that BIIB800 can alleviate collagen-induced arthritis in monkeys.

BIIB800 (i.v.) and the reference products showed similar primary PK characteristics after single and multiple dosing in cynomolgus monkeys. No differences between BIIB800 and the reference products were observed in toxicology or immunogenicity studies in cynomolgus monkeys.

The s.c. formulation of BIIB800 also showed similar PK characteristics to the reference products (Actemra and RoActemra) in cynomolgus monkeys, with only minor differences. After multiple doses, some differences by sex were observed, and the drug exposure was slightly higher in male than in female monkeys with both products. The ADA rate of BIIB800 was slightly higher than that with RoActemra. Subcutaneous BIIB800 injection did not produce irritation in New Zealand rabbits and did not show *in vitro* hemolytic reactions.

3.2.2.2. Clinical Experience

BIIB800 is currently in clinical development. Bioequivalence of BIIB800 i.v. versus the reference products RoActemra and Actemra was established in a randomized, double-blind, Phase I PK study in healthy Chinese males [1]. In a randomized, double-blind Phase 3 study in patients with moderate to severe RA despite methotrexate treatment, BIIB800 i.v. demonstrated clinical equivalence to Actemra, as assessed by the ACR20 response at 12 and 24 weeks after initiation.

3.3. Benefit-Risk Assessment

The participants participating in this study will not obtain any clinical benefit from the treatment; however, the information obtained from this study will contribute to the development of additional therapy for immune-mediated inflammatory diseases such as rheumatoid arthritis.

Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of BIIB800 is provided in the Investigator's Brochure and informed consent form (ICF). A high-level summary is provided here.

In this study, BIIB800 s.c. will be administered to healthy male participants. As discussed in Sections 3.1 and 3.2, the extensive nonclinical/physicochemical characterization, and nonclinical evaluations of BIIB800 fully support its biosimilarity to Actemra and RoActemra. Based on those data, it is expected that BIIB800 s.c. will show a comparable PK and safety profile to its reference and thus administration of BIIB800 to healthy participants can be considered to be low risk.

In the Phase I study of a single dose of i.v. tocilizumab (4 mg/kg BIIB800, RoActemra, or Actemra [1]) approximately 70% of participants experienced treatment-related AEs. The most common treatment-related AEs were neutrophil count decreased (44%), white blood cell count decreased (27%), hypertriglyceridemia (20%), alanine aminotransferase (ALT) increased (18%), and aspartate aminotransferase (AST) increased (18%) which is in line with the safety profile of the reference products. AEs were transient and no serious AEs (SAEs) occurred.

The participants included in this Phase I study will receive a single dose (162 mg) of study treatment s.c. The AE profile is expected to be similar to that observed in the Phase I study of a single i.v. dose of tocilizumab.

Due to the mechanism of action of tocilizumab, as stated in the reference product label, recipients may be at an increased risk of infections and serious infections including tuberculosis or other opportunistic infections, however these were not observed in the previous Phase I healthy volunteer study.

Neutropenia and thrombocytopenia may occur during tocilizumab treatment. Neutrophil and platelet counts will be closely monitored.

Due to the risk of serious hypersensitivity reactions [6] following study treatment administration, all participants will be closely monitored on site, and treatments needed to manage anaphylactic reactions must be readily available at the study sites. Injection site reactions including erythema, pruritus, pain, and hematoma may occur. In clinical studies these were mild to moderate, and the majority resolved without any treatment. Injection site reactions will be closely monitored on site [6-8].

Due to transient or intermittent mild and moderate elevations of hepatic transaminases and observed serious drug-induced liver injury, including acute liver failure, hepatitis, and jaundice, with the reference product, bilirubin (total and direct), alkaline phosphatase, ALT, AST, and gamma glutamyl transferase will be closely monitored. The ALT, AST, and total bilirubin values of eligible participants must be below <1.1 × upper limit of normal (ULN) at Screening.

Complications of diverticulitis have been reported with the reference product. All participants will be closely monitored for signs and symptoms of diverticulitis by the Investigator by means of physical examination and laboratory blood tests at the study sites. Development of ADAs was observed in some participants with the reference product but there was no correlation of antibody development with AEs [6].

4. STUDY OBJECTIVES AND ENDPOINTS

• Primary Objective	• Co-Primary Endpoints
To show equivalence in PK of BIIB800 and Actemra following s.c. administration of a single dose to healthy male participants	European Medicines Agency (EMA): • Maximum tocilizumab serum concentration (C_{max}) • Tocilizumab area under the concentration-time curve from time zero to infinity (AUC_{0-inf}) Food and Drug Administration (FDA): • Tocilizumab C_{max} • Tocilizumab area under the concentration-time curve up to the last measurable concentration (AUC_{0-t})
Secondary Objectives	**Secondary Endpoints**
To evaluate PK of BIIB800 and Actemra over time	Time to reach C_{max} (T_{max}) Apparent total body clearance (CL/F) Apparent terminal half-life ($t_{1/2}$)
To evaluate the clinical safety of BIIB800 and Actemra	Incidence of AEs and SAEs from time of administration to end of study (EoS)
To evaluate PD profiles BIIB800 and Actemra	For sIL-6R: • Area under the effect–time curve (AUE) • Maximum observed effect (E_{max}) • Time to E_{max} (tE_{max}) For high sensitive C-reactive protein (hsCRP): • AUE • Minimum observed effect E_{min} • Time to E_{min} (tE_{min})

To evaluate the immunogenicity of BIIB800 and Actemra	ADA and neutralizing antibodies (nAbs) ADA titers

5. STUDY DESIGN

5.1. Study Overview

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

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

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

See Figure 1 for a schematic of the study design and Table 1 for Schedule of Activities.

5.2. Study Duration for Participants

The total study duration for each participant will be up to 13 weeks:

- Screening period up to 5 weeks
- Treatment period: single dose at Day 1
- Post-dose period: 8 weeks

Participants will undergo a screening visit, will be admitted on Day –1 and will remain resident until Day 8. After discharge participants will have 7 scheduled outpatient visits. All visits and assessments must be performed within the time windows from Day 1. Study days are counted from Day 1; timing of assessment by hour is relative to time of dosing on Day 1.

Participants are considered enrolled at admission (Day -1).

5.3. Study Stopping Rules and Study Termination

There are no formal stopping rules.

The Sponsor may terminate this study at any time after informing the Investigator, ethics committee, and applicable regulatory agencies. The Sponsor will notify Investigators in the event that the study is to be placed on hold, completed, or terminated.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- Potential health risk for participants deemed unacceptable by an Investigator or the study Sponsor
- High withdrawal rate
- New scientific knowledge becomes available that makes the objectives of the study no longer feasible or valid
- Insufficient enrolment of participants
- Request of the Sponsor or regulatory authority, or independent ethics committee withdraws its approval

5.4. Unscheduled Visits

Data collected during unscheduled visits should be recorded on electronic case report forms (eCRFs) only if the data support protocol objectives and/or are required for safety monitoring.

5.5. End of Study

The EoS date for a participant is the date of the last outpatient study visit (Day 57) or the date of last contact with the participant in case of early termination, or AE follow-up to Day 57.

6. STUDY POPULATION

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the timepoint specified for the individual eligibility criterion.

6.1. Inclusion Criteria

1. Ability to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.

2. Healthy Male participants aged 18 to 55 years inclusive, at the time of signing the informed consent.

3. Have a body mass index between 18.5 and 29.9 kg/m^2, inclusive.

4. Total body weight between 60.0 and 90.0 kg, inclusive.

5. Systolic blood pressure <135 mmHg or >85 mmHg at Screening, after being supine for at least 5 minutes.

6. No clinically significant (as determined by the Investigator) 12-lead electrocardiogram (ECG) abnormalities, no cardiac pacemaker.

7. All participants must agree to adhere to the contraception requirements (see Section 12.5).

8. Hematology and blood chemistry results at Screening:

   - platelet count ≥ lower limit of normal (LLN)
   - absolute neutrophil count ≥ LLN
   - ALT and AST <1.1 × ULN
   - Total bilirubin <1.1x ULN
   - CRP ≤1.1 x ULN
   - Fasting serum low density lipoprotein-cholesterol ≤190 mg/dL and/or fasting serum triglycerides ≤150 mg/dL

6.2. Exclusion Criteria

Medical History

1. History or positive test result at Screening for human immunodeficiency virus (HIV).

2. History of hepatitis C infection or positive test result at Screening for hepatitis C virus antibody.

3. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and total hepatitis B core antibody [anti-HBc]). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

4. Serious infection (as determined by the Investigator) within the 6 months prior to Screening.

5. Any active infection, even if minor, ongoing at the time of Screening or Day -1.

6. History of systemic hypersensitivity reaction to the active drug substance, the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study.

7. History of any cancer, including carcinoma in situ, lymphoma or leukemia.

8. History of immunodeficiency or other clinically significant immunological disorders, or autoimmune disorders, ongoing or frequent/ recurring infection defined as more than 3 per year requiring treatment or active herpes zoster (according to the Investigator's discretion, including the post-herpetic neuralgia period if occurring) within one year prior to randomization or history of systemic fungal infection at any time.

9. History of clinically significant (in the opinion of the Investigator) atopic allergy (e.g., asthma, urticaria, eczematous dermatitis, allergic rhinitis), hypersensitivity, or allergic reactions.

10. History of angioedema.

11. History or presence of any clinically relevant nervous system disease including, but not restricted to any stroke/Transient Ischemic Attack, demyelinating conditions or of seizures other than febrile seizures before the age of 5 years.

12. Current use of antihyperlipidemic drugs.

13. Presence of any non-healed wound or bone fracture of a clinically relevant size (in the Investigator's opinion).

14. History of, or current, intestinal ulceration or diverticulitis.

15. History of any condition that increases the current risk of bleeding, such as hemorrhoids with bleeding symptoms, acute gastritis, or gastric and duodenal ulcers, which required medical intervention.

16. History of sensitivity to heparin or heparin-induced thrombocytopenia.

17. History of alcohol or substance abuse within the past 5 years (as determined by the Investigator), a positive urine drug screen or alcohol test at Screening and Day -1, or an unwillingness to adhere to visit window alcohol restrictions, or to refrain from illicit drugs throughout the study.

18. History or evidence of habitual use of tobacco- or nicotine-containing products within 90 days of Screening or a positive urine cotinine test at Screening or at Day -1 and unwillingness to abstain throughout the study.

19. Any history of difficulty in blood sampling or any vasovagal attack during blood sampling which in the opinion of the Investigator may interfere with the study sampling.

20. A positive diagnostic tuberculosis test result within 35 days prior to Day -1, defined as a positive QuantiFERON® test result or 2 successive indeterminate QuantiFERON test results.

Medications

21. Prior use of any biological products within 90 days before Screening.

22. Any prior exposure to tocilizumab or to any other agent directly acting on IL-6 or on its receptors including investigational products (e.g., siltuximab, sarilumab etc.).

23. Administration of immunoglobulins for anti-tetanus and anti-rabies post-exposure prophylaxis within 3 weeks prior to administration of study drug.

24. Any live or attenuated immunization or vaccination given within 30 days prior to Day -1 or planned to be given during the study period.

Other

25. Blood donation, participation in any study requiring repeated blood sampling, or hemorrhage requiring treatment, or any blood/platelet transfusion, where more than one unit of blood was taken, in the 3 months prior to Screening.

26. Clinically significant abnormal laboratory test values, as determined by the Investigator, at Screening or Day -1.

27. Plans to undergo elective procedures or surgeries at any time after signing the ICF until EoS.

28. Previous participation in this study or previous studies with reference tocilizumab (Actemra or RoActemra).

29. Previous or current enrolment in any other drug, device, or clinical study, or plan to take part in other clinical studies during this study, or treatment with an investigational drug or approved therapy for investigational use within 90 days prior to Day 1, or 5 half-lives, whichever is longer.

30. Non-suitable skin for dosing or post-dosing evaluations of upper arm for any reasons (including presence of tattoos, skin pigmentation disorders, scarring etc., which may obscure the injection site).

31. Inability to comply with study requirements.

32. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the participant unsuitable for enrolment.

6.3. Screening, Retesting, Screen Failures, Rescreening, and Randomization

6.3.1. Screening

No screening procedures can be carried out prior to participant providing informed consent.

Participants will have a unique identification number used at Screening. Subjects will be assigned a subject number prior to dosing. Assignment of subject numbers will be in ascending order and no numbers will be omitted (e.g., Subjects 101, 102, 103). Any identification numbers that are assigned will not be reused even if the participant does not continue in the study. Replacement subjects will be assigned a subject number corresponding to the number of the subject he is replacing plus 1000 (e.g., Subject 1101 replaces Subject 101).

Participants will be identified on all study documentation only by a screening identification number and/or subject number. A list identifying the subjects by subject number will be kept in the site master file. Study sites are required to document all screened participants initially considered for inclusion in the study. Screening is performed between Day -35 and Day -2.

6.3.2. Retesting

Laboratory assessments or vital signs assessments not meeting inclusion criteria may be repeated once at the Investigator’s discretion, during the screening period.

Participants who have clinically significant abnormal laboratory test values as determined by the Investigator are not eligible for retesting.

6.3.3. Screening Failures

Screening failures are defined as participants who sign the ICF but are not subsequently randomized. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log.

6.3.4. Rescreening

Participants may be re-screened once in the study, only if the reason for screen-fail was not a clinically significant out-of-range laboratory evaluation. At the rescreening all eligibility criteria must be confirmed and met.

6.3.5. Randomization

Participants will be randomized pre-dosing at Day 1, only after all screening assessments have been completed and after the Investigator has verified that the participants are eligible per criteria in 6.1 and 6.2.

Participants will be randomized, according to the stratification factor body weight (<75kg, ≥ 75 kg), to receive either BIIB800 or Actemra in a 1:1 ratio based on the study randomization scheme provided by the biostatistician.

The master randomization list is kept at each site pharmacy in a locked location to which only the unblinded pharmacists have access. The list is accessed to randomize a patient and dispense the corresponding treatment. The randomization is captured on the randomization tracker to indicate which subject numbers have been allocated. This is done in a blinded manner and all sites have access to the randomization tracker.

The randomization tracker will document the date, the site and the randomization numbers used. Pharmacy staff at each site will be responsible for updating the tracker in order to inform the other sites of the data recorded. Study Project Management will ensure that different sites are scheduled to randomize participants at different times, taking time zones into consideration and allowing sites sufficient time to update the tracker. The CRO's standard operating procedure (SOP) "provides further information about the process.

7. STUDY TREATMENT

7.1. Regimen

Refer to and follow the Dose Handling and Administration (DHA) document.

Participants will receive a single dose of 162 mg BIIB800 or Actemra via autoinjector, administered s.c. in the outer area of the upper arm. To maintain the blind, participants will be blindfolded in the presence of the IMP.

7.2. Study Treatment Management

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practices.

The IMP will be prepared by the Unblinded pharmacist from supplies of BIIB800 or Actemra, based upon the randomization schedule.

Site staff should follow the DHA document for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Study treatment will be administered by qualified site staff only to participants enrolled into the study. Autoinjectors are for single-use only and should not be reused.

7.3. BIIB800

BIIB800 will be provided by the Sponsor as a ready to-use, single-dose 0.9 mL autoinjector that delivers 162 mg tocilizumab, 0.112 mg of histidine, 0.605 mg of histidine hydrochloride monohydrate, 17.06 mg of arginine hydrochloride, 18.00 mg of sucrose, 0.45 mg polysorbate 80, and water for injection.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The study label will be added by the unblinded pharmacist. Study treatment must not be used after the expiration date.

7.3.1. Preparation for Administration

The unblinded study site staff member administering BIIB800 should carefully review the instructions provided in the DHA document.

Check that the autoinjector package is not damaged and that the liquid in the autoinjector is clear, not cloudy or discolored, and has no floating particles.

Do not use the autoinjector if the liquid is cloudy, discolored or has floating particles in it. The autoinjector in question should be saved at the study site and the product complaint reported immediately to the Sponsor.

Contact information for reporting a product complaint is provided in the study reference guide.

7.3.2. Storage

Study treatment must be stored in a secure location.

BIIB800 is to be stored at 2°C to 8°C (36°F to 46°F), in a locked refrigerator, with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA document.

7.3.2.1. Handling and Disposal

The Investigator must securely store and then destroy all used and unused autoinjectors of BIIB800 unless otherwise instructed by the Sponsor.

Full drug accountability as described in Section 7.3.2.2 must be completed before any destruction may be performed. After such destruction, the Sponsor must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction. The documentation will be filed in the Investigator Site File (ISF) and the trial master file (TMF).

7.3.2.2. Accountability

Accountability for study treatment is the responsibility of the Investigator and will be performed by unblinded study site staff/unblinded CRAs in order to maintain the blind. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed, and accounts of any study treatment accidentally or deliberately destroyed or lost. Appropriate forms to ease study treatment accountability will be provided by the contract research organization (CRO).

By the end of the study, reconciliation must be made between the amount of BIIB800 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

7.4. Reference Product

Actemra (reference product) will be provided by the CRO as a ready to-use, single-dose 0.9 mL autoinjector that delivers 162 mg tocilizumab, L-arginine hydrochloride (19 mg), L--histidine (1.52 mg), L-histidine hydrochloride monohydrate (1.74 mg), L-methionine (4.03 mg), polysorbate 80 (0.18 mg), and water for injection.

Actemra will be labeled for study use in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. Study treatment must not be used after the expiration date.

Storage, handling, disposal, and accountability will follow the procedures described above for BIIB800.

The respective reference product labelling (i.e., US Prescribing Information [USPI], Summary of Product Characteristics) will be included in the Study Reference Guide.

7.5. Blinding Procedures

The site staff responsible for administering the dose will be unblinded. The unblinded site staff must not participate further with the participant management or reporting. Details regarding blinding will be documented in a study specific blinding plan.

In the event of a medical emergency that requires unblinding of a participant's treatment assignment, refer to 12.4.4.1

7.6. Precautions

Due to the risk of serious hypersensitivity reactions following study treatment administration, treatments needed to manage anaphylactic reactions must be readily available at the study sites. For other precautions please see the Actemra product labeling.

7.7. Concomitant Therapy and Procedures

7.7.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between Day 1 and Day 57 or EoS.

Participants should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs, dietary supplements, and herbal preparations. Subjects are also advised that in the event of a medically urgent indication where delay in taking a concomitant medication could place the subject at risk, they should alert the study team as soon as possible about concomitant medications taken at the direction of non-study medical professionals.

7.7.1.1. Allowed Concomitant Therapy

- Nonprescription medications for symptomatic relief of mild discomfort are permitted.
- Therapies that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion.

The Investigator will record all concomitant medications taken by the participants in the participant source data and in the appropriate section of the eCRF. Any AE(s) requiring concomitant medication must be reported in the eCRF.

7.7.1.2. Prohibited Concomitant Therapy

Prohibited medicines are indicated in the exclusion criteria (Section 6.2).

7.7.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between time of consent and Day 57 or EoS.

7.8. Continuation of Treatment

There is no provision to provide study treatment after the study.

7.9. Lifestyle Considerations

The following will not be allowed:

- Alcohol
  - within 48 hours prior to Screening.
  - from 48 hours prior to Day -1 (admission) through discharge from the clinical research unit (CRU) on Day 8.
  - within 48 hours prior to each outpatient visit until EoS.
- Nicotine and tobacco-containing products from Screening to Day 57/EoS.
- Illicit/recreational drugs during the study, or evidence of recent illicit/recreational drug use in the screening period.
- Caffeine- or theophylline-containing food or beverages or dietary supplements (including but not limited to coffee, green tea, black tea, cola, energy drinks, and cacao) from 36 hours before dosing through discharge from the CRU (Day 8) and 24 hours prior to each outpatient visit until EoS.
- Significant changes in diet (at the Investigator discretion) from 2 weeks prior to Screening up to Day 1.
- Foods and beverages containing poppy seeds within 7 days prior to Screening and Day -1.

8. RULES FOR WITHDRAWAL FROM STUDY FOR INDIVIDUAL PARTICIPANTS

8.1. Lost to Follow-Up

Participants will be considered 'lost to follow-up' if they fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the subject's medical record.

- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.2. Withdrawal of Participants from the Study

Participants must be withdrawn from the study for any one of the following reasons:

- The participant withdraws consent for participation in the study, at their own discretion (the participant may or may not give a reason for withdrawal).

- The participant participates in another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.

- The participant is unwilling or unable to comply with the protocol.

- Any events that endanger the safety of the participant (at the Investigator's and/or Sponsor's discretion).

The primary reason for the participant's withdrawal from the study must be recorded in the participant's eCRF, if provided.

Participants must undergo an EoS visit and respective assessments, and every attempt must be made to complete an EoS visit, except in the event of death, withdrawal of consent, or other reasons that feasibly make completion of an EoS visit not possible.

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Participants who withdraw from the study before dosing may be replaced at the discretion of the Sponsor.

9. SAFETY ASSESSMENTS

The timing of assessment of safety events is stated in Table 1 Section 1.3 Schedule of Assessments.

9.1. Clinical Assessments

The following clinical assessments will be performed:

- AE and SAE recording from dosing throughout the study.
- Injection site examination including local reactions (pain, tenderness, erythema/redness, and induration/swelling) and systemic reactions (fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia) according to Appendix 1.
- A full physical examination (Screening) with subsequent symptom-directed physical examination during the study. The full physical examination will include the examination of the head, neck, eyes, ears, nose, and throat, cardiovascular system, pulmonary system, lymphatic system, endocrine system, muscular and skeletal system, general appearance, extremities, abdomen, skin, and neurological system.
- Vital sign measurements at frequency as per Table 1: temperature, heart rate, systolic and diastolic blood pressure (to be assessed on the arm not used for administration of study treatment), and respiratory rate. Measurements should be made before blood is drawn for laboratory tests, if applicable, and after the participant has been in supine position for at least 5 minutes (except for body temperature). All measurements will be performed singly and repeated once if outside the relevant reference ranges.
- Height, weight, and body mass index measurements at Screening and Day -1.
- 12-lead ECGs will be performed following a minimum of 5 minutes rest in the supine position, at frequency as per Table 1. All ECG tracings will be reviewed by the Investigator and repeated once, if necessary, at the Investigator's discretion. The Investigator will perform an overall evaluation of the 12-lead ECG for safety purposes and recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'.
- Concomitant therapy and procedure recording throughout the study.

9.2. Laboratory Assessments

Samples will be analyzed using Good Laboratory Practice validated assays. All samples will be clearly identified. Details about the handling and labeling of biological samples are provided in the Laboratory Manual.

The laboratory reports received from the laboratory will be reviewed, signed, and dated by the Investigator or delegate, and filed at the site. Clinically significant abnormal laboratory findings as judged by the Investigator must be recorded as AEs in the eCRF.

The following laboratory assessments will be performed at intervals specified in Table 1:

- Hematology: red blood cell count, white blood cell count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, hemoglobin and hematocrit, platelet count, white blood cell count differential (absolute and %, comprising basophils, eosinophils, lymphocytes, monocytes, neutrophils)

- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, gamma glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, low density lipoprotein and triglycerides, C-reactive protein (C-reactive protein only at Screening)

- Urinalysis: blood, glucose, ketones, pH, protein, specific gravity, bilirubin, color, nitrites, urobilinogen; microscopy will be done in case of abnormal urinalysis findings

- Coagulation: prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT)

- Serology: hepatitis C virus antibodies, hepatitis B surface antigen and total hepatitis B core antibody, hepatitis B surface antibody, HIV antigen/antibody, tuberculosis test (QuantiFERON Gold)

- Urine drug screen

- Alcohol test (urine/breath/blood per site standard)

- Cotinine

9.3. Immunogenicity Assessments

The following assessments will be performed to evaluate immunogenicity:

- ADA

- nAb

- ADA titers

Serum samples for ADA evaluation will be collected and processed according to standard procedures as described in the Laboratory Manual. ADA-positive samples will be further investigated for determination of nAbs and ADA titers The actual date and time of each sample

collection will be recorded. The serum samples will be stored frozen before shipment to a central bioanalytical laboratory for evaluation. Details of ADA blood sample collection, processing, storage, and shipping procedures are described in the Laboratory Manual.

The ADA and nAb levels will be measured using a validated electrochemiluminescence assay. Details of the method validation and sample analysis will be described in bioanalytical method validation reports and the bioanalytical sample analysis report.

10. PHARMACOKINETIC ASSESSMENTS

See Section 1.3 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the clinic to have the evaluations repeated.

The following parameters will be calculated to assess PK:

- C_{max}
- $AUC_{0\text{-}inf}$
- $AUC_{0\text{-}t}$
- T_{max}
- CL/F
- $t_{1/2}$

The quantification of tocilizumab in serum will be performed using a validated enzyme-linked immunosorbent assay. The analytical methods used to measure serum concentrations of tocilizumab will be described in a bioanalytical sample analysis report. Details on processes for collection and handling (labeling, disposal, storage, and transportation) will be described in the Laboratory Manual.

The exact date and time of sample collection (24-hour clock time) must be recorded in the eCRF and will be used to calculate PK parameters. PK parameters will be derived using noncompartmental methods with validated software.

11. PHARMACODYNAMIC ASSESSMENTS

See Section 1.3 for the timing of all assessments.

PD profiles will be assessed using the following biomarkers:

- sIL-6R
- hsCRP

The quantification of biomarkers will be performed using validated assay methods. Details on processes for collection and handling of biomarker samples (labeling, disposal, storage, and transportation) will be described in the Laboratory Manual.

The exact date and time of sample collection (24-hour clock time) must be recorded in the eCRF.

12. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the participant. If necessary, according to Investigator's clinical judgment, appropriate medical intervention should be provided.

At the signing of the ICF, each participant must be given the site medical telephone number for reporting AEs and medical emergencies. Throughout the protocol, the Sponsor is named, but reporting may be done through a CRO.

12.1. Definitions

12.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical investigation participant (participant) who has received a pharmaceutical product, regardless of causal relationship with the product. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal assessment (e.g., laboratory value, vital sign, 12-lead ECG) result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless the result is considered by the Investigator to be clinically significant.

12.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that:

- Results in death.
- In the view of the Investigator, places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Is a medically important event.

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring

intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

12.2. Safety Classifications

12.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 12.1.2.
- The relationship of the event to study treatment as defined in Section 12.2.2.
- The severity of the event as defined in Section 12.2.3.

12.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

12.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms.
Moderate	Symptoms of sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptoms may be needed.

Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or participant hospitalized.

12.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor according to the Investigator's Brochure.

12.3. Monitoring and Recording Events

12.3.1. Adverse Events

Any AE experienced by the participant between the time of consenting and the administration of the study treatment is to be recorded on the AE pre-dose page of the eCRF if related to any study procedures regardless of the severity or seriousness of the event. Any AE experienced by the participant between the time of administration of study treatment and EoS is to be recorded on the AE page of the eCRF, regardless of the severity or seriousness of the event or its relationship to study treatment. At each study visit, the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the eCRF.

AEs that are ongoing when the participant completes or discontinues the study will not be followed by the Investigator.

12.3.2. Serious Adverse Events

Any SAE experienced by the participant between the time of study drug administration at Day 1 and Day 57/EoS is to be recorded on the SAE form and the AE page of the eCRF, regardless of the severity of the event and/or its relationship to study treatment. After EoS the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

SAEs must be reported to the Sponsor's Global Patient Safety and Pharmacovigilance (GPSP) Mailbox within 24 hours of study site staff awareness of the SAE, as described in Section 12.3.3. Follow-up information regarding an SAE also must be reported within 24 hours of study site staff awareness.

Any SAE that is ongoing when the participant completes or discontinues the study will not be followed by the Investigator.

12.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the Sponsor's GPSP Mailbox within 24 hours of the site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs
The SAE Form ***must be submitted*** to the Sponsor's GPSP Mailbox via the email address: BBUsafetyreporting@biogen.com regardless of the severity of the event or relationship of the event to study treatment. To report initial or follow-up information on an SAE, email a completed SAE form; refer to the Study Contact List for complete contact information.

12.3.3.1. Deaths

Death is an outcome of an event. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor. The term 'Death' should be reported as an SAE only if the cause of death is not known and cannot be determined.

12.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Appropriate personnel at the Sponsor will unblind SUSARs for the purpose of regulatory reporting. The Sponsor will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

12.4. Procedures for Handling Special Situations

12.4.1. Pregnancy

Participants should not impregnate their partners during the study and for 90 days after their dose of study treatment.

A pregnancy occurring in a female partner of a study participant within 90 days of administration of the study drug to the male participant must be reported by the Investigator on the Pregnancy Form to the Sponsor's GPSP Mailbox BBUsafetyreporting@biogen.com within 24 hours of the site staff becoming aware of the pregnancy.

Refer to the Study Contact List for complete contact information.

The Investigator or site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE eCRF.

Congenital abnormalities and birth defects in the offspring of a female partner of the male study participants should be reported as an SAE if conception occurred during the study treatment period or within 90 days from the dose of study treatment.

12.4.2. Product Complaint

The Investigator must enter any device malfunction and/or failure into Biogen's Clinical Site Support (CSS) portal (https://biogen.service-now.com/csmcss), as a product complaint.

If the device malfunction and/or failure results in an AE, an AE CRF also needs to be completed.

The study site must formally notify the Sponsor's GPSP Mailbox (BBUsafetyreporting@biogen.com) within 24 hours of awareness of any SAE(s) associated with the product complaint, by submitting the study-specific SAE Form.

12.4.3. Overdose

An overdose is any dose of study treatment administered to a participant that exceeds the dose assigned to the participant according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and emailed to the Sponsor's GPSP Mailbox BBUsafetyreporting@biogen.com within 24 hours of the site becoming aware of the overdose.

An overdose must be reported to the Sponsor even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and emailed to the Sponsor.

All study treatment-related dosing information must be recorded on the dosing eCRF.

12.4.4. Medical Emergency

In a medical emergency requiring immediate attention, site Investigator will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Monitor as soon as possible to discuss the case. Refer to the Study Contact List for complete contact information.

12.4.4.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the participant's treatment assignment may influence the participant's clinical care, the Investigator may access the participant's assigned treatment. The Investigator must document the reasons for unblinding in the participant's source documents. The site will follow their (CRO's) internal SOPs regarding emergency unblinding. The Investigator is strongly advised not to divulge the participant's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator must contact the Sponsor or study's

Medical Monitor as soon as possible to inform of such situations. Refer to the Study Contact List for complete contact information.

12.5. Contraception Requirements

All participants must ensure that effective contraception is used during the study and for 90 days after their dose of study treatment. This includes barrier methods to prevent exposure to participant's sperm. In addition, participants should not donate sperm for at least 90 days after their dose of study treatment.

Pregnancy reporting is described in Section 12.4.1.

12.6. Safety Responsibilities

12.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor all AEs, including SAEs, and report on the eCRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record any pregnancies and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and email to the Sponsor within 24 hours of the site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information.
- Ensure all AE and SAE reports are detailed and have supporting documentation in the participants' medical records.
- Pursue AE follow-up information, if possible, until EoS. Record AE follow-up information, including resolution, on the eCRF, as applicable.
- Report SAEs to Ethics Committees or IRBs in accordance with local requirements.

12.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Retention of overall accountability for safety reporting. The study CRO is responsible for reviewing with site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs, SAEs, pregnancies, and product complaints.

- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

13. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 4. The details of analysis methods will be documented in statistical analysis plan (SAP).

13.1. General Considerations

Except for the primary endpoint analyses, all analyses will be descriptive with no hypothesis testing. No imputation will be applied for missing values except for those specified in the protocol. No multiplicity adjustment will be applied in the hypothesis testing for the primary analysis.

13.2. Analysis Sets

PK concentration analysis set (PKCS): includes all study participants with at least one post-dose assessment. The serum concentration of tocilizumab will be summarized based on the PKCS.

PK analysis set (PKAS): includes all randomized study participants with at least one calculable PK parameter. Participants with a major protocol violation that would affect PK evaluation will be excluded from the PKAS. Determination of exclusion, with a list of excluded participants , will be made prior to the unblinding.
The PKAS will be used to evaluate the PK equivalence between study treatments. Major protocol violations will be specified in the SAP.

Safety analysis full set (SAFS): all randomized study participants who receive the study treatment. Safety analysis will be presented according to treatment received. The SAFS will be used for the analysis of safety and immunogenicity.

13.3. Methods of Analysis

13.3.1. Safety

All safety analyses will be performed descriptively on the SAFS according to treatment received. No hypothesis testing will be performed. Previous medication and concomitant medications will be coded and summarized according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.

13.3.1.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity from time of study drug administration to EoS. The incidence of TEAEs will be summarized by primary system organ class (SOC) and preferred term within each SOC. AEs will also be tabulated by severity, seriousness, and relationship to study treatment. All data will be presented in summary

tables by treatment received group and overall. TEAEs leading to premature study discontinuation or death will be listed.

A listing of non-TEAEs will be provided.

13.3.1.2. Laboratory Results

All laboratory assessments will be analyzed descriptively and presented in summary tables. No hypothesis testing between treatment groups will be performed. For each variable the summary tables will present actual values, and number and proportion of participants with out-of-range values by visit.

13.3.1.3. Vital Signs and 12-lead Electrocardiogram

Vital signs (body temperature, heart rate, systolic and diastolic blood pressure, respiratory rate) and 12-lead ECG evaluations will be analyzed descriptively and presented in summary tables by visit.

13.3.2. Pharmacokinetics

Tocilizumab concentrations will be summarized for the PKCS using descriptive statistics by actual time of measurement for each treatment separately.

Co-primary endpoints and statistical analysis for bioequivalence assessment

Primary estimand 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 (reference product) and BIIB800 (test product).

Handling intercurrent events:

- Premature discontinuation of study for any reason with available PK parameters
- Incomplete or partial dose delivery

All the intercurrent events will be handled with the *Treatment policy strategy.*

Contingency measures and missing data handling:

Considering the safety profile of Actemra as per USPI and EPAR, and the healthy study population, fatal events are unexpected. Should such fatal events occur, 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 utilised.
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.

The statistical analysis of the PK endpoints, area under the concentration-time curve ($AUC_{0\text{-}inf}$ for EMA and $AUC_{0\text{-}t}$ for FDA [9,10]) and C_{max}, is based upon the 90% confidence intervals for the ratio of the population geometric means between the test (BIIB800) and reference (Actemra) groups. This method is equivalent to two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance level. The 90% confidence interval (for the average bioequivalence) is derived for the ratio of the averages (population geometric means) of the outcomes for BIIB800 and Actemra. The data will be transformed prior to analysis using a logarithmic transformation and the corresponding confidence interval for the difference between products will be obtained from an analysis of variance (ANOVA) model (fixed effects for treatment, site and body weight). If one site has recruited fewer than 30 participants then the primary analysis of ANOVA analysis will include only treatment and body weight as fixed effects. To establish bioequivalence, the derived 90% confidence intervals back-transformed on the original scale should fall within 80-125% limits (including 100%) for the ratio of the product averages.

Due to the testing procedure that all null hypotheses of bioinequivalence need to be rejected at the 5% significance level, no adjustment for multiplicity will be performed.

Other PK endpoints

Except for T_{max}, which will be summarized by n, minimum, median, and maximum, all PK parameters will be summarized by treatment group using n, mean (arithmetic and geometric), standard deviation (SD), percentage of variation coefficient (including geometric variation coefficient), minimum, median, and maximum.

For PK parameter calculations, concentrations that are below the limit of quantification (BLQ) or missing will be set to zero. Further details of the PK parameter analysis will be described in the SAP.

Pharmacodynamics

All PD measurements (i.e., biomarkers, see Section 11) and the changes from baseline for the continues PD endpoints will be summarized by treatment group using n, mean (arithmetic and geometric), SD, percentage of variation coefficient (including geometric variation coefficient), minimum, median, and maximum. Further details of the PD parameter analysis will be described in the SAP.

13.3.3. Immunogenicity Data

Incidence of ADAs to BIIB800 and Actemra, their neutralizing potential and ADA titer of positive samples will be summarized for the participants in the SAFS dataset by incidence of ADA-positive and nAb positive samples for each timepoint and overall for each treatment separately. Further details of the analysis will be described in the SAP.

13.4. Interim Analyses

No formal unblinded interim analysis is planned to be performed.

13.5. Sample Size Considerations

13.5.1. Initial Sample Size Calculation

A sample size of 300 participants (150 per arm), assuming a non-evaluable rate of 10%, will provide approximately 90% power for the bioequivalence testing of each pair of co-primary endpoints for each Regulatory Agency: C_{max} and $AUC_{0\text{-}t}$ for FDA, and C_{max} and AUC_{0inf} for EMA. Enrolled participants will be randomized (equal allocation ratio 1:1) to receive a single dose of either BIIB800 or Actemra. An inter-subject CV of approximately 0.5 is initially assumed based on published PK outcome data in healthy participants [4,11,12], and a single injection site will be specified (upper arm).The geometric mean ratio is assumed to be 1.05.

The PK endpoints are known to be highly correlated [13]; this correlation is initially assumed to be 1 and will be revisited with the BSSR procedure prespecified to recalculate the CV of PK endpoints.

13.5.2. Blinded Sample Size Recalculation (BSSR)

A BSSR will be performed when the first 100 participants have completed their Day 29 outpatient visit, to assess the CV and its correlation between co-primary endpoints.

The first 100 participants in the BSSR are expected to be sufficient to provide a precise estimate of the nuisance parameter (CV) for the primary endpoints and correlation between the primary endpoints. The BSSR will be conducted on the PK parameters based on the post-dose data up to the Day 29 outpatient visit. Previous studies have shown that 29 days post-administration represent a sufficient duration in which to measure the evolution of the PK parameters relevant to the primary endpoints [5,12].

The initially targeted sample size (see Section 13.5) corresponds to a CV of approximately 0.5, a correlation of 1.0 and a non-evaluable rate of approximately 10%. Based on the recalculated CV and evaluation of the correlation between the coprimary endpoints at the BSSR timepoint, the sample size will be recalculated, and enrolment may be adjusted accordingly to ensure that the targeted study power is approximately 90%. Details will be specified in a separate SAP.

In principle, a BSSR might lead to a type I error inflation. However, the risk of inflation is expected to be small [14,15]. The effect of the BSSR on the type I error rate will be evaluated in

a simulation study. Details will be specified in a technical simulation report and the SAP or protocol may subsequently be amended."

14. ETHICAL REQUIREMENTS

The Sponsor, any contracted third party, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigators are responsible for demonstrating timely oversight of all clinical study data from their site, including data external to the electronic data capture (EDC) system, such as laboratory data. Investigators must e-sign all their data on completed eCRFs, at the participant, visit, or casebook level, prior to database lock, as well as before any subsequent re-lock.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator must maintain a list of the appropriately qualified persons to whom study-related duties have been delegated. The Investigator is responsible for oversight of those individuals and for ensuring the integrity of the tasks performed and any data generated.

14.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

14.2. Ethics Committee and Institutional Review Boards

The Investigator must obtain ethics committee or Institutional Review Board (IRB) approval of the protocol, ICF, and other required study documents prior to starting the study, as applicable according to national and local regulations.

If the Investigator makes any changes to the ICF, the Sponsor must approve the changes before the ICF is submitted to the ethics committee or IRB. A copy of the approved ICF must be provided to the Sponsor. After approval, the ICF must not be altered without the agreement of the relevant ethics committee or IRB and the Sponsor.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor must receive a letter documenting ethics committee or IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be participant to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee or IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee or IRB and the Sponsor.

14.3. Changes to Final Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 14.4).

14.4. Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, informed consent utilizing the approved ICF must be obtained.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the participant must be explained to the participant. The participant must be given sufficient time to consider whether to participate in the study.

A copy of the signed and dated ICF must be given to the participant. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the participant's medical record.

Should additional information that may affect participants' willingness to continue in the study become available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

14.5. Participant Data Protection

Prior to any testing under this protocol, including screening tests and assessments, participants must also provide all authorizations required by applicable national and local privacy regulations (e.g., Protected Health Information authorization in North America).

Study reports will be used for research purposes only. The participant will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. The Sponsor, its

partners and designees, ethics committees, IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the participant's personal medical data confidential.

14.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

14.7. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor or partnering company) with the participant before the participant makes a decision to participate in the study.

14.8. Study Report Signatory

The Sponsor will designate one of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or participant enrolment, or by other factors determined to be relevant by the Sponsor.

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

14.9. Registration of Study and Disclosure of Study Results

The Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

The Sponsor also will notify, when required, the regulatory authorities and ethics committees or IRBs about the completion or termination of this study and send a copy of the clinical study report in accordance with necessary timelines.

14.10. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

15. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

15.1. Vendors

The Sponsor will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

15.1.1. Contract Research Organization

A CRO will be responsible for operational aspects of the study including but not limited to study initiation, site staff training, monitoring of source data, and data management.

15.1.2. Electronic Data Capture

Participant information will be captured and managed by study sites via an EDC system. The designated study personnel can access the EDC system only upon training and will be responsible for entry and update of the raw data in the eCRFs, in a timely manner. To ensure the quality of clinical data across all sites, automatic edit checks will be programmed into the database, and a data management review will also be performed on data entered into the EDC database; data will be checked for consistency and apparent omissions and/or discrepancies. Data queries will be raised in the database for resolution by the site. Entry of data into eCRFs and all updates made throughout the study will be documented automatically in the software audit trail. The site Investigator is responsible for signing off completed, individual participants' eCRFs.

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate. Biogen retains all data, programs, and outputs generated during the study. At study close, data are uploaded from the EDC database and stored in accordance with Biogen standard operating procedures. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

15.1.3. Central Laboratories for Laboratory Assessments

A central laboratory will perform the PK, ADA, IL-6R and hsCRP analyses. All other blood and urine samples will be analyzed locally at the site.

16. ADMINISTRATIVE PROCEDURES

16.1. Study Site Initiation

The Investigator must not screen any participants prior to completion of a study initiation visit. The Investigator and other site staff, as appropriate, will attend the study initiation visit, which must include a detailed review of the protocol, study procedures, and study responsibilities, including safety reporting.

16.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate.

During and/or after completion of the study, the Sponsor and/or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested. The Investigator must notify the Sponsor immediately if notified of a potential inspection by a regulatory authority.

16.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the participants' clinic records. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The CRA will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on participant safety, maintaining the blind, data integrity, and critical data and processes. An unblinded CRA will be responsible for monitoring randomization and medication records.

During these visits, eCRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to the Sponsor or designee in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of participant rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

16.4. Study Funding

The Sponsor is responsible for study funding. All financial details are provided in the separate contracts between the institution, Investigator, and the Sponsor organization.

16.5. Publications

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals 2018, which states:

Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.

Acquisition of funding, collection of data, or general supervision of the research alone does not justify authorship.

All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Biogen for review.

17. REFERENCES

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18. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "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," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date (*DD MMM YYYY*)

_____

Investigator's Name (Print)

_____

Study Site (Print)

19. APPENDIX 1: GRADING SCALES

A-Table 1: Local and systemic reaction grading scale

	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.

From [16] (slightly adapted).