Product Code GP2017 (INN: Adalimumab)

Clinical Study Protocol

GP17-302 / NCT02744755

A randomized, double-blind, parallel-group, multicenter study to demonstrate similar efficacy and to compare safety and immunogenicity of GP2017 and Humira® in patients with moderate to severe active rheumatoid arthritis

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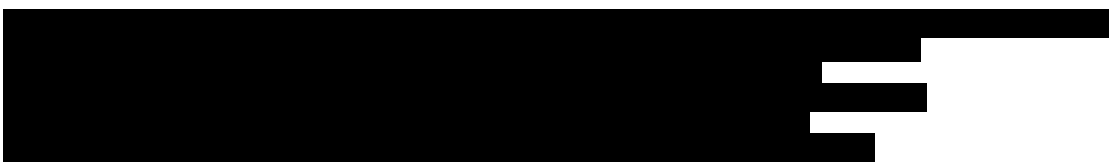

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List of abbreviations

ACR	American College of Rheumatology
ADA	anti-drug antibodies
AE	Adverse Event
ALT	Alanine aminotransferase
anti-CCP	Anti-citrullinated protein anti-
HBc	Hepatitis B core antibody AP
	Alkaline phosphatase
aPTT	Activated Partial Thromboplastic Time
AST	Aspartate aminotransferase
AUEC	Area under the effect-time curve
CD20	B-lymphocyte antigen
CDBL	Clinical Data Base Lock
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cm	Centimeter
COX-2	Cyclooxygenase-2
(e)CRF	(electronic) Case Report/Record Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria AE
DAS	Disease activity score
DI	Disability Index
dl	Deciliter
DMARD	Disease modifying anti-rheumatic drug
DMC	Data Monitoring Committee
[redacted]	[redacted]
ECG	Electrocardiogram
EMA	European Medicines Agency

[redacted]

ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GH	General health
GWA	Genome Wide Associations
HAQ	Health Assessment Questionnaire
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV-Ab	Hepatitis C virus antibody
HDL	High density lipoprotein
i.v.	Intravenous(ly)
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
IL-6	Interleukin 6
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
IU	International Unit
IUD	Intrauterine device

IUS	Intrauterine system
L	Liter
LDL	Low density lipoprotein
mg	Miligram
min	Minutes
ml	Milliliter
mm	Milimeter
MMRM	Mixed-Model Repeated Measures
mRNA	Messenger Ribonucleic Acid
MTX	Methotrexate
µl	Microliter
µmol	Micromole
NAb	Neutralizing antibody
NSAID	Non-steroidal anti-inflammatory drug
o.d.	Once a day
p.o.	Oral(ly)
PA	posteroanterior
[redacted]	[redacted]
PCR	Polymerase chain reaction
PhGA	Physician Global Assessment
PI	Prescribing Information
PK	Pharmacokinetics
PPD	Purified protein derivative
PPS	Per-protocol set
PRN	Pro re nata (as needed)
PsA	Psoriatric Arthritis
PtGA	Patient Global Assessment
RA	Rheumatoid Arthritis
RBC	Red blood cell
REB	Research Ethics Board
RF	Rheumatoid Factor

s.c.	Subcutaneous
SAE	Serious adverse event
SJC	Swollen joint count
SmPC	Summary of Product Characteristics
SNP	Single nucleotide polymorphism
sqrt	Square root
TB	Tuberculosis
TJC	Tender joint count
TP	Treatment period
VAS	Visual analogue scale
VHP	Voluntary Harmonization Procedure
WBC	White blood cell
WOCB	Women of child-bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Baseline	Assessments taken during Visit 2/Randomization
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Enrollment	Point/time of patient entry into the study; the point at which informed consent (ICF) must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US 21CFR 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each medication package in studies that dispense medication using an Interactive Response Technology (IRT) system.
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, treatment, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs.
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

Amendment 3

Amendment rationale

The main purpose of this protocol amendment is to reflect changes in the result reporting strategy and remove the CSR (and accompanying database lock) previously planned at week 12. Also, provided additional patient consent is given, samples taken for adalimumab trough concentration and ADA assessment may now be used [redacted] instead of being discarded. In addition minor editorial corrections and clarifications were made throughout the protocol.

Rationale for removing Week 12 CSR

The purpose of this protocol amendment is to reflect a modified the study reporting strategy. With this current approach, a single CSR is now planned at the end of the study and will cover objectives for all study periods, including the primary endpoint analysis at week 12, the head-to-head comparison of GP2017 to Humira in study period 1 as well as the switching to or continuation on GP2017 of all patients in study period 2. Consequently, the Week 12 CSR is no longer required and the study team will remain blinded until the end of the study.

Rationale for using remaining samples for future research and additional biomarker assessments

The purpose of this protocol amendment is to allow for use of already collected serum samples that are left over after the adalimumab trough concentration and ADA assessments for additional research. [redacted]

Study status

All patients have been randomized into the study.

Main Changes to the protocol

Section List of abbreviations

- Abbreviation added

Section Protocol summary

- Study design section updated to reflect changes in Section 5

Section 1 Introduction

- Humira licensure updated in Section 1.1

Section 3 Investigational Plan

- Week 12 CSR and corresponding timepoints of analyses removed from Section 3.5

[redacted]

Section 4 Population

- Definition of moderate disease activity harmonized

Section 5 Treatment

- Section 5.2 and 5.5.4 updated to allow for additional training for self-administration
- Week 12 CSR and corresponding timepoints of analyses removed from Section 5.4
- Section 5.4 updated to reflect changes in Section 5.5.10
- Section 5.5.10 updated

Section 6 Visit schedule and assessment

- Updated to allow for additional training for self-administration
- Table 6-1 clarified
- Section 6.2.2.3.1 harmonized with Section 4
- Section 6.2.3 corrected and harmonized with table 6-1
- Definition of moderate disease activity in table 6-2 harmonized with Section 4
- Section 6.5.4 harmonized with table 6-1
- Section 6.5.4.8.1 corrected to reflect actual lab sampling
- Section 6.5.6 clarified and changed to allow for use of left over samples according to Section 6.8.1
- Section 6.5.6.2 adapted to removal of Week 12 CSR
- Clarification of abbreviation in section 6.8
- Section 6.8.1 added for future research

Section 8 Data review and database management

- Section 8.2 corrected

Section 9 Data analysis

- Week 12 CSR and corresponding timepoints of analyses removed
- Clarification of W12 PPS, SP1 PPS, SP2 PPS, SP2 FAS and SP2 SAF in section 9.1
- Section 9.3 corrected
- Section 9.4.2 corrected
- Section 9.4.4 clarified
- Section 9.5.1.1 clarified and corrected
- Section 9.5.2 corrected
- Section 9.5.4 adapted to removal of Week 12 CSR
- Section 9.7 added for clarification
- References to Week 12 CSR and corresponding timepoints of analyses removed from Section 9.8

Section 12 References

- Updated to reflect new SmPC and USPI information in section 1

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

This amended protocol will be sent to the IEC and HA for approval or notification as required according to local regulations. The changes described in this amended protocol are substantial.

The changes herein affect the Informed Consent, which will be revised accordingly and the site is required to submit a revised Informed Consent that takes into account the changes described in this amended protocol, for approval, patients will be re-consented. For future research an additional Informed Consent will be submitted by the site for approval, patient consent is optional.

Amendment 2

Amendment rationale

With this protocol amendment 2, exclusion criterion 15 will be modified to confirm the seronegativity of the enrolled subjects through the HIV testing at screening. Furthermore sodium and calcium parameters will be amended and harmonized based on CTCAE version 4 while for hyponatremia based on "Clinical practice guideline on diagnosis and treatment of hyponatraemia". These changes have been implemented to include feedback from review of the version 2.0 of the protocol by the centralized Voluntary Harmonization Procedure (VHP) for participating EU countries.

Study status

At the time of this protocol amendment, the study is not recruiting.

Main Changes to the protocol

Section 4 Population

- Exclusion criterion 15 adapted

Section 6 Visit schedule and assessments

- HIV test added in Table 6-1 and Section 6.2.3

Appendix 1 Clinically notable laboratory parameters

- Sodium and calcium value ranges harmonized

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

This amended protocol will be sent to the IEC and HA for approval or notification as required according to local regulations. The changes described in this amended protocol are substantial.

The changes herein affect the Informed Consent, which will be revised accordingly and the site is required to submit a revised Informed Consent that takes into account the changes described in this amended protocol, for approval.

Amendment 1

Amendment rationale

The amendment is to provide further clarifications to Section 2, 4, 5, 6, 8 and 10 of the protocol and inclusion of additional blood sampling for anti drug antibody (ADA) analysis . In addition, formatting errors and inconsistencies in the protocol are corrected.

Study status

Study is not recruiting. Protocol version 1.0 has not been submitted to Health Authorities, EthicsCommittees and Intitutional Review Boards.

Main Changes to the protocol

Protocol summary

- Addition of complete exclusion criteria

Section 2 Study Objectives

- [redacted]

Section 4 Population

- Inclusion criteria 4, 5, 7, 8 and 9 clarified
- Exclusion criterion 2, 7, 19, 20 and 21 clarified

Section 5 Treatment

- Use of rescue medication clarified
- Prohibited medications and the respective wash out periods explained, Table 5.2 title corrected

Section 6 Visit schedule and assessments

- [redacted]
- Blood volume increase for ADA sampling and a procedural change introduced

Section 8 Data review and database management

- Data collection and quality control clarified

Section 10 Ethical considerations

- Additional Informed Consent procedure explained
- Inconsistencies in pregnancy monitoring corrected

[redacted]

Protocol summary

Protocol number	GP17-302
Title	A randomized, double-blind study to demonstrate similar efficacy and safety of GP2017 and Humira® in patients with moderate to severe active rheumatoid arthritis
Brief title	Efficacy and safety of GP2017 in rheumatoid arthritis
Sponsor	Hexal AG, Industriestr. 25, D-83607 Holzkirchen, Germany Sandoz Inc., 100 College Road West, Princeton, NJ 08540, USA for US
Clinical Phase	III
Investigation type	Biological Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate similar efficacy and safety of GP2017 and US-licensed Humira® in patients with moderate to severe rheumatoid arthritis (RA) with inadequate response to Disease modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX). This study is part of the clinical development program of GP2017 and aims to support the worldwide registration of GP2017 as a biosimilar product to Humira®.
Primary Objective(s)	To demonstrate similar efficacy of GP2017 and US-licensed Humira® in patients with moderate to severe active RA with respect to DAS28-CRP score change from baseline at Week 12.
Secondary Objectives	**Study period 1 (baseline (randomization) - Week 24):** • To demonstrate similar efficacy of GP2017 and US-licensed Humira® with respect to time-weighted averaged change from baseline in DAS28-CRP until Week 24. • To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving European League against Rheumatism (EULAR) criterion for remission at Week 4, 12, 24 • To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving EULAR criterion for good response at Week 4, 12, 24 • To compare proportion of GP2017 and US-licensed Humira® treated patients achieved EULAR moderate response at Week 4, 12, 24 • To compare DAS28-CRP and DAS28-ESR changes from baseline in GP2017 and US-licensed Humira® treated patients at Week 2, 4, 24 • To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving remission according to Boolean definition (TJC ≤1, SJC≤1, C-reactive Protein (CRP)≤1 mg/dl and patient global assessment (PtGA)≤1) at Week 4, 12, 24 • To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving ACR20/50/70 (based on

[redacted]

	CRP & Erythrocyte Sedimentation Rate (ESR)) responses at Week 4, 12, 24 • To compare Health Assessment Questionnaire-Disability Index (HAQ-DI) changes from baseline in GP2017 and US-licensed Humira® treated patients at Week 4, 12 and 24 • To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving HAQ-DI score ≤0.5 at Week 4, 12 and 24 • To compare proportion of GP2017 and US-licensed Humira® treated patients with HAQ-DI score improvement >0.3 at Week 4, 12 and 24 • To compare Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale changes from baseline in GP2017 and US-licensed Humira® treated patients at Week 4, 12 and 24 • To compare CRP and ESR changes from baseline in GP2017 and US-licensed Humira® treated patients over time • To compare clinical safety of GP2017 and US-licensed Humira® as assessed by changes in vital signs, clinical laboratory parameters and incidence and severity of Adverse Events (AEs) • To compare incidence and severity of injection site reactions (ISRs) in GP2017 and US-licensed Humira® treated patients • To compare immunogenicity as determined by measuring the rate of anti-drug antibody (ADA) formation against adalimumab in GP2017 and US-licensed Humira® treated patients **Study period 2 (Week 24 - Week 48):** • To evaluate clinical safety in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira® as assessed by changes in vital signs, clinical laboratory parameters and incidence and severity of AE • To evaluate incidence and severity of injection site reactions (ISRs) in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira® • To evaluate immunogenicity as determined by measuring the rate of ADA formation against adalimumab in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira® • To evaluate efficacy in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira® as assessed by DAS28-CRP, DAS28-ESR score changes from Week 24 at Week 48 and ACR20/50/70 responses at Week 48 • To compare Health Assessment Questionnaire-Disability Index (HAQ-DI) changes from Week 24 in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira® at Week 48 • To compare the proportion of patients treated continuously with GP2017 and patients treated with GP2017 after switch

[redacted]

	from US-licensed Humira® achieving HAQ-DI score ≤0.5 at Week 48 • To compare FACIT Fatigue scale changes from Week 24 in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira® at Week 48
[redacted]	[redacted]
Study design	This study has a parallel-group, randomized, double-blind design and it is planned to randomize approximately 308 patients with moderate to severe active RA at approximately 110 study sites worldwide. A screening period of up to 4 weeks will be used to assess patient´s eligibility. All patients must be on stable dose of MTX at least 4 weeks prior to randomization and continue throughout the study on this dose. At the baseline visit (Day 1, Visit 2); eligible patients will be randomized using a 1:1 ratio to one of the two treatment arms: GP2017 or US-licensed Humira®. Randomized patients will enter a 24-week treatment phase Study Period 1 and shall be treated with either GP2017 or US-licensed Humira®. Study drug administration will be performed at the site by designated unblinded personnel. At Week 24 all patients will be evaluated for their DAS28-CRP response. Patients who did not show at least a moderate DAS28-CRP response will have their final assessment at Week 24 and will not continue in the study. Irrespective of their treatment during Study Period 1, all patients with at least a moderate response at Week 24 by DAS28-CRP score, will be switched to or continue with subcutaneous injection of GP2017 from Week 24 up to Week 46. End of Study (EoS) Visit will be performed at Week 48. In Study Period 2, all patients will self-administer GP2017 injections. At Week 24 (Visit 14), appropriate training for administration of GP2017 will be provided and first self-administration will be done under the supervision of designated unblinded study personnel at the study site.

[redacted]

	After being considered proficient at self-administration, patient will receive written Instructions for Use (IFU) for GP2017 and will self-administer GP2017 injections. Until deemed proficient the patient will return to the site for additional self-administration training during subsequent injection. Total maximal duration of the study for a patient is 53 weeks assuming maximal visit window duration.
Population	The patient population consists of adult male and female patients who are at least 18 years of age at screening with active moderate to severe RA having previously received MTX with or without other DMARDs as therapy for RA. The study is planned to randomize approximately 308 patients. Patients who drop out after they have been randomized will not be replaced.
Inclusion criteria	1. Patients at least 18 years of age at screening who have given written informed consent (ICF) before any study related procedure is performed 2. Patients must have been diagnosed with RA according to the ACR 1987 or ACR/EULAR 2010 modified criteria ≥ 6 months prior to screening 3. Patients must have active disease, defined as DAS28-CRP ≥ 3.2 at the time of screening 4. Patients must have CRP levels above 5mg/l or ESR levels above the upper limits of normal as determined by a central lab for CRP and locally for ESR at screening 5. Patients must have had inadequate clinical response to MTX 10 - 25 mg/week after appropriate dose escalation according to local standards. Patients are required to have been on MTX therapy for ≥ 3 months and on a stable dose for at least 4 weeks prior to and at baseline. Patients, who failed any other DMARD treatment used alone or in combination with MTX, will be allowed to enter into the study after an appropriate wash-out period as defined in Table 5-2 prior to baseline 6. Patients must be on a stable dose of folic acid (≥ 5 mg per week) prior to baseline and must continue on a stable dose during the course of the study 7. Patients taking regular NSAIDs, Cyclooxygenase-2 (COX-2) inhibitors, paracetamol/acetaminophen for treatment of RA symptoms are required to be on stable dose for at least 4 weeks before baseline 8. Patients (male and female) who are willing to remain compliant throughout the study and after study completion with the safety precautions outlined in the local MTX label, particularly in relation to contraception requirements to prevent fathering a child or becoming pregnant. See Section 10.2 for details. 9. Patients must have following parameters at screening visit: • Hemoglobin ≥ 10g/dl • White blood count (WBC) ≥ 3,500/µl, neutrophil count ≥ 1,500/µl

	• Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤ 2.5 x ULN • Serum creatinine level ≤ 176.8 µmoll/L (2.0 mg/dL) • Negative QuantiFERON®-TB Gold test (QFT) • Negative imaging (e.g. chest X-ray, chest Computerized Tomography(CT) scan, Magnetic Resonance Imaging (MRI)) for tuberculosis NOTE: in case imaging was done before screening, it must not be older than 3 months prior to randomization (baseline) .
Exclusion criteria	Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study: 1. Previous treatment with adalimumab, other anti-TNFα therapies or cell depleting agents, e.g. anti-CD20 therapy 2. Prior treatment with investigational therapy, or prior treatment with a biologic for RA within 6 months or 5 half-lives before baseline (whichever is longer) 3. History of hypersensitivity to any recombinant protein drugs or any of the excipients used in GP2017 or US-licensed Humira® 4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception (as defined in Section 6.5.7) during treatment. They should also confirm the intention to use similar methods of contraception for duration of approximately 70 days post the last dose of adalimumab (5 times the terminal half-life of adalimumab). Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential 5. Nursing (lactating) or pregnant women where pregnancy is defined as the state of a woman after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL) 6. History of or ongoing inflammatory or autoimmune diseases other than RA, e.g. mixed connective tissue disease, systemic lupus erythematosus etc. 7. Functional RA status of class IV according to the ACR 1991 revised criteria at screening 8. Subjects taking high potency opioid analgesics, or any intramuscular corticosteroid injection, or any therapy by intra-articular injection required for treatment of acute RA flare within 4 weeks before screening 9. Systemic corticosteroids > 7.5mg/day within 4 weeks prior to baseline

[redacted]

	10. Subjects having chronic arthritis diagnosis before the age of 17 years 11. Systemic manifestation of RA, except for rheumatoid nodules and Sjogren syndrome 12. Subjects having undergone joint surgery within the preceding two months before screening (at joints to be assessed within the study) 13. History or presence of cancer or lymphoproliferative disease other than a successfully and completely treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix and/or removed non-invasive colon polyps, with no evidence of recurrence 14. History of uncontrolled diabetes, unstable ischemic heart disease, congestive heart failure (New York Heart Association III-IV), active peptic ulcer disease, recent stroke (within 3 months) and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the protocol 15. Subject known to have immune deficiency, positive human immunodeficiency virus (HIV) status or immunocompromised for other reasons 16. Previous diagnosis or signs of demyelinating disease 17. History of clinically significant hematologic (e.g. severe anemia, leucopenia, thrombocytopenia), renal or liver disease (e.g. glomerulonephritis, fibrosis, cirrhosis, hepatitis) 18. History of persistent chronic infection; recurrent infection or active infections requiring hospitalization or treatment with systemic anti-infective therapy within 30 days before screening (counted from anti-infective therapy stop date), except for fungal infection of nails or nail beds 19. History of tuberculosis, presence of active tuberculosis, latent tuberculosis as detected by imaging (e.g. chest X-ray, chest Computerized Tomography(CT) scan, Magnetic Resonance Imaging (MRI)) and/ or positive QuantiFERON®-TB Gold test (QFT) NOTE: Positive QTF test and/or positive imaging result excludes a patient from participation in the study 20. History or evidence of opportunistic infections, e.g. histoplasmosis, listeriosis, legionellosis 21. Positive serology Hepatitis B (either HBsAg or anti-HBc) or Hepatitis C (positive HCV-Ab or HCV-RNA) indicative of previous or current infections 22. History or evidence of ongoing significant drug or alcohol abuse in the last year 23. Known depression or other psychiatric condition, which in the investigator's opinion may preclude the participant to adhere to the study protocol requirements 24. History of vaccination with live vaccines within the preceding 3 months prior to baseline or known to require live vaccines during the study period 25. Participants who are scheduled for elective major surgery within the time of study participation

	26. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins) and to perform self-administration 27. Allergic to rubber or latex (the needle cover on the prefilled syringes for both GP2017 and Humira® contains dry natural rubber) 28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study including the inability to understand/ complete any of the required patient questionnaires in the local languages available at the site. See Table 6-1 and Section 6.4 for details. 29. Patients who are legally institutionalized, or patients under judicial protection (France and any other country where stipulated by local regulations) 30. Patients with an immediate family member (i.e., spouse, parent/legal guardian, sibling or a child) being a member of study site staff or being a member of the sponsor's study team.
Investigational and reference therapy	The investigational therapy is GP2017, a proposed biosimilar to Humira® (adalimumab). The comparator is US-licensed Humira®. GP2017 or US-licensed Humira® will be administered as a subcutaneous injection with a dose of 40 mg s.c. every other week from Week 0 to Week 22 and subsequently patients will receive GP2017 from Week 24 to Week 46.
Efficacy assessments	• DAS28-CRP score • DAS28-ESR score • ACR20, ACR50, ACR70 • HAQ-DI (Health-related Quality of life disability index) and FACIT Fatigue scale • CRP and ESR levels
Safety and immunogenicity assessments	• Physical examination and vital signs • Electrocardiogram (ECG) • AEs and serious adverse events • Injection site reactions as assessed by the investigator • Laboratory assessments: hematology, clinical chemistry, • Pregnancy tests, urine analysis • HBV and HCV testing • TB testing (Quantiferon TB-Gold and imaging) • ADA levels • Trough serum levels as part of immunogenicity assessment
Other assessments	• [redacted]
Data analysis	To conclude equivalence between GP2017 and US-licensed Humira® with regards to DAS28-CRP change from baseline at Week 12, both the 90% and 95% CI of the treatment difference must be completely contained within the interval [-0.6, 0.6]. Treatment estimates and 90/95%

[redacted]

	CI shall be estimated using a mixed-model repeated measures (MMRM) model. Time-weighted averaged change from baseline in DAS28-CRP until Week 24 (standardized AUEC approach) will be estimated using the same MMRM used to analyze the primary endpoint.
Key words	Similar efficacy, safety and immunogenicity GP2017 to US-licensed Humira® in patients with rheumatoid arthritis (RA).

[redacted]

1 Introduction

1.1 Background

The development of GP2017 aims for a marketing authorization as a biosimilar product to Humira® according to the guidelines and legal framework of the European Medicines Agency (EMA) and those of the Food & Drug Administration (FDA). Marketing authorization is also planned to be sought in further countries and geographic regions.

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, biological activity, efficacy and safety, based on a comprehensive comparability exercise (Weise et al 2011; Schneider 2013). It is intended to be used at the same dose(s) and dosing regimen(s) to treat the same disease(s) as the reference product. The development and commercialization of biosimilars can help address unmet medical needs by improving access to well-established therapeutic interventions while improving healthcare affordability (McCamish and Woollett 2012).

Humira® (adalimumab; US: AbbVie Inc., EU: AbbVie Ltd.) is a "fully human" monoclonal antibody that binds specifically to Tumor Necrosis Factor alpha (TNF-α), a pleiotropic inflammatory cytokine, and thus blocks its interaction with the p55 and p75 cell-surface TNF receptors.

Humira® received licensure in the US in 2002 and marketing authorization in the EU in 2003. It is indicated for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, psoriatic arthritis (PsA), ankylosing spondylitis, ulcerative colitis, Crohn's disease, pediatric Crohn´s disease, plaque psoriasis, hidradenitis suppurativa and uveitis. Only in EU it is also indicated for enthesitis-related arthritis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis and pediatric plaque psoriasis. For information regarding the efficacy and safety of this product please refer to the Humira Prescribing Information (USPI) or the European Summary of Product Characteristics (EU SmPC).

[redacted]

GP2017 has also been shown to be similar to EU-authorized and US-licensed Humira® at the functional level in vitro: GP2017 and Humira® bind to TNFα with similar kinetics and affinity. The binding affinities to all relevant Fc receptors (FcR), like FcγRI, FcγRII, FcγRIII and the neonatal Fc receptor (FcRn) are similar between GP2017 and Humira®, and the biological functionality in terms of neutralization of TNFα and induction of antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity are also similar.

In summary, comparative physicochemical and biological characterization in terms of target and Fc-receptor binding affinities and in vitro functionality, showed a good degree of similarity

[redacted]

between GP2017 and Humira® (US-licensed and EU-authorized), and non-clinical studies demonstrated similar bioavailability, pharmacokinetics (PK), pharmacodynamics, safety and tolerability for GP2017 and EU-authorized Humira®. A comprehensive background to all previous preclinical studies and development plan with GP2017 is available in the Investigators Brochure (IB -GP2017 Investigators Brochure).

First clinical data in humans on GP2017 have become available. In total, 73 healthy volunteers received a single injection of GP2017. The results of this first trial have not revealed any difference in the safety and immunogenicity profile of GP2017 and US-licensed or EU-authorized Humira®. In this study similar pharmacokinetic, safety and immunogenicity profiles were demonstrated between GP2017 and US-licensed Humira®. GP2017 is currently being investigated in a confirmatory efficacy and safety clinical trial in patients with moderate to severe chronic plaque psoriasis.

GP2017 is developed to be provided as pre-filled syringe as well as a pre-filled pen for subcutaneous (s.c.) administration and in the same strength for adults as the originator product (40 mg/0.8 ml). The development of GP2017 aims to claim all indications currently approved for Humira®.

1.2 Purpose

The purpose of this study is to demonstrate similar efficacy and to compare safety and immunogenicity of GP2017 and US-licensed Humira® in patients with moderate to severe RA with inadequate response to Methotrexate (MTX) with or without other Disease modifying anti-rheumatic drugs (DMARDs). This treatment schema follows the EULAR/ACR recommendations for management of RA with synthetic and biological DMARDs (Smolen et al 2014(a)).

This study is part of the clinical development program of GP2017 and aims to support the worldwide registration of GP2017 as a biosimilar to Humira®.

2 Study Objectives

The objectives of Study Period 1 are to demonstrate similar efficacy and to compare safety and immunogenicity of GP2017 and US-licensed Humira® over 24 weeks of treatment.

The objectives of Study Period 2 are to evaluate long-term safety, immunogenicity and efficacy of GP2017 up to Week 48 and to investigate the effects of a switch from US-licensed Humira® to the proposed biosimilar GP2017 in patients with at least a moderate response, with respect to efficacy, safety and immunogenicity.

2.1 Primary objective

To demonstrate similar efficacy of GP2017 and US-licensed Humira® in patients with moderate to severe active RA with respect to DAS28-CRP score change from baseline to at Week 12.

[redacted]

2.2 Secondary objectives

Key secondary objective

Study period 1: baseline (randomization) - Week 24

- To demonstrate similar efficacy of GP2017 and US-licensed Humira® with respect to time-weighted averaged change from baseline in DAS28-CRP until Week 24.

Other secondary objectives

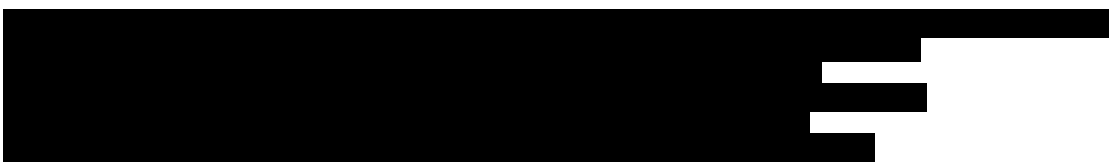
Study period 1: baseline (randomization) - Week 24

- To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving EULAR criterion for remission at Week 4, 12, 24
- To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving EULAR criterion for good response at Week 4, 12, 24
- To compare proportion of GP2017 and US-licensed Humira® treated patients achieved EULAR moderate response at Week 4, 12, 24
- To compare DAS28-CRP and DAS28-ESR changes from baseline in GP2017 and US-licensed Humira® treated patients at Week 2, 4, 24
- To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving remission according to Boolean definition (TJC ≤1, SJC≤1, CRP≤1 mg/dl and patient global assessment (PtGA)≤1) at Week 4, 12, 24
- To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving ACR20/50/70 (based on CRP & ESR) responses at Week 4, 12, 24
- To compare Health Assessment Questionnaire-Disability Index (HAQ-DI) changes from baseline in GP2017 and US-licensed Humira® treated patients at Week 4, 12 and 24
- To compare the proportion of GP2017 and US-licensed Humira® treated patients achieving HAQ-DI score ≤0.5 at Week 4, 12 and 24
- To compare proportion of GP2017 and US-licensed Humira® treated patients with HAQ-DI score improvement >0.3 at Week 4, 12 and 24
- To compare FACIT Fatigue scale changes from baseline in GP2017 and US-licensed Humira® treated patients at Week 4, 12 and 24
- To compare CRP and ESR changes from baseline in GP2017 and US-licensed Humira® treated patients over time
- To compare clinical safety of GP2017 and US-licensed Humira® as assessed by changes in vital signs, clinical laboratory parameters and incidence and severity of Adverse Events (AE)
- To compare incidence and severity of injection site reactions (ISRs) in GP2017 and US-licensed Humira® treated patients

- To compare immunogenicity as determined by measuring the rate of anti-drug antibody (ADA) formation against adalimumab in GP2017 and US-licensed Humira® treated patients

Study period 2: Week 24 - Week 48

- To evaluate clinical safety in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira® as assessed by changes in vital signs, clinical laboratory parameters and incidence and severity of AE
- To evaluate incidence and severity of injection site reactions (ISRs) in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira®
- To evaluate immunogenicity as determined by measuring the incidence of ADA formation against adalimumab in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira®
- To evaluate efficacy in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira® as assessed by DAS28-CRP, DAS28-ESR score changes from Week 24 at Week 48 and ACR20/50/70 responses at Week 48
- To compare Health Assessment Questionnaire-Disability Index (HAQ-DI) changes from Week 24 at Week 48 in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira®
- To compare the proportion of patients treated continuously with GP2017 and patients treated with GP2017 after switch from US-licensed Humira® achieving HAQ-DI score ≤0.5 at Week 48
- To compare Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale changes from Week 24 at Week 48 in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from US-licensed Humira®



[redacted]

3 Investigational plan

3.1 Study design

This study has a parallel-group, randomized, double-blind design and it is planned to randomize approximately 308 patients with moderate to severe active RA at approximately 110 study sites worldwide. A screening period of up to 4 weeks will be used to assess patient´s eligibility. All patients must be on a stable dose of MTX at least 4 weeks prior to randomization and continue throughout the study on this dose.

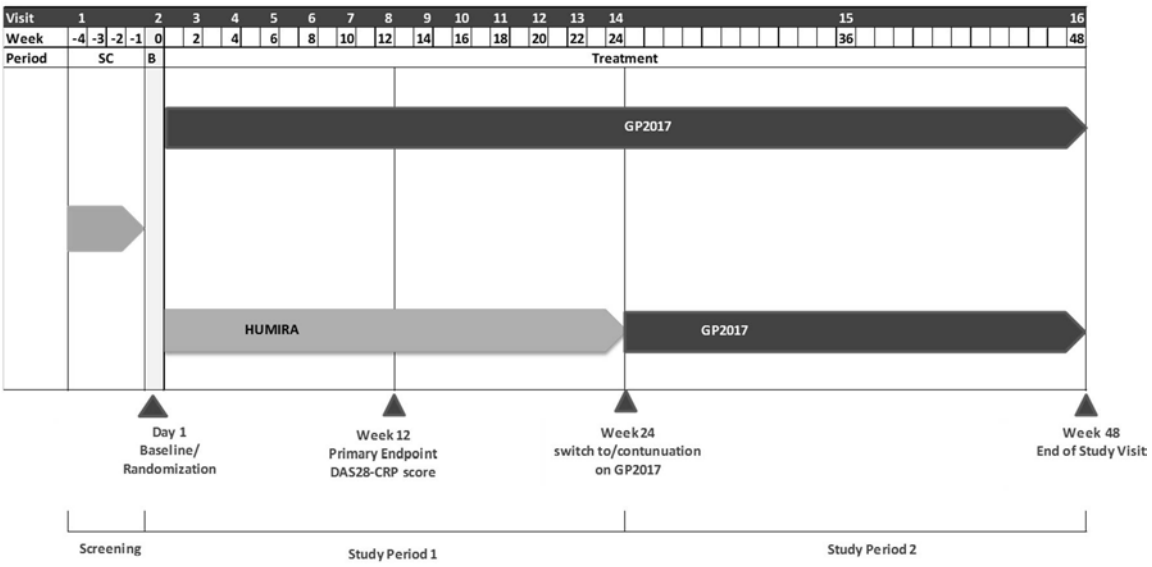
At the baseline visit (Day 1, Visit 2); eligible patients will be randomized using a 1:1 ratio to one of the two treatment arms: GP2017 or US-licensed Humira®. Randomized patients will enter a 24-week treatment phase Study Period 1 and shall be treated with s.c. injection of either GP2017 or US-licensed Humira®. Study drug administration will be performed at the site by designated unblinded personnel. At Week 24 all patients will be evaluated for their DAS28-CRP response. Patients who did not show at least a moderate DAS28-CRP response will have their final assessment at Week 24 and will not continue in the study.

Irrespective of their treatment during Study Period 1, all patients with at least a moderate response at Week 24 by DAS28-CRP score, will be switched to or continue with subcutaneous injection of GP2017 from Week 24 up to Week 46. EoS Visit will be performed at Week 48.

In Study Period 2, all patients will self-administer GP2017 injections. At Week 24 (Visit 14), appropriate training for administration of GP2017 will be provided and first self-administration will be done under the supervision of designated unblinded study personnel at the study site. Afterwards, the patient will receive written Instructions for Use (IFU) of GP2017 and will self-administer GP2017 injections.

[redacted]

Figure 3-1 Study design



3.2 Rationale of study design

GP2017 is developed to claim the same indications as currently approved for Humira®. This double-blind, randomized, comparator drug controlled, parallel-group design is aligned with the key features of similar trials investigating adalimumab with various conventional synthetic therapies for RA.

Current recommendations for first line treatment of RA are the established conventional synthetic DMARDs such as MTX. Anti-TNFα agents are first line biologics used in conventional synthetic DMARD failure patients.

The study design resembles the ARMADA study reported by Weinblatt et al 2003. Patients with active RA despite previous MTX treatment were included in the ARMADA study. Patients were treated with Humira®, while continuing on stable dose of MTX until the end of study. The primary endpoint was ACR20 response rate, which was demonstrated to be significantly higher when adding Humira® to MTX than MTX treatment alone. However the primary endpoint in the current study is different to the ARMADA trial. DAS28-CRP score was not yet fully established and validated at the time of the ARMADA study. Later, several studies investigated the clinical relevance of DAS28-CRP parameter to monitor the disease activity and response to treatment and established its validity (e.g. OPTIMA, CONCERTO, HIT HARD, ReAct studies) (Smolen et al 2014(b), Burmester et al 2015, Detert et al 2013, Burmester et al 2007). Consequently, Committee for Medicinal Products for Human Use (CHMP) draft guideline on clinical investigation of medicinal products other than NSAIDs for treatment of RA (CPMP/EWP/556/95 Rev. 2) recommends DAS28 score as a validated efficacy measure. This score represents a continuous measure of disease activity and is considered to be more sensitive than a categorical endpoint, such as ACR response rate. DAS28 score provides thresholds for disease activity for which a patient could be classified as having achieved remission, or as a

[redacted]

good or moderate responder. DAS28 score is now well established in the clinical practice as a parameter to evaluate disease activity and activity changes while on DMARD treatment and will be used for primary endpoint evaluation in this study. DAS28 score is calculated using either CRP or ESR as a parameter of inflammation. CRP is less affected by confounding factors such as age, gender and measures more short-term inflammation than ESR (Matsui et al 2007). DAS28-CRP score is also considered to be more sensitive and less variable when compared to DAS28-ESR score (Matsui et al 2007, Wells et al 2009). Therefore DAS28-CRP is prioritized above DAS28-ESR in this study for the primary endpoint.

According to EULAR/ACR guidelines (Smolen et al 2014(a)) for the management of RA the improvement should be assessed 3 months after initiation of new treatment, meaning a reduction of disease activity from high to at least moderate should be seen. The maximum efficacy of new treatment (low disease activity or remission) should generally be achieved 6 months after the therapy initiation.

Therefore, in this double-blind study the primary endpoint of change in DAS28-CRP from baseline will be evaluated at Week 12. This will allow for the comparison of similar efficacy and safety of GP2017 and US-licensed Humira®. The overall parallel double-blind treatment with GP2017 or US-licensed Humira® will continue until Week 24. Afterwards, patients with at least moderate DAS28-CRP response will continue on or will be switched to self-administer GP2017. Data on long-term (48 weeks) safety, efficacy and immunogenicity of GP2017 as well as safety, efficacy and immunogenicity of the switch from US-licensed Humira® to GP2017 will be generated.

Approximately 30 – 40% of patients fail to respond to anti-TNFα or lose response over time (Papagoras et al 2010). The ability to predict those RA patients, who will respond to adalimumab treatment, would prevent accumulation of inflammatory joint and bone damage and avoid unnecessary drug exposure in patients, who will be unlikely to respond to adalimumab treatment. Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Atkinson et al 2001).

[redacted]

3.3 Rationale of dose/regimen, duration of treatment

GP2017 is developed as a biosimilar to Humira®. Therefore the dose and route of administration are chosen according to the current label of Humira® for the therapy of active moderate to severe RA with background MTX treatment.

[redacted]

3.4 Rationale for choice of comparator

GP2017 is developed as a biosimilar to Humira®. The results of the phase I PK trial (GP17-101) showed that PK parameters of GP2017 and US-licensed Humira® met bioequivalence criteria. No clinically relevant differences concerning safety and immunogenicity were observed between the products. Consequently, US-licensed Humira® is chosen as the comparator in this clinical study to assess similar efficacy, safety and immunogenicity of GP2017.

3.5 Purpose and timing of interim analyses

No interim analysis is planned. For further details on the analysis refer to Data Anaysis (Section 9).

3.6 Risks and benefits

Comparative physicochemical and biological characterization in terms of target and Fc-receptor binding affinities and in vitro functionality, showed a high degree of similarity between GP2017 and Humira® (US-licensed and EU-authorized) and non-clinical studies demonstrated similar bioavailability, pharmacodynamics potency and tolerability for GP2017 and EU-authorized Humira®. A human pharmacokinetic study confirmed the bioequivalence of GP2017 and US-licensed Humira®. In total, 73 healthy volunteers received a single injection of GP2017. The results of this trial have not revealed any difference in the safety and immunogenicity profile of GP2017 and US-licensed or EU-authorized Humira®. Furthermore, a confirmatory efficacy and safety clinical trial with GP2017 in patients with moderate to severe chronic plaque psoriasis is currently ongoing. Safety data from this trial undergo regular Data Monitoring Committee (DMC) reviews and no concerns have been observed till date. Consequently, the efficacy and safety of GP2017 in patients with active RA is expected to be similar to that of US-licensed Humira®, the favorable risk-benefit ratio of which has been established in a wide range of clinical studies and by a substantial amount of post-marketing experience. All patients in the study will thereby receive active therapy following the approved dosing schedule for US-licensed Humira® with similar expectations for benefits.

Given the expected similarity between GP2017 and US-licensed Humira®, the contraindications, precautions and warnings that are summarized in the originator product's Humira Prescribing Information (USPI) should also apply to GP2017.

One of the potential risks associated with any biopharmaceutical product is the induction of an immunogenic response and therefore assessment of anti-drug antibodies is an essential part of the study procedures.

Compliance with the eligibility criteria as well as regular assessments of disease activity and clinical status ensure that safety is monitored closely and that both, patient and investigator have the opportunity to assess, if the continued participation in the study is to the patient's benefit. If the patient's participation is deemed not to be of benefit, the patient can exit the study at any time.

[redacted]

4 Population

The study population will consist of male and female patients who are at least 18 years of age with active moderate to severe RA who failed previous treatment with MTX with or without other DMARDs. RA diagnosis must be established according to the ACR 1987 or revised ACR/EULAR 2010 criteria (Aletaha et al 2010) with a disease duration of ≥ 6 months, and with disease activity defined as DAS28-CRP score ≥3.2 at screening. Patients must be on a stable MTX dose for at least 4 weeks prior to baseline (randomization) and should continue on this stable dose throughout the study. The selection of the population is based on the EULAR/ACR recommendations (Smolen et al 2014(a)) for management of RA and CHMP draft guideline on clinical investigation of medicinal products other than NSAIDs for treatment of RA.

The study is planned to randomize approximately 308 patients in approximately 110 centers worldwide. Patients that drop out after they have been randomized will not be replaced. A screen failure rate of 30% and a post-randomization dropout rate of 20% are anticipated. If the screen failure rate appears to be higher than expected, more patients will be screened. Screening will stop when the target number of randomized patients is anticipated. All patients in screening at that point of time will remain eligible for randomization.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Patients at least 18 years of age at screening who have given written informed consent (ICF) before any study related procedure is performed
2. Patients must have been diagnosed with RA according to the ACR 1987 or ACR/EULAR 2010 modified criteria ≥ 6 months prior to screening
3. Patients must have active disease, defined as DAS28-CRP ≥ 3.2 at the time of screening
4. Patients must have CRP levels above 5mg/l or ESR levels above the upper limits of normal as determined by a central lab for CRP and locally for ESR at screening
5. Patients must have had inadequate clinical response to MTX 10 - 25 mg/week after appropriate dose escalation according to local standards. Patients are required to have been on MTX therapy for ≥ 3 months and on a stable dose for at least 4 weeks prior to and at baseline. Patients, who failed any other DMARD treatment used alone or in combination with MTX, will be allowed to enter into the study after an appropriate wash-out period as defined in Table 5-2 prior to baseline
6. Patients must be on a stable dose of folic acid (≥ 5 mg per week) prior to baseline and must continue on a stable dose during the course of the study
7. Patients taking regular NSAIDs, COX-2 inhibitors, paracetamol/acetaminophen for treatment of RA symptoms are required to be on stable dose for at least 4 weeks before baseline
8. Patients who are willing to remain compliant throughout the study and after study completion with the safety precautions outlined in the local MTX label, particularly in relation to contraception requirements to prevent fathering a child or becoming pregnant. See Section 10.2 for details.
9. Patients must have following parameters at screening visit:

[redacted]

- Hemoglobin ≥ 10g/dl
- White blood count (WBC) ≥ 3,500/µl, neutrophil count ≥ 1,500/µl
- AST, ALT ≤ 2.5 x ULN
- Serum creatinine level ≤ 176.8 µmol/L (2.0 mg/dL)
- Negative QuantiFERON®-TB Gold test (QFT)
- Negative imaging (e.g. chest X-ray, chest Computerized Tomography(CT) scan, Magnetic Resonance Imaging (MRI)) for tuberculosis

  NOTE: in case imaging was done before screening, it must not be older than 3 months prior to randomization (baseline).

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

1. Previous treatment with adalimumab, other anti-TNFα therapies or cell depleting agents, e.g. anti-CD20 therapy
2. Prior treatment with investigational therapy, or prior treatment with a biologic for RA within 6 months or 5 half-lives before baseline (whichever is longer)
3. History of hypersensitivity to any recombinant protein drugs or any of the excipients used in GP2017 or US-licensed Humira®
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception (as defined in Section 6.5.7) during treatment. They should also confirm the intention to use similar methods of contraception for duration of approximately 70 days post the last dose of adalimumab (5 times the terminal half-life of adalimumab).

   Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential
5. Nursing (lactating) or pregnant women where pregnancy is defined as the state of a woman after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
6. History of or ongoing inflammatory or autoimmune diseases other than RA, e.g. mixed connective tissue disease, systemic lupus erythematosus etc.
7. Functional RA status of class IV according to the ACR 1991 revised criteria at screening
8. Subjects taking high potency opioid analgesics, or any intramuscular corticosteroid injection, or any therapy by intra-articular injection required for treatment of acute RA flare within 4 weeks before screening
9. Systemic corticosteroids > 7.5mg/day within 4 weeks prior to baseline
10. Subjects having chronic arthritis diagnosis before the age of 17 years

[redacted]

11. Systemic manifestation of RA, except for rheumatoid nodules and Sjogren syndrome
12. Subjects having undergone joint surgery within the preceding two months before screening (at joints to be assessed within the study)
13. History or presence of cancer or lymphoproliferative disease other than a successfully and completely treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix and/or removed non-invasive colon polyps, with no evidence of recurrence
14. History of uncontrolled diabetes, unstable ischemic heart disease, congestive heart failure (New York Heart Association III-IV), active peptic ulcer disease, recent stroke (within 3 months) and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the protocol
15. Subject known to have immune deficiency, positive human immunodeficiency virus (HIV) status or immunocompromised for other reasons
16. Previous diagnosis or signs of demyelinating disease
17. History of clinically significant hematologic (e.g. severe anemia, leucopenia, thrombocytopenia), renal or liver disease (e.g. glomerulonephritis, fibrosis, cirrhosis, hepatitis)
18. History of persistent chronic infection; recurrent infection or active infections requiring hospitalization or treatment with systemic anti-infective therapy within 30 days before screening (counted from anti-infective therapy stop date), except for fungal infection of nails or nail beds
19. History of tuberculosis, presence of active tuberculosis, latent tuberculosis as detected by imaging (e.g. chest X-ray, chest Computerized Tomography(CT) scan, Magnetic Resonance Imaging (MRI)) and/ or positive QuantiFERON®-TB Gold test (QFT)

    NOTE: Positive QTF test and/or positive imaging result excludes a patient from participation in the study
20. History or evidence of opportunistic infections, e.g. histoplasmosis, listeriosis, legionellosis
21. Positive serology Hepatitis B (either HBsAg or anti-HBc) or Hepatitis C serology (positive HCV-Ab or HCV RNA) indicative of previous or current infections
22. History or evidence of ongoing significant drug or alcohol abuse in the last year
23. Known depression or other psychiatric condition, which in the investigator's opinion may preclude the participant to adhere to the study protocol requirements
24. History of vaccination with live vaccines within the preceding 3 months prior to baseline or known to require live vaccines during the study period
25. Participants who are scheduled for elective major surgery within the time of study participation
26. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins) and to perform self-administration
27. Allergic to rubber or latex (the needle cover on the prefilled syringes for both GP2017 and Humira® contains dry natural rubber)

28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study including the inability to understand/ complete any of the required patient questionnaires in the local languages available at the site. See Table 6-1 and Section 6.4 for details.
29. Patients who are legally institutionalized, or patients under judicial protection (France and any other country where stipulated by local regulations)
30. Patients with an immediate family member (i.e., spouse, parent/legal guardian, sibling or a child) being a member of study site staff or being a member of the sponsor's study team.

5 Treatment

5.1 Investigational and control drugs

GP2017 and US-licensed Humira® will be available for subcutaneous injection in pre-filled syringes containing 40 mg of active ingredient in 0.8 ml of solution. Both products will be supplied by the Sponsor.

Main characteristics of both treatments are shown below.

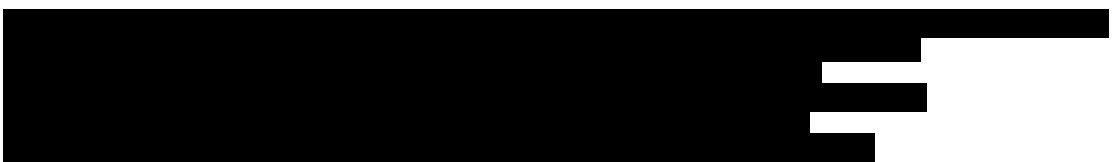
Table 5-1 Characteristics of GP2017 and US-licensed Humira®

Parameter	GP2017	US-licensed Humira®
Active ingredient	Adalimumab	Adalimumab
Formulation / Strength	40mg/0.8mL solution	40mg/0.8mL solution
Presentation	Solution in prefilled syringe	Solution in prefilled syringe
Appearance	Clear, colorless to slightly yellowish	Clear, colorless to slightly yellowish
Excipients	Mannitol	Mannitol
	Citric monohydrate	Citric acid monohydrate
	- (not present)	Sodium citrate
	- (not present)	Sodium dihydrogen phosphate dehydrate
	- (not present)	Disodium phosphate dehydrate
	Adipic acid	- (not present)
	Sodium chloride	Sodium chloride
	Polysorbate 80	Polysorbate 80
	Water for injection	Water for injection
Route of administration	s.c.	s.c.

5.2 Treatment arms

At the baseline visit (Visit 2) patients will be randomized using a 1:1 ratio to treatment group 1 and 2 with approximately 154 patients per treatment arm as described below:

- Group 1: GP2017: s.c. injection of 40 mg/0.8 ml from Day 1 (Visit 2) to Week 46



- Group 2: US-licensed Humira®: s.c. injection of 40 mg/0.8 ml from Day 1 (Visit 2) to Week 22 (Visit 13) and then switched to GP2017 from Week 24 (Visit 14) until Week 46

Study Period 1 (baseline - Week 24)

Patients will receive doses of GP2017 or US-licensed Humira® every other week during their visits at the study site in a blinded fashion. The dosage and frequency will not be changed.

Study Period 2 (Week 24 - Week 48)

At Week 24 (Visit 14) all patients with at least moderate DAS28-CRP response, as defined by EULAR response criteria (see Table 6-3) will continue or will be switched to GP2017. The dosage and frequency will not be changed.

In Study Period 2, all patients will self-administer GP2017 injections. At Week 24 (Visit 14) after appropriate training, patient will self-administer GP2017 under the supervision of qualified study personnel at study site. After being assessed as proficient at self-administration, the patient will receive written IFU for GP2017 and will continue to self-administer GP2017 injections. However, if the unblinded study team member concludes at the Visit 14 (Week 24) that the patient cannot perform self-administration as per study protocol and needs further training the patient should be invited back to the site for further training until deemed proficient.

Patients not achieving at least a moderate response will have their final assessment at Week 24 (as per assessment schedule defined for EoS/ Visit 16) and will not continue in the study.

5.3 Treatment assignment

At Visit 2, all eligible patients will be randomized via the Interactive Response Technology (IRT) system to one of the treatment arms. The investigator or his/her delegate will contact the IRT system and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT system will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. The randomization list will be produced by the IRT system provider (or by an independent provider) using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs.

Randomization will be stratified at baseline (Visit 2) by region (Americas and RoW), body weight and prior therapy. The stratification ensures balanced allocation of patients to treatment groups within the strata. The strata for body weight will be “body weight < 80 kg” or “body weight ≥ 80 kg”. The strata for prior RA therapy will be “prior treatment with MTX only”,

[redacted]

"prior treatment with other conventional synthetic DMARDs", or "prior treatment with biologic DMARDs". Stratification will occur at Visit 2 using the body weight assessed at Visit 2.

5.4 Treatment blinding

The study drug cannot be blinded due to differences in primary packaging. To maintain the double-blind design of Study Period 1 it is necessary to involve unblinded staff at the study site for handling and administration of the study drug. During Study Period 1, unblinded investigational staff will receive, store, dispense, collect used IMP and during Study Period 2 also assist patients with self-administration but must not perform any assessments. Measures (blindfolding, using a screen or asking the patient to look away) shall be taken to blind the patient during IMP administration in Study Period 1. Blinded site staff will not have any contact with IMP.

All data will be collected fully blinded until the end of the trial with regard to treatment allocation during study period 1.

Patients, blinded investigator staff and persons performing the assessments or being responsible for patient´s treatments will remain blinded to the Study Period 1 treatment from the time of randomization until end of study. Randomization data, including any documentation identifying the treatment allocation, are kept strictly confidential until the time of unblinding with the following exceptions: unblinded staff at the site and staff of the sponsor or delegated Contract Research Organization (CRO) responsible for study drug management including unblinded monitors.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.10) and at the time of the database lock for analyses.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. Upon signing the ICF, the patient is assigned a unique patient number by the investigator. The unique patient number is a combination of the corresponding site number followed by a consecutive screening number at that site. Once assigned to a patient, the unique patient number will not be reused.

If the patient fails to be randomized, the IRT system must be notified about the reason for screening failure. Patients can be re-screened once. For a patient to be re-screened, the patient must re-consent, a new patient number has to be assigned and all screening assessments have to be repeated. Screening log should be completed for all patients.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in open-label secondary packaging.

Each medication kit will be labelled with a 2-part tear-off label. A unique medication number is printed on each part of this label, which corresponds to one of the treatments. For each visit,

the IRT system will allocate treatment drug to be dispensed/administered to the patient by providing the respective medication numbers to the unblinded site staff. Immediately before administration/ dispensing the package to the patient, unblinded site staff will detach the tear-off part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.5.3 Study drug supply, handling and storage

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only designated unblinded site staff has access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be administered/dispensed only in accordance with the protocol.

Any technical complaint about the study drug needs to reported to the sponsor within 24 hours of identification of the defect (for details refer to the study drug handling manual). Technical complaints are complaints about an optical, organoleptic, qualitative, quantitative, mechanical or functional defect of a pharmaceutical product or medical device. This may include:

- Any fault of quality and/or effectiveness e.g. particles
- Any fault of the containers and outer packages e.g. surface imperfection, container leakage, broken syringe/plunger, missing contents, device malfunction
- Any fault of the labeling e.g. missing or illegible label
- Any falsification of the medicinal product or device e.g. suspected product mix-up, or tampering.

For reporting of AEs caused by the defect (if applicable) refer to Section 7.

IMP handling manual provided to the site will contain information about storage conditions on site. In addition, site staff will verbally instruct the patient on transport and storage, and provide them with written patient instructions for use during the self-administration period. Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug, but no information about the patient.

The unblinded site staff must ensure an accurate record of the shipment and administration/ dispensing of study drug in the drug accountability form. Monitoring of drug accountability will be performed by the unblinded monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the site will destroy locally or return all unused study drug, packaging, drug labels to the designated depot as per instructions provided by the sponsor. A copy of the completed drug accountability ledger will be returned as instructed by the sponsor or delegated CRO.

5.5.4 Instructions for prescribing and administering the study drug

Both study treatments (GP2017 and US-licensed Humira®) are provided in pre-filled syringes (40mg/0.8mL) for subcutaneous use. For all administrations, one pre-filled syringe of the respective study treatment is to be given at visits as described in Table 6-1.

All study treatment kits will be assigned to the patient using the IRT system and these would be recorded in the IRT system and the electronic Case Report Form (eCRF).

The first study treatment administration will occur following randomization at Day1/Visit 2 (Baseline) and after all scheduled study assessments have been performed, including confirmation of defined in- and exclusion criteria, and only after the scheduled blood samples have been drawn (see Table 6-1).

During Study Period 1, a total of twelve GP2017 or US-licensed Humira® injections will be administered from Randomization on Day 1/Visit 2 to Week 22/Visit 13. Measures shall be taken to blind the patient during IMP administration.

During Study Period 2, a total of twelve GP2017 injections from Week 24/ Visit 14 until Week 46 will be administered. The last study visit will be performed at Week 48.

At study visits, when pre-dose blood samples have to be drawn (see Table 6-1) GP2017 and US-licensed Humira® will be administered to the patient only after the blood samples have been taken.

At each visit, all study assessments, including the completion of HAQ-DI should be completed prior to the administration of study treatment as described in Table 6-1 and Section 6.4.7.

All dates of injections given to the patient during the study must be recorded on the Dosage Administration Record eCRF.

All doses of study treatment will be administered at the study site until Week 24. At this Visit 14 (Week 24) a patient eligible per protocol to continue in the study will be trained how to self-administer the IMP by self-administering one GP2017 injection at the site under the supervision of the unblinded qualified study personnel. If the patient is assessed as proficient at self-administration, the patient will receive IFU and 5 GP2017 pre-filled syringes for self-administration every other week until protocol Visit 15 (Week 36). However, if the unblinded team member concludes at the Visit 14 (Week 24) that the patient cannot perform self-administration as per the study protocol and needs further training the patient should be invited back to the site for further training until deemed proficient. In this case syringes assigned to the patient may continue to be stored at the site. At Visit 15 (Week 36), a patient will undergo all assessments as defined in the protocol, will perform a self-administration under supervision of unblinded site personnel at the site and subsequently will receive 5 pre-filled syringes with GP2017 for self-administration. Last self-administration will be done at Week 46. At Week 48, defined as EoS Visit, a patient will undergo all assessments as defined in the protocol. All unused syringes should be brought back to the site for the purpose of drug accountability.

All injections administered to the patient and all changes during the study must be recorded on the Dosage Administration Record CRF (eCRF).

[redacted]

The investigator or designated staff will instruct the patient on how to self-administer the study drug at the start of Study Period 2, and provide the patient with written instructions for use on study drug administration. The patient will receive a diary booklet to document the self-administration dates. All study administration details must be checked by site personnel and should then be transcribed from the patient diary into the eCRF at each visit in Study Period 2.

The investigator should promote compliance by instructing the patient to administer the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to attend the scheduled study visit or administer the study drug as prescribed.

5.5.5 Permitted study drug interruptions

Study drug interruptions or missed injections are generally not permitted.

It is possible for the investigator to interrupt study treatment for one or more doses when the patient is suffering from an adverse event that in the opinion of the investigator needs to be sufficiently resolved before study drug can be resumed.

These interruptions/missed injections must be recorded on the Dosage Administration Record CRF (eCRF).

5.5.6 Rescue medication

As all other RA treatments are prohibited per protocol, therefore a use of rescue medication for RA would lead to discontinuation of the patient from study treatment and withdrawal from the study. If any rescue medication for RA is used, this must be recorded in the (e)CRF.

5.5.7 Background and Concomitant treatment

5.5.7.1 Background treatment of RA

Methotrexate

Patients have to be treated with MTX for at least 3 months. Dose of MTX (≥ 10 mg/week to ≤ 25 mg/week) must be stable for at least 4 weeks before baseline (randomization). Dose should be maintained stable throughout the study participation with the same route of administration. The maximum tolerated dose is defined by the investigator for each particular patient based on individual circumstances as the maximum dose that was tolerated by the patient.

If MTX is administered by a subcutaneous administration, then the injection site must not coincide with US-licensed Humira® or GP2017 injection sites at the given administration time. Dose adjustments of MTX are not permitted unless patient has developed MTX-related toxicity. MTX discontinuation will lead to patient´s withdrawal from both treatment and the study.

Note: MTX affects gametogenesis during the period of its administration and has been reported to cause fetal death and/or congenital anomalies as described in MTX label. Patients and their partners should have been advised by the investigator to this effect at the initiation of MTX

therapy. Conceiving a child should be avoided for both male and female participants in the study during the period of MTX administration, and an appropriate level of contraception should be maintained in accordance with the local MTX label safety recommendations. A decision about the eventual suspension or change of the contraception should be made only under guidance from the treating physician, and in accordance to the recommendations of the local MTX label.

Folic Acid

Patients should have received folic acid or equivalent from at least 4 weeks prior randomization at a stable dose (≥ 5 mg per week) and during the trial to minimize the likelihood of MTX associated toxicity. Folic acid supplementation should not be taken on the day of MTX intake, but preferably one day after MTX administration.

5.5.7.2 Concomitant treatments

The investigator should instruct the patient to notify the study site about any new treatments (including over-the-counter drugs, supplements, calcium and vitamins) that he/she takes after signing the ICF. Concomitant therapy with NSAIDs/COX-2 inhibitors/ paracetamol/acetaminophen/low strength opioids and oral corticosteroids and all other concomitant medications (including any treatments started during the screening period) and significant non-drug therapies (including physical therapy and blood transfusions) will be recorded on the appropriate eCRF page. While conventional synthetic DMARDs and biologics received before study entry have to be specified without time limitation in details on a separate eCRF page (previous RA related therapies), all other past medications and significant non-drug therapies not related to the study indication have only to be recorded if given 6 months prior to signing ICF.

Patients will be informed that they are not permitted to take any additional medication, including over-the-counter preparations, without first consulting the investigator. The investigator should instruct the patient to notify the study site about any new medications, he/she takes during the course of the study.

Guidelines for the use of specific medications are provided below:

Oral corticosteroids

Oral treatment with systemic corticosteroids will be allowed if the dose was stable for at least 4 weeks before randomization and maintained stable throughout the study participation. A maximum daily dosage of 7.5 mg prednisone (or equivalent) will be allowed. Any change in the dose of oral corticosteroids during the study should be recorded on the corresponding eCRF page.

Non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, acetaminophen/paracetamol, low strength opioids

Patients on regular use of NSAIDs, COX-2 inhibitors, paracetamol/acetaminophen or low strength opioids for the treatment of RA symptoms should be on stable dose for at least 4 weeks

before randomization to allow inclusion and during the treatment period of 48 weeks. Patients taking NSAIDs, COX-2 inhibitors, paracetamol/acetaminophen or low strength opioids on a PRN basis (as required, no fixed dose schedule) within the 4 weeks before randomization can continue to do so in the study. However, they should stop any intake during at least the 24 hours before a study visit.

Any change of the NSAID, COX-2 inhibitor, paracetamol/acetaminophen or low strength opioids treatment during the trial should be recorded on the corresponding Concomitant medication eCRF page.

Note: All precautions related to the allowed concomitant medications should be adhered to in line with the respective label.

5.5.8 Prohibited medications

Use of the following treatments is NOT allowed until study completion:

- Any biologic or conventional synthetic DMARDs and/or immunosuppressant's other than MTX and adalimumab
- Any intra-articular injection (i.e. corticosteroid, hyaluron) within 4 weeks prior to baseline and during the study
- Any intramuscular corticosteroid injection within 4 weeks prior to baseline and during the study
- Administration of live vaccines within 3 months prior to baseline and during the study

Treatment of RA with other TNF-antagonists and/or anti-CD20 agents is not allowed before or during the study. If the use of other prohibited medication specified in Table 5-2 is required, then the patient should **NOT** be randomized into the study. If these treatments are stopped because their use is no longer required before the patient is being considered for screening in this study, wash out periods for these treatments should be applied as indicated in Table 5-2.

Table 5-2 Prohibited Medication

Medication	Washout period before randomization (baseline)
Other biological DMARDs (for example alefacept, briakinumab, efalizumab, ustekinumab, anakinra, abatacept)	**6** months
Other synthetic DMARDs	
Cyclosporine	4 weeks
Cyclophosphamide	6 months
Leflunomide	8 weeks, unless a cholestyramine wash-out has been performed
Hydroxychloroquine, chloroquine, azathioprine	at least 5 half-lives to account for the pharmacokinetic profile of these products
Other systemic non-biologic DMARDs	4 weeks
Any investigational treatment or participation in any interventional trial	6 months or 5 half-lives (whichever is longer)
Live vaccinations‡	3 months
Intra articular corticosteroids	4 weeks

‡ If the patient received a live vaccination during the study, the patient must discontinue study treatment.

No other medications for treatment of RA are allowed to be used routinely during the study. Treatments displayed in Table 5-2 could confound the efficacy and may affect safety, and are **NOT** allowed after randomization (baseline; Visit 2) for any indication. If the use of these treatments is required, then the patient should **NOT** be randomized into the study.

If the medication listed in Table 5-2 was used during the study, it must be discontinued if the subject wishes to continue in the study. If the medication is not discontinued, subject will be withdrawn. If the patient received a live vaccination during the study, the patient must discontinue study treatment.

The investigator should instruct the patient to notify the study site about any new treatments that he/she takes after the start of study. All treatments and significant non-drug therapies administered after the patient entered the study must be listed on the Concomitant medications eCRF or the Procedures and Significant non-drug therapies eCRF.

5.5.9 Study drug discontinuation and premature patient withdrawal

Study drug discontinuation

Patients may voluntarily discontinue study treatment for any reason at any time. The investigator should discontinue study treatment for a given patient if, based on benefit/risk assessment, he/she believes that continuation would not be favorable to the patient's well-being or if a patient did not improve (did not achieve the treatment target) or the disease activity deteriorated compared to previous DAS28-CRP score.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent

[redacted]

- Violation of methods of contraception as described in Section 6.5.7
- Emergence of the following AEs:
  - Any severe or serious AE that is not compatible with the administration of study drug
  - In case of a serious infection or sepsis
  - Severe heart failure (NYHA class III or IV), or other severe, uncontrolled cardiovascular disease
  - Uncontrolled hypersensitivity to study medication
  - Any persisting laboratory abnormalities that in the judgement of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study
  - Hepatitis B virus (HBV) infection. Should a patient develop HBV infection during the study, the study medication should be discontinued and should not be re-started, even after the infection is controlled or resolved. MTX should also be discontinued until the HBV infection is controlled or resolved.
  - Occurrence of any signs or symptoms of tuberculosis or suspicion of tuberculosis (per the investigator's discretion) during study course will lead to discontinuation of study drug and the patient will be withdrawn from the study
  - Malignancy, except for basal cell carcinoma
- Pregnancy
- Use of the prohibited medications as described in Section 5.5.8
- Any other protocol deviation that results in a significant risk to the patient's safety
- Non-responders at Week 24
- Emergency unblinding

The date and primary reason for stopping study treatment should be recorded in the eCRF (e.g. Study Drug Discontinuation Form).

See Section 6 for the required assessments of these patients after study drug discontinuation.

The investigator must also notify the IRT system of the study drug discontinuation.

Premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they:

- State an intention to withdraw
- Fail to return for visits and after several attempts by the site personnel to reach this patients
- Become lost to follow up for any other reason

If such withdrawal occurs for any reason the investigator must determine the primary reason for a patient's premature withdrawal and record this information on the Study completion eCRF page. The investigator must also notify the IRT system of the premature withdrawal.

[redacted]

Patients who prematurely withdraw from the study, should be scheduled for a final assessment visit (as defined for EoS/ Visit 16), as described in Table 6-1. For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, other.

If the investigator decides that a patient is not responding adequately to the study medication, patient should be withdrawn and may receive thereafter any anti-rheumatic treatments at the discretion of the investigator. Patient should undergo a final assessment visit which should be performed prior to treatment with the new anti-rheumatic therapy, and will then be withdrawn from the study. Lack of study drug efficacy should be stated on the study completion eCRF page for these patients.

Patients who are prematurely withdrawn from the study will not be replaced by newly enrolled patients.

5.5.10 Emergency unblinding of treatment assignment

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the monitor for the site and the Study lead that the code has been broken.

It is the investigator’s responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator must provide oral and written information to the patient how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that unblinding can be performed at any time. The investigator will provide protocol number, study treatment name if available, patient number, and instructions for contacting the local Sponsor representative (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

Study treatment **must** be discontinued after emergency unblinding by the site. Study drug must also be discontinued for any subject whose treatment code has been broken inadvertely or for any non-emergency reason by the site. Any unblinding by the site, be it inadvertely or for non-emergency reasons, must be reported to the monitor. Patients who are prematurely unblinded will be discontinued from study treatment and requested to return 2 weeks after the last study drug intake to perform the EoS (Visit 16).

5.5.11 Study completion and post-study treatment

A patient will be considered to have completed the study when all scheduled study assessments and procedures up to and including Visit 16 (Week 48) have been performed.

The trial will be completed when the last patient completed the last visit as per protocol.

Information on when the last administration of study drug took place, the subject's completion or discontinuation from the study and the reason for discontinuation of the study will be recorded on the Study Completion eCRF page. Study Completion evaluations must also be performed when a subject prematurely withdraws from the study for whatever reason.

The investigator or site staff must enter study completion (at Week 48) and/or discontinuation of a patient as soon as possible in the IRT system.

It is the investigator's responsibility to provide follow-up medical care for all patients who are prematurely withdrawn from the study. This care may include: initiating another treatment outside of the study as deemed appropriate by the investigator. This treatment may be any non-biologic DMARD. In case of a biologic treatment, a waiting period of 3-4 weeks before initiating the treatment is recommended.

5.5.12 Early study termination

The study can be terminated at any time for any reason by the sponsor. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) of the early termination of the trial. The Sponsor will inform the relevant Competent Authorities accordingly.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" the visits when they are performed.

Patients should be seen for all visits on the designated day within the allowed "visit window" specified below. All visits should be planned from the baseline visit date (Day 1/Visit 2) as a reference point and not to the previous visit.

A "visit window" will be allowed during the study as follows:

- Visit 2: latest 4 weeks after the screening visit
- Visit 3 to Visit 14: ± 2 days
- Visit 15 to Visit 16: ± 3 days

Visit window relates to the originally planned visit schedule. The patient should be instructed to contact the investigator, if he/she is unable for any reason to attend a study visit as scheduled.

During the treatment periods, patients may be seen between scheduled protocol visits, e.g. if they experience deterioration of RA, or AEs that in the opinion of the investigator need

intervention or laboratory testing. During these unscheduled visits, study treatment will NOT be administered and other study procedures as defined per protocol will NOT be performed.

During study period 2 between visits 14 and 16 additional visits to the site are allowed if the patient requires further training to become proficient at self-administration of study treatment. Except for treatment self-administration at the site, no other study procedures would be performed and no additional data will be collected.

Patients who discontinue study drug before completing the study, and those who prematurely withdraw from the study treatment for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the Visit 16 will be performed. Patients who prematurely stop study medication for any reason may refuse to attend a final visit and assessments, in this case the investigator should document the attempt to explain to the patient that a final visit and assessments would be advisable for safety reasons.

If patients refuse to return for these assessments or are unable to do so, every effort should be made to contact them, or their family or primary care physician/ family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, other. At this contact, the safety (e.g. potential occurrence of AEs or SAEs) and the efficacy (overall disease status self-assessed by the patient) outcome as well as the primary reason for a patient's premature withdrawal should be determined. Documentation of attempts to contact the patient should be recorded in the source documentation.

Patients who prematurely withdraw consent for the study will stop all study procedures and will continue treatment according to local standards of care. No further information about the patient will be collected.

Patients should report any SAE which occurs during the period of 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later).

The investigator should ensure regular contact with the patient (as per routine medical practice) for at least 30 days after the study drug discontinuation and capturing/reporting all SAEs (regardless of causality) which may occur in this period.

In addition, the investigator should report SAEs that occur at any time after study completion/discontinuation in case the investigator suspects a causal relationship to the study drug.

SAEs reporting needs to be performed as described in Section 7.2.2 of this protocol.

[redacted]

Table 6-1 Assessment schedule

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16 EoS**
Study Period	**S**	**B**	**SP1**												**SP2**	
Day	**≤ -28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**253**	**337**
Week	**≤ 4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**36**	**48**
Visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**± 3**
Obtain informed consent	x															
Demography	x															
Tuberculosis screening	x															
HIV, Hepatitis B + C serology[1)]	x															
Serum pregnancy test	x															
Urine pregnancy test		x		x		x		x		x		x		x	x	x
History of RA	x															
Medical history	x	x														
Randomization		x														
IMP administration		x	x	x	x	x	x	x	x	x	x	x	x	x Self-administration by patient until Week 46 (Treatment diary and Insructions for use to be provided)		
Physical Exam[2)]	x[2]	x[2]	x	x	x	x	x	x	x	x	x	x	x	x[2]	x	x[2]
Height	x															
Weight	x	x														x
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x													x		x

[redacted]

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16 EoS**
Study Period	**S**	**B**	**SP1**												**SP2**	
Day	**≤ -28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**253**	**337**
Week	**≤ 4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**36**	**48**
Visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**± 3**
Tender joint count	x	x	x	x				x						x		x
Swollen joint count	x	x	x	x				x						x		x
HAQ-DI, FACIT		x		x				x						x		x
Physician's global assessment (PhGA) of disease activity (VAS)	x	x	x	x				x						x		x
Patient's global assessment (PtGA) of disease activity (VAS)	x	x	x	x				x						x		x
Patient's global assessment of pain (VAS)	x	x	x	x				x						x		x
CRP + ESR	x	x	x	x				x					x[3]	x	x	x
Safety lab test [4)]	x	x		x				x						x	x	x
[redacted]																
Special proteins[6)]	x							x						x		x
ADA sampling[7)]		x	x	x				x						x	x	x
Adalimumab trough level sampling[7)]		x	x	x				x						x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Injection site reactions		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	X[8]	X[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study Completion form																x

[redacted]

S=Screening, B=Baseline, SP1 = Study period 1, SP2 = Study period 2, EoS = End of Study

[1)] HIV-ab, HBsAg, Anti-HBc, and HCV RNA-PCR, HCV-Ab

[2)] Complete physical examination

[3)] Only CRP

[4)] Hematology: Hb, Hct, platelets, RBC and WBC with differential. Chemistry: Serum creatinine, total bilirubin, AST, ALT, GGT, alkaline phosphatase, sodium, potassium, calcium, total protein, albumin, total cholesterol, IgA, IgG, HDL, LDL and uric acid, Coagulation: Activated Partial Thromboplastic Time (aPTT), INR and Urinalysis by strip test®

[redacted]

[6)] Rheumatoid factor, anti-CCP

[7)]Concurrent samples will be drawn before IMP administration for ADA sampling and to determine adalimumab concentration to support evaluation of immunogenicity. Separate tubes for ADA and for adalimumab trough level have to be used

[8)] Only SAEs to be reported after informed consent

Assessment specifications:

Visit assessments should be performed following the guidelines below:

1. All visits should be planned from the baseline visit date (Day 1/Visit 2) as a reference point and not to the previous visit.
2. Patient to complete FACIT and HAQ-DI© prior to any investigator assessments.
3. Investigator to enter component parts (TJC, SJC and PGA) of DAS28-CRP score into the eCRF.
4. Perform all remaining visit procedures as per visit schedule, i.e. all laboratory sample collections including ADA (to be drawn prior to study treatment administration), physical examination, vital signs, and assessment of ISR (at site of previous injection).
5. Use DAS28-CRP derived by clinical database at screening to assess inclusion criteria and for contacting IRT at Visit 2 (Day 1, baseline (randomization))
6. Enter DAS28-CRP component assessments performed at Visit 14 (Week 24) into the eCRF, then the clinical database shall derive the DAS28-CRP score. However due to several days needed to obtain the CRP results from central laboratory, the decision to continue patients in the study after Week 24 will be made based on Week 24 DAS28-CRP parameters and the CRP value from Week 22 (Visit 13).

After all measurements are completed unblinded study site personnel should access IRT and dispense study treatment.

[redacted]

6.1 Information to be collected on screening failures

Patients who sign the informed consent form and discontinue prior to randomization at Visit 2 (Day 1) are considered screening failures.

If a patient discontinues before randomization and entering the double-blind treatment period, IRT must be notified within 5 days and the reason for not being randomized entered on the Screening Phase Disposition eCRF. The Screening visit date, the Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion Criteria eCRF, and patient re-screening eCRF (if appropriate) at a minimum must be completed.

The AE eCRF and a SAE form should be completed for any SAEs that occurred during the screening period. The Withdrawal of consent eCRF should be completed if consent was withdrawn during the screening period. The Death eCRF should be completed in the case of a death during the screening period.

Patients can be re-screened once. For a patient to be re-screened, the patient must re-consent, a new patient number has to be assigned and all screening assessments have to be repeated.

6.2 Patient demographics/ other baseline characteristics

All assessments to determine the baseline characteristics at Visit 2 shall be performed prior to first study treatment administration.

6.2.1 Patient demographics

The following patient demographic and baseline characteristic data are to be collected for all patients: year of birth, age at screening, sex, race and child-bearing potential (for females only).

6.2.2 Baseline characteristics

6.2.2.1 Rheumatoid arthritis medical history

The information to be collected and entered in the eCRF includes:

- Date of first diagnosis of RA (by a physician)
- Previous treatments of RA (including previous use of biologic therapies) and the reason for their discontinuation.

6.2.2.2 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions, excluding RA, will be recorded in the eCRF.

Relevant medical history/current medical condition data includes data up to 6 months prior to signature of ICF. Whenever possible, diagnoses and not symptoms should be recorded.

Clinical relevant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions eCRF. Significant clinically relevant

findings made after the start of study drug which meet the definition of an Adverse Event must be recorded in the AE eCRF.

6.2.2.3 Determination of tuberculosis status

Determination of TB status is required before administration of study treatment. TB status must be determined by medical history, signs, symptoms, imaging and TB testing (QuantiFERON®-TB Gold assay). Any significant findings should be recorded in the eCRF, as necessary.

6.2.2.3.1 Imaging

A chest X-ray (posteroanterior (PA) or PA and lateral according to the local practice), CT scan or MRI obtained within 3 months prior to baseline should be used to determine eligibility. If patients do not have a chest X-ray (PA or PA and lateral according to the local practice), CT scan, or MRI available at screening (Visit 1) a chest X-ray (PA or PA and lateral according to the local practice) must be done prior to randomization. This should only be performed after the patient fulfils all other inclusion/exclusion criteria, in order to minimize unnecessary exposure to X-ray radiation.

If the chest X-ray (PA or PA and lateral according to the local practice), CT scan, or MRI evaluated by a qualified physician shows evidence of ongoing infectious disease or inactive (latent) TB, the patient will not be eligible to enter the study.

If presence of latent TB is established then TB treatment must be initiated and maintained according to local country guidelines

If the X-ray (PA or PA and lateral according to the local practice), CT scan, or MRI shows evidence of any malignant process the patient will not be eligible to enter the study.

6.2.2.3.2 QuantiFERON®-TB Gold In-Tube assay

A QuantiFERON®-TB Gold In-Tube assay (QFT) will be performed to assess the TB status at screening (Visit 1) for all patients. This test will only be used to determine the patient's eligibility for the trial.

This blood-based assay is specific for *Mycobacterium tuberculosis* and is not influenced by previous Bacillus Calmette-Guérin vaccination or exposure to other Mycobacteria species. This test, in contrast to the Purified Protein Derivative (PPD) Skin Test, is also insensitive to a booster effect since the patient is not exposed to the bacterial antigen. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample. Further information is available in the referenced article (Manuel and Kumar 2008).

The QFT test will be supplied and analyzed by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

6.2.3 Other baseline characteristics

Other baseline characteristic data to be collected on all patients include (see also Table 6-1):

[redacted]

ECG, vital signs, hematology, clinical chemistry, CRP, ESR urinalysis; for women of child-bearing potential a serum pregnancy at screening and urine pregnancy test at baseline; HIV test and Hepatitis B or C status (serologic or virologic markers for active or latent Hepatitis B and Hepatitis C infections), immunogenicity to adalimumab (ADA), trough serum level, DAS28-CRP score, FACIT and HAQ-DI©, Tender joint count, Swollen joint count, Physician's global assessment (PhGA) of disease activity (VAS), Patient's global assessment (PhGA) of disease activity (VAS) and Patient's global assessment of pain (VAS).

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page.

Compliance during Study Period 1 is not applicable since study treatment will be administered by the unblinded study personnel.

Usage of IMP will also be assessed by an unblinded field monitor using medication pack numbers, Drug Label Form information, information collected by IRT and provided by the unblinded study personnel. Compliance with IMP administration will first be assessed by the appropriate site personnel.

During Study Period 2 patients will record their self-administered doses in a patient diary.

Compliance during Study Period 2 will be assessed after interviewing the patient and checking the entries in the diary. The appropriate site personnel will transfer these entries to the eCRF. The patient must bring back the unused syringes to support study drug accountability.

6.4 Efficacy

The investigator or qualified designee will perform assessments necessary for DAS28 score and ACR rate calculation at defined study visits. Whenever possible, the same evaluator should perform these assessment at all visits. Assessments must be conducted prior to the next scheduled dosing of study drug.

6.4.1 Assessment of Disease Activity Score (DAS28)

The disease activity score (DAS) is a combined index to measure the disease activity in patients with RA. In this study DAS28-CRP and DAS28-ESR will be measured. The DAS28-CRP will be used for primary and key secondary endpoint analysis, whereas DAS28-ESR will only be used for secondary endpoint analysis. The efficacy assessments will be done at screening, baseline, Week 2, Week 4, Week 12, Week 24 and Week 48 (Visits 1, 2, 3, 4, 8, 14 and 16).

In order to calculate the DAS28-CRP or DAS28-ESR, information about the following disease variables is needed:

The number of swollen joints and tender joints should be assessed using 28-joint count (TJC28 and SJC28), see Figure 6-1.

The patient's general health (GH) or global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm (both are useable for this purpose) must be obtained (Prevoo et al 1995).

[redacted]

CRP should be measured in mg/L

and

ESR should be measured in mm/hour.

Using this data, the DAS28 can be calculated using the following formula:

DAS28-CRP = 0.56 * sqrt(TJC28) + 0.28* sqrt(SJC28) + 0.36 * ln(CRP+1) + 0.014 * GH + 0.96

DAS28-ESR = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.70 * ln(ESR) + 0.014 * GH

Swollen joints, tender joints and patient's general health assessment will be entered into the eCRF and CRP/ESR will be used to determine DAS28-CRP and DAS28-ESR scores.

In addition CRP values provided by the central laboratory at both screening and Week 22 will be entered into the eCRF and be used to calculate DAS28-CRP scores for the purpose of assessing eligibility at randomization and Week 24 only (see Table 6-1).

The DAS28 provides a number on a scale from 0 to 10 indicating the current activity of the RA of the patient. Disease activity definition is described in Table 6-2.

Table 6-2 Definition of disease activity according to DAS28

Index	Disease activity state	Cut-off value
DAS28	High disease activity	> 5.1
	Moderate disease activity	≥3.2 to ≤ 5.1
	Low disease activity	> 2.6 to < 3.2
	Remission	≤ 2.6

The decision to randomize a patient will be made based on DAS28-CRP score at screening.

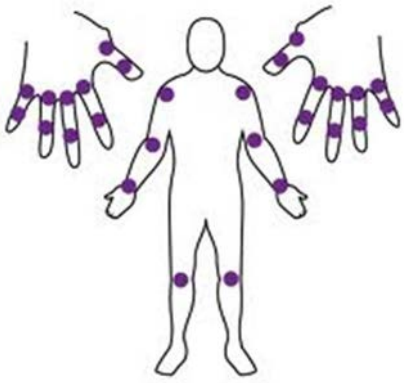
Patients achieving at least moderate DAS28-CRP response at Week 24 (calculated using CRP value from Week 22 and DAS28 parameters from Week 24) will either continue or be switched to GP2017 at Week 24 and will continue in the study until Week 48. Moderate DAS28-CRP response at Week 24 is assessed as defined in Table 6-3.

Patients not achieving at least a moderate DAS28-CRP response at Week 24 will have their final study assessments (EoS/ Visit 16) at this time point and will discontinue the study.

[redacted]

Due to several days needed to obtain the CRP results from central laboratory, the decision to continue patients in the study after Week 24 will be made based on Week 24 DAS28 parameters and the CRP value from Week 22. However for the statistical analysis the DAS28-CRP score at Week 24 will be calculated based on the Week 24 CRP value provided by the central laboratory.

Figure 6-1 28-Joint Count



6.4.2 EULAR Response Criteria

The EULAR response criteria based on the DAS are defined as follows (van Gestel et al 1996; Fransen & van Riel 2009):

Table 6-3 EULAR Response Criteria

	Improvement in DAS28 from baseline		
Present DAS28	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 3.2	good response	moderate response	no response
> 3.2 to ≤ 5.1	moderate response	moderate response	no response
> 5.1 (high)	moderate response	no response	no response

6.4.3 American College of Rheumatology (ACR) Response Criteria

This efficacy variable is the clinical response to treatment according to ACR improvement criteria (Felson et al 1995), (see Appendix 2).

A patient will be considered a responder according to ACR20 criteria if she/he fulfills all following three criteria:

- at least 20% improvement from baseline in tender joint count, using the 68-joint count
- at least 20% improvement from baseline in swollen joint count, using the 66-joint count
- and at least 20% improvement from baseline in at least 3 of the following 5 measures:
  a. Patient's assessment of RA pain (VAS 100 mm)
  b. Patient's global assessment of disease activity (VAS 100 mm)

[redacted]

c. Physician's global assessment of disease activity (VAS 100 mm)
d. Patient self-assessed disability (Health Assessment Questionnaire [HAQ] Disability Index)
e. CRP or ESR

ACR50 and ACR70 are defined as ACR20 replacing '20% improvement' by '50% improvement' and '70% improvement' respectively.

The ACR criteria will be calculated for screening, baseline, Week 4, Week 12, Week 24 and Week 48 (Visits 1, 2, 4, 8, 14 and 16).

6.4.4 Patient assessment of RA pain

The patient's assessment of pain will be performed at screening, baseline, Week 2, Week 4, Week 12, Week 24 and Week 48 (Visits 1, 2, 3, 4, 8, 14 and 16) using 100 mm visual analog scale (VAS) ranging from 'no pain' to 'unbearable pain' after the question "*please indicate with a vertical mark (|) through the horizontal line the most pain you had from your rheumatoid arthritis over the last 24 hours".* At the investigator's site the distance in mm from the left edge of the scale will be measured and the value will be entered on the eCRF.

6.4.5 Patient global assessment of disease (PtGA)

The patient's global assessment of disease activity will be performed at screening, baseline, Week 2, Week 4, Week 12, Week 24 and Week 48 (Visits 1, 2, 3, 4, 8, 14 and 16) using 100 mm VAS ranging from "very good" to "very poor", after the question "*Considering all the ways rheumatoid arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing*". At the investigator's site the distance in mm from the left edge of the scale will be measured and the value will be entered on the eCRF. To enhance objectivity, the treating physician performing the PhGA must not be aware of the specific patient's global assessment of disease activity.

6.4.6 Physician global assessment of disease activity (PhGA)

The physician's global assessment of disease activity will be performed at screening, baseline, Week 2, Week 4, Week 12, Week 24 and Week 48 (Visits 1, 2, 3, 4, 8, 14 and 16) using 100 mm VAS ranging from "very good" to "very poor", after the question "*Considering all the ways rheumatoid arthritis affects your patient, how would you rate his or her condition today?"*

To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his/her own assessment on that patient. The investigator will make this evaluation on a paper VAS, then measure the distance in mm from the left edge of the scale to the vertical mark, and report the value on the eCRF.

6.4.7 Health-related Quality of Life Disability Index

The patient health assessment questionnaire disability index (HAQ-DI©), will be used to assess physical ability and functional status of patients as well as quality of life (Fries et al 1980; Bruce and Fries 2003). HAQ-DI© will be available to centers in validated versions of all local languages. Patients will not be eligible for the study if they are not fluent with the HAQ-DI©

languages available at the site. Patients will complete the questionnaire at baseline, Week 4, Week 12, Week 24 and Week 48 (Visits 2, 4, 8, 14 and 16).

Scoring of the HAQ©

The HAQ© will be scored in accordance with the recommendation from the developers outlined in the "HAQ PACK" from Stanford University, California.

The following coding is to be used for the 8 categories of the disability outcome dimension. Without ANY difficulty = 0; with SOME difficulty = 1; with MUCH difficulty = 2; UNABLE to do = 3.

Within each of the 8 categories only the item indicating the most severe impairment contributes to the category score. If the subject requires the use of aids, devices or help from another to accomplish any of the activities in an associated category, then the score for that category will be assigned the value 2, unless the score is already 3 (i.e. scores of 0 or 1 are increased to 2). Associated categories are defined in the "HAQ PACK". From the scores for each category a Standard Disability Index (SDI) is computed by summing the computed scores for each category and dividing by the number of categories answered. The SDI is not computed if the subject does not have scores for at least 6 categories. This SDI is the HAQ© score, which will be used in the statistical analyses of this instrument. The range for this score is (0, 3).

HAQ© Data Collection

The HAQ© is to be completed by the subjects in their local languages. The questionnaires should be completed by the subjects in a quiet area free from disturbance, and before any visit assessments. Subjects should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the doctor or nurse should read the questions and record the subject's responses without influencing their answers. The information provided is strictly confidential and will be treated as such.

6.4.8 Functional Assessment of Chronic Illness Therapy - Fatigue Scale (FACIT- Fatigue©)

The Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue©) is a 13- item questionnaire (Cella et al 1993; Yellen et al 1997) that assesses self-reported fatigue and its impact upon daily activities and function. The purpose of FACIT-Fatigue© in this study is to assess the impact of fatigue on patients. The score is calculated as described in the appendix section (Appendix 3). This instrument/questionnaire will be completed by the patient at baseline, Week 4, Week 12, Week 24 and Week 48 (Visits 2, 4, 8, 14 and 16).

[redacted]

6.4.9 CRP

Blood for this assessment will be obtained at screening, baseline, Week 2, Week 4, Week 12, Week 22, Week 24, Week 36 and Week 48 (Visits 1, 2, 3, 4, 8, 13, 14, 15 and 16) in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. CRP will be analyzed centrally.

6.4.10 ESR

Blood for this assessment will be obtained at screening, baseline, Week 2, Week 4, Week 12, Week 24, Week 36 and Week 48 (Visits 1, 2, 3, 4, 8, 14, 15 and 16) in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. ESR will be analyzed locally and ESR results will be entered in the eCRF.

6.4.11 Appropriateness of efficacy measurements

The efficacy variables selected are standard for this indication/patient population.

6.5 Safety

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed in addition to the above at screening, baseline, Week 24 and Week 48 (Visits 1, 2, 14 and 16).

A short physical exam will include the examination of general appearance. A short physical exam will be done at all visits starting from Visit 3 except where a complete physical examination is required (see above).

Information for all physical examinations must be included in the source documentation at the study site. Clinical relevant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions eCRF. Clinically relevant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event eCRF.

6.5.2 Vital signs

Vital signs include blood pressure (BP) and pulse measurements and will be done at each study visit starting from Visit 1. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

[redacted]

6.5.3 Height and weight

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at screening, baseline and Week 48 (Visits 1, 2 and 16). The same scale should be used throughout the study.

Height (in cm) will be recorded without shoes only at screening (Visit 1).

6.5.4 Laboratory evaluations

Blood samples for safety laboratory evaluation will be taken at screening, baseline, Week 4, Week 12, Week 24, Week 36 and Week 48 (Visits 1, 2, 4, 8, 14, 15, and 16). A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Following laboratory parameters will be performed locally: urine pregnancy tests, urinalysis strip test and ESR. For more details refer to Table 6-1.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

6.5.4.2 Clinical chemistry

Serum creatinine, total bilirubin, AST, ALT, GGT, alkaline phosphatase (AP), sodium, potassium, calcium, total protein, albumin, total cholesterol, IgG, IgA, HDL, LDL and uric acid will be measured.

6.5.4.3 Coagulation

aPTT and INR will be measured.

6.5.4.4 HBV testing

Blood will be obtained to measure HBsAg, anti-HBc at the screening visit. See Section 6.2.3 for more details.

6.5.4.5 HCV testing

Blood will be obtained to measure HCV-RNA-PCR and HCV-Ab at the screening visit. See Section 6.2.3 for more details.

6.5.4.6 HIV testing

Blood will be obtained to measure HIV-Ab at the screening visit. See Section 6.2.3 for more details.

6.5.4.7 QuantiFERON®-TB Gold In-Tube assay

A QuantiFERON®-TB Gold In-Tube assay (QFT) will be performed to assess the TB status at screening (Visit 1) for all patients. This test will only be used to determine the patient's eligibility for the trial. Further information is available in Section 6.2.2.3.2 and in the referenced article (Manuel and Kumar 2008).

6.5.4.8 Special Proteins

Special proteins will be measured to evaluate the baseline immunological status of RA as well as the changes during treatment with adalimumab.

6.5.4.8.1 Rheumatoid factor

Rheumatoid factor assessment as a measure of changes in RA serological status will be performed at screening, Week 12, Week 24 and Week 48 (Visits 1, 8, 14 and 16). All parameters will be analyzed centrally.

6.5.4.8.2 Anti-CCP Antibodies

Anti-citrullinated protein (Anti-CCP) antibody assessment will be performed as a measure of changes in RA serological status at screening, Week 12, Week 24 and Week 48 (Visits 1, 8, 14 and 16). Anti-CCP Antibodies will be analyzed centrally.

6.5.4.9 Urinalysis

Striptest® analysis including leukocytes, nitrites, urobilinogen, proteins, pH, hemoglobin, specific gravity, ketones, bilirubin, glucose will be performed screening, baseline, Week 4, Week 12, Week 24, Week 36 and Week 48 (Visits 1, 2, 4, 8, 14, 15, and 16).

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at screening, Week 24 and Week 48 (Visits 1, 14 and 16/ EoS). Interpretation of the tracing is documented on the ECG eCRF. Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities detected at screening (Visit 1) should also be recorded on the relevant Medical history/Current medical conditions eCRF page. Clinically significant abnormalities newly detected during the study should be recorded on the AE eCRF page. Clinically significant findings must be discussed with the Medical Monitor prior to enrolling the patient in the study.

6.5.6 Immunogenicity and adalimumab trough levels

As with all therapeutic proteins, there is a potential for immunogenicity and the emergence of antibodies to human recombinant proteins is well documented. Antibodies directed against a therapeutic agent may have neutralizing activity and interfere with the efficacy of the treatment. For safety reasons, screening for anti-adalimumab antibodies (ADA) has been included in this study.

Immunogenicity will be assessed by measuring anti-adalimumab antibody levels in serum of all subjects. During the study, immunogenicity will be assessed at:

- baseline, Week 2, Week 4, Week 12, Week 24, Week 36 and Week 48 (at Visits 2, 3, 4, 8, 14, 15, and 16)

For details on blood collection time points and sample information please refer to Table 6-4.

To support the evaluation of immunogenicity, adalimumab trough levels will be determined at every time-point when blood samples for ADA assessment are taken. Thereby, the drug tolerance level of the ADA method (which will be determined during method validation) can be compared with the determined drug levels. For details on blood collection time points and sample information please refer to Table 6-5.

6.5.6.1 Collection and handling of blood samples for immunogenicity and serum drug trough levels

Blood samples will be obtained pre-dose at baseline, Week 2, Week 4, Week 12, Week 24, Week 36 and Week 48 (at Visits 2, 3, 4, 8, 14, 15, and 16) for detection of antibody formation against adalimumab and analysis of serum drug trough levels. All samples will be taken by direct venipuncture into serum separator tubes.

Serum collection for ADA assessment

Four aliquots of serum samples per scheduled time-point for ADA assessment will be generated. The detailed sample handling and serum preparation will be described in the laboratory manual. Aliquot one and two and aliquot three on request will be used for bioanalysis. The fourth aliquot will be used as back-up sample. Dates and times of blood collection will be recorded in the Immunogenicity Blood Collection eCRF page. For details on immunogenicity blood sample collection, labeling, handling and shipment, please refer to the Laboratory Manual.

Table 6-4 Blood sampling for immunogenicity assessment

Trial Visit #	Relative time to IMP start	ADA Sample #	Volume [ml]
Visit 2	Baseline	201	8.0
Visit 3	Study Week 2	202	8.0
Visit 4	Study Week 4	203	8.0
Visit 8	Study Week 12	204	8.0
Visit 14	Study Week 24	205	8.0
Visit 15	Study Week 36	206	8.0
Visit 16	Study Week 48	207	8.0
Total number of samples	7	Total blood volume	56 ml

Serum collection for serum drug trough levels determination

Three aliquots of serum samples per scheduled time point for the determination of serum drug concentrations will be generated. The detailed sample handling and serum preparation will be described in the laboratory manual. Aliquot one and aliquot two on request will be used for bioanalysis. The third aliquot will be used as back-up sample. The actual time of blood

collection will be recorded in the drug concentration blood collection eCRF page. For details on serum drug concentration blood sample collection, labeling, handling and shipment, please refer to the Laboratory Manual.

Table 6-5 Blood sampling for serum drug trough levels determination

Trial Visit #	Relative time to IMP start	Serum drug trough level Sample #	Volume [ml]
Visit 2	Baseline	101	5.0
Visit 3	Study Week 2	102	5.0
Visit 4	Study Week 4	103	5.0
Visit 8	Study Week 12	104	5.0
Visit 14	Study Week 24	105	5.0
Visit 15	Study Week 36	106	5.0
Visit 16	Study Week 48	107	5.0
Total number of samples	7	Total blood volume	35 ml

Storage and archiving of serum drug concentration and ADA samples

All serum drug concentration samples and ADA samples will be stored at ≤ -70°C. For serum drug concentration samples, the following archiving applies:

- Aliquot 1: will be discarded 6 months after availability of the final clinical study report.
- Aliquot 2: storage at the central lab should not exceed the duration of 6 months after availability of the final clinical study report; after this time the Sponsor has to decide if these aliquots will be discarded.
- Aliquot 3: will be stored by the Sponsor at approximately ≤-70°C until marketing authorization in a regulated market (e.g. EU, US), but maximally up to 15 years.

For serum ADA samples, the following archiving applies:

- Aliquot 1 and 2: will be discarded 6 months after availability of the final clinical study report.
- Aliquot 3: storage at the central lab should not exceed the duration of 6 months after availability of the final clinical study report; After this time the Sponsor has to decide if these aliquots will be discarded.
- Aliquot 4: will be stored by the Sponsor at approximately ≤-70°C until marketing authorization in a regulated market (e.g. EU, US), but maximally up to 15 years.

Alternatively, samples which are left over after assessment of serum drug concentration or ADA assessment can be used for future research as described in section 6.8.1 after the specified archiving/storage period. All optional future research will be done at the sponsor's discretion if patients consent to do so by signing a separate optional informed consent form. Samples will be stored maximally up to 15 years.

[redacted]

Labels used in this study will not contain information, which would allow identifying the treatment given. This assures that the analysts will analyze the samples in a blinded manner. All samples will be given a unique barcode number.

6.5.6.2 Analytical methods for ADA

Immunogenicity of adalimumab as determined by the formation of antibodies against the drug will be evaluated by using validated immunoassays. The validation procedure and serum sample analysis will follow international guidelines.

All samples will first be analyzed in a binding ADA screening assay. Study samples with a result below the validated screening cut-point are negative for anti-adalimumab antibodies and will be reported accordingly. In the event of a positive result (result above the screening cut-point) the sample will be additionally analyzed in a secondary confirmatory assay (specificity assay). In case the assay signal can be reduced after addition of excess of adalimumab beyond the validated confirmatory cut-point, a sample will be reported as confirmed positive for binding anti-adalimumab antibodies. In contrast, samples with a result above the screening cut-point in the screening assay but which are negative in the confirmatory assay will be reported as negative.

The titer of all confirmed positive results will be reported in the CSR. In addition, all confirmed positive ADA samples will be further analyzed for their neutralization potential in a neutralizing antibody (NAb) assay. NAb results will also be reported in the CSR.

6.5.6.3 Analytical methods for determination of serum drug trough levels

Serum concentration of [redacted] adalimumab will be measured [redacted] The validation procedure and serum sample analysis will follow international guidelines. [redacted]

6.5.6.4 Additional research/analyses

The subject's remaining adalimumab trough concentrations and ADA samples (aliquot 3 and aliquot 4 respectively) will be stored until approval of the drug in a highly regulated market (e.g. EU, US), but maximally up to 15 years and may be used for additional research and/or analysis [redacted]

In addition, development activities such as method evaluation and validation related to adalimumab might be done. All optional additional analyses will be done at the sponsor's discretion if subjects consent to do so. A decision to perform such research analysis would be based on outcome data of this trial or from new scientific findings related to the drug class, as well as reagent and assay availability.

[redacted]

6.5.7 Pregnancy and assessments of fertility

Neither GP2017 nor Humira® should be given to pregnant women; therefore a highly effective method of birth control must be used for women of child-bearing potential (see Section 4.2).

Women of child-bearing potential (WOCBP) are all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partner have been sterilized by vasectomy or other means.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment she is considered not of child-bearing potential.

All women of child-bearing potential (WOCBP) according to the definition above should have a serum pregnancy test at Visit 1 (Screening). In addition, all women of child-bearing potential (WOCBP) will have a urine pregnancy test at Visits 2, 4, 6, 8, 10, 12, 14, 15, 16. A positive urine pregnancy test requires immediate discontinuation of study drug and should be confirmed with a serum pregnancy test.

WOCBP, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 70 days after stopping treatment. Highly effective contraception i.e. one that results in an annual pregnancy rate < 1%, is defined as either:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Note: Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception and will lead study drug discontinuation and patient withdrawal.
- Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, this is only acceptable when the reproductive status of the woman has been confirmed by follow up hormone level assessment. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female study subjects, the vasectomized male partner should be the sole partner for that patient).
- Use of a combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception;
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
  c. Barrier methods of contraception: condom or occlusive cap (diaphragm or Cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Sexually active men should continue to practice the barrier method of contraception as already initiated at the start of their MTX treatment.

6.5.8 Appropriateness of safety measurements

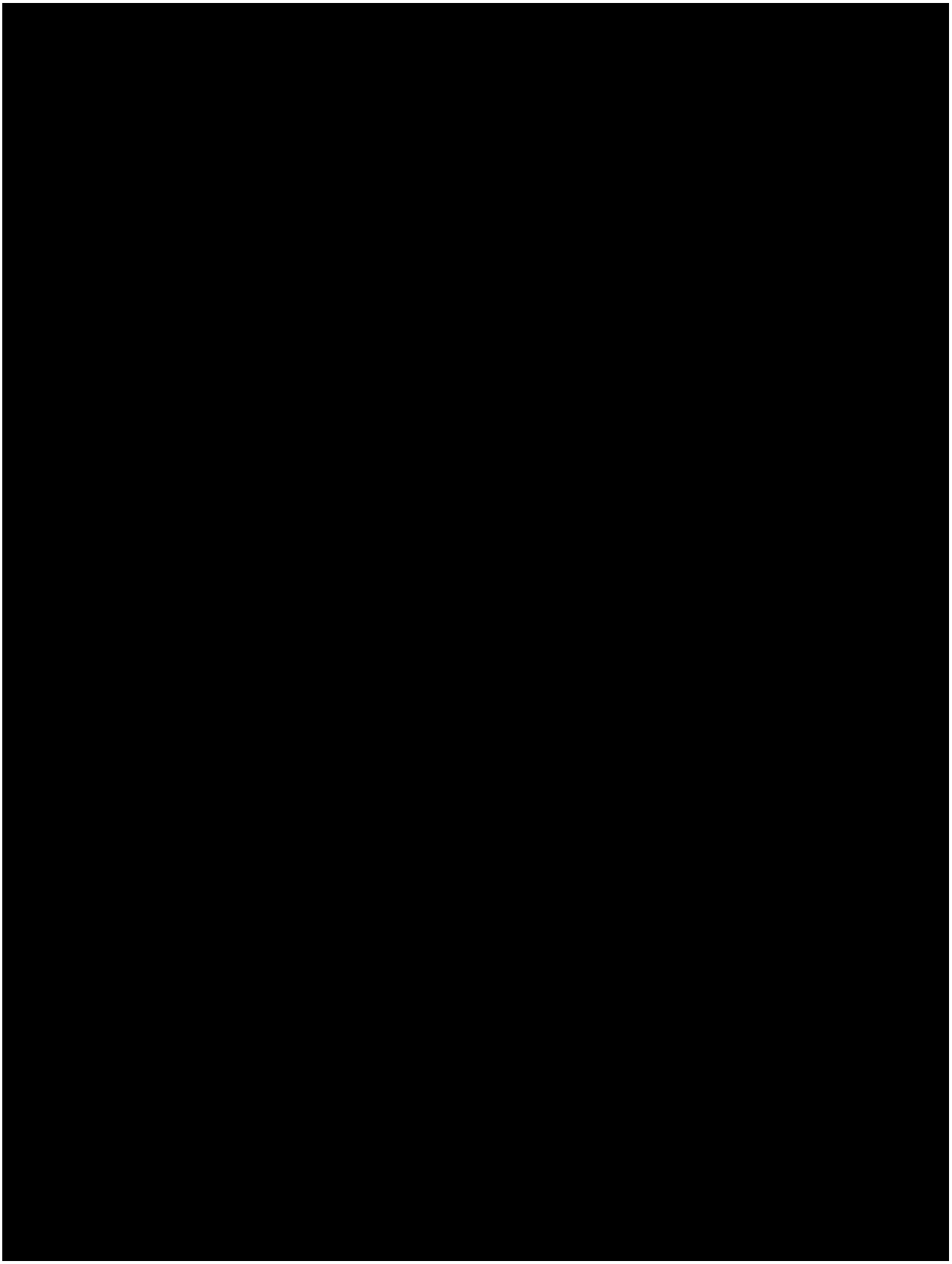
The safety assessments selected are standard for this indication/patient population.

6.6 Pharmacokinetics

No formal PK will be performed. Trough levels of adalimumab will be measured in support of immunogenicity assessment. Blood samples for determination of trough level of adalimumab will be collected at the same time points as samples for ADA assessment. (see Section 6.5.6).

6.7 Pharmacodynamics

Not applicable.



[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator

[redacted]

drug that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events.

Adverse events must be recorded on the Adverse Events (e)CRF with the following information:

1. the severity grade if Common Toxicity Criteria AE (CTCAE) grading does not exist for an adverse event, use
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities

If CTCAE grading exists for an adverse event, use:

1=mild

2=moderate

3=severe

4=life-threatening

CTCAE Grade 5 (death) is not used, but is collected in other CRFs (Study Completion, Death/Survival).

2. its relationship to the study drug(s) (suspected/not suspected)
   - Not suspected: The temporal relationship of the clinical event to trial drug administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

[redacted]

- Suspected: The temporal relationship of the clinical event to trial drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
- If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is as follows:
  - the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration
  - both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient

3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE) (see Section 7.2.1 for definition of SAE)

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

5. action taken

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given, patient hospitalized/patient's hospitalization prolonged . The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

6. It's outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to the sponsor.

[redacted]

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of or worsening of any pre-existing undesirable sign(s), symptom(s) or medical conditions(s)), which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later)

[redacted]

must be reported to the sponsor [or designated CRO] within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to the sponsor [or designated CRO] if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form within 24 hours to the sponsor or delegated CRO. The contact information for SAE/pregnancy reporting is listed in the investigator folder provided to each site.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study drug, the sponsor may urgently require further information from the investigator for Health Authority reporting. The sponsor may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

[redacted]

8 Data review and database management

8.1 Site monitoring

Before study initiation at a site, the protocol and (e)CRFs will be reviewed with the investigators and their staff by a sponsor representative or representative of the delegated CRO at an investigator meeting or a site initiation visit. During the study, the blinded monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice and the progress of enrollment. In order to maintain blinding of the study, an unblinded monitor will be assigned to ensure that study drug is being received, stored, dispensed and accounted for according to specifications. Key study personnel must be available to assist the monitors during monitoring visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on (e)CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents for monitoring to confirm their consistency with the (e)CRF entries. The sponsor’s monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information available in source documents about the identity of the patients will be disclosed.

8.2 Data collection and quality control

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the Electronic Data Capture system until they have been trained. Automatic validation programs check for data discrepancies by generating appropriate error messages and allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of the sponsor. Monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper data query form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the CRO who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

The Investigator must certify with his electronic signature that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a password protected CD-ROM or paper copies of the patient data for archiving at the investigational site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Results of laboratory samples that will be processed centrally will be sent electronically to the designated CRO while result of the ESR performed locally would be entered into the Electronic Case Report Form by the site staff. Randomization codes and data about all study drugs dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology System (IRT). The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to the sponsor (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after reviewing of all code break reports and unused drug supplies to the sponsor or delegated CRO. The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of the sponsor.

8.3 Data Monitoring Committee

A DMC will review the safety data of the study on a regular basis in order:

- to independently assess the causality of suspected SAEs
- to ensure periodic monitoring and periodic review of patient data on suspected SAEs
- to make recommendations based on risk assessments

A charter will be established between sponsor and the DMC to outline the DMC's responsibilities and procedures.

8.4 Adjudication Committee

Not required.

9 Data analysis

All data will be analyzed at the end of the trial.

The data collected in Study Period 1 will be analysed to demonstrate similar efficacy and to compare safety and immunogenicity of GP2017 and US-licensed Humira® over 24 weeks of treatment with the primary endpoint being assessed using data up to week 12.

The data including Study Period 2 will be evaluated to assess long-term safety, immunogenicity and efficacy of GP2017 up to Week 48 and to investigate the effects of a switch from US-licensed Humira® to the proposed biosimilar GP2017 in patients with at least a moderate response, with respect to efficacy, safety and immunogenicity.

All data will be collected fully blinded. All analyses shall be performed after all patients have completed or were prematurely withdrawn from the study and the study CSR shall be written.

Treatment groups for analysis will include:

- Study period 1: GP2017
  US-licensed Humira®
- Study period 2: continuous GP2017
  US-licensed Humira® switched to GP2017

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, median and maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals (CI) will be displayed.

9.1 Analysis sets

The following analysis sets will be used in this study:

Study Period 1 Full analysis set (SP1 FAS): consists of all randomized subjects to whom IMP has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned at randomization. Subjects will be analyzed as per the actual true strata and not necessarily the assigned strata.

Study Period 2 FAS (SP2 FAS): The SP2 FAS set includes all SP1 FAS patients entering Study Period 2.

Week 12 Per-protocol analysis set (W12 PPS): consists of all subjects in the SP1 FAS who complete Week 12/Visit 8 and do not have any **major** protocol deviations regarding the evaluation of the study's primary objective.

Study Period 1 PPS (SP1 PPS): consists of all subjects in the SP1 FAS who complete Week 24/Visit 14 and do not have any **major** protocol deviations regarding the evaluation of the study's key secondary objective.

Study Period 2 PPS (SP2 PPS): consists of all subjects in the SP2 FAS who complete the full study (Week 48/Visit 16) and do not have any **major** protocol deviations with regards to any efficacy assessment.

Additional potential exclusions from the PPS analysis sets will be assessed and confirmed during the BDRMs.

[redacted]

Study Period 1 Safety analysis set (SP1 SAF): consists of all subjects who received at least one dose of IMP, whether randomized or not. Subjects will be analyzed according to the treatment received.

Study Period 2 SAF (SP2 SAF): The SP2 SAF set includes all SP1 SAF patients entering Study Period 2 who received at least one dose of IMP in Study Period 2.

9.2 Patient demographics/other baseline characteristics

Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized by treatment group using frequency tables and descriptive statistics depending variable type. The analyses will be performed for all the FAS and PPS analysis sets.

Medical History

Any condition entered as medical history or current medical conditions will be coded using the MedDRA dictionary. Medical history will be summarized by system organ class and preferred term for all the FAS and PPS analysis sets. Summaries for RA specific medical history will be provided in addition.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

The analysis of treatment data by treatment group will be based on the SAF analysis sets.

Study treatment

Study drug exposure (including patient exposure years), duration of patient observation and compliance to study drug (including number of missed injections).

Prior and concomitant medication

Prior and concomitant medications will be summarized by treatment group and for all patients separately.

Prior medications are defined as medications taken and stopped prior to first dose of study treatment. Any medication given at least once between first dose of randomized study treatment and the last day of study will be considered a concomitant medication, including those medications started prior to study treatment and which continued to be taken during the study.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the percentage of patients receiving at least one medication of a particular ATC code and at least one medication in a particular anatomical main group.

RA specific prior treatments will be presented including the number of prior systemic and biologic therapies, as well as the reason for discontinuation.

In addition, medical procedures and significant non-drug therapies as coded by MedDRA will be summarized.

9.4 Analysis of the primary objective(s)

9.4.1 Variable

The primary variable is DAS28-CRP change from baseline at Week 12.

9.4.2 Statistical hypothesis, model, and method of analysis

The following statistical hypotheses will be used to assess equivalence between GP2017 and US-licensed Humira® with regards to DAS28-CRP change from baseline at Week 12:

H0: $|GP2017 - Humira^{®}| \geq 0.6$ versus H1: $|GP2017 - Humira^{®}| < 0.6$

To address both EMA and FDA regulatory requirements for establishing therapeutic equivalence both 95% and 90% confidence intervals shall be estimated and used to assess equivalence of DAS28-CRP change from baseline at Week 12.

Therapeutic equivalence in terms of DAS28-CRP will be concluded if the 95% (as required by EMA) or 90% (as required by FDA) confidence interval for the difference in DAS28-CRP change from baseline at Week 12 between the two treatment groups is completely contained within the interval [-0.6; 0.6]. This is statistically equivalent to calculating two independent one-sided tests at a 2.5%/5% alpha level (one in each direction), of which both have to be successful.

A mixed-model repeated measures (MMRM) analysis will be performed for DAS28-CRP change from baseline as the endpoint including treatment, stratification factors, time, the interaction between time (visits) and treatment all as categorical variables, and baseline DAS28-CRP as a continuous variable.

$$DAS28CRP_{CFB} = treat + strata + time + (time * treat) + baseline\ DAS28CRP$$

MMRM is a standard approach to longitudinal analysis of continuous endpoints. Its roots bear into linear mixed modeling methodology and it is specified as a multivariate normal model of the longitudinal data. More specifically, this model includes a saturated visit-by-treatment structure for the mean. That is, time is considered as a factor rather than a continuous variable, and thus MMRM makes no assumption about trends over time. Traditional linear mixed models make further assumptions about the covariance of within/intra-patient observations, which can either originate from random effects or residual errors. With MMRM the covariance structure is specified only through the residual error term. The most flexible covariance matrix is unstructured, that is, all variance and covariance parameters are estimated. The actual covariance matrix to be used shall be determined within the statistical analysis plan prior to unblinding.

Mean change from baseline at Week 12, standard errors and the two-sided 95%/90% CI for the mean difference between GP2017 and US-licensed Humira® will be estimated from the model and the 95%/90% CI compared to the pre-specified equivalence margin of [-0.6; 0.6]. An effect

[redacted]

size of 0.6 in DAS28-CRP score is considered to be clinically meaningful for comparison of GP2017 with US-licensed Humira® in this patient population.

The primary analysis will be performed on the Week 12 Per-protocol set (W12 PPS) which is the most appropriate analysis set to use when testing for equivalence.

9.4.3 Handling of missing values/censoring/discontinuations

No imputation will be performed for missing components of the DAS28-CRP score or the computed DAS28-CRP score itself.

9.4.4 Supportive analyses

The same MMRM analysis as used for analysis of the primary endpoint will be conducted as a sensitivity analysis using the SP1 FAS.

[redacted]

9.5 Analysis of secondary objectives

9.5.1 Key secondary variable

The key secondary variable is time-weighted averaged change from baseline in DAS28-CRP until Week 24.

9.5.1.1 Statistical hypothesis, model, and method of analysis

Time-weighted averaged change from baseline in DAS28-CRP until Week 24 (standardized AUEC approach) will be estimated from an ANCOVA

The averaged change from Week 2 and Week 24 will be estimated by a time-weighted mean across visits. The weights are derived using the standard formula from the trapezoidal rule across the visits. Mean averaged change from baseline from Week 2 to Week 24, standard errors and the two-sided 95%/90% CI for the mean difference between GP2017 & and US-licensed Humira® will be estimated from the model and the 95%/90% CI compared to the pre-specified equivalence margin of [-0.6; 0.6].

To address both EMA and FDA regulatory requirements for establishing therapeutic equivalence both 95% and 90% confidence intervals shall be estimated and used to assess equivalence of time-weighted averaged change from baseline in DAS28-CRP until Week 24. No imputation will be performed for missing components of the DAS28-CRP score or the computed AUEC value itself.

The key secondary analysis will be performed on the Study Period 1 Per-protocol set (SP1 PPS) which is the most appropriate analysis set to use when testing for equivalence.

An idential sensitivity analysis as specified above for the SP1 PPS will be carried out using the SP1 FAS.

[redacted]

9.5.2 Efficacy

Efficacy variables will be presented for both the FAS and PPS analyses sets and include:

- DAS28-CRP, DAS28-ESR
- ACR20, ACR50, ACR70 (CRP & ESR) response rate
- CRP, ESR
- HAQ-DI
- FACIT Fatigue scale.

Incidence rates over time shall be presented for ACR 20/50/70 and DAS28-CRP EULAR defined criteria. Summary statistics of absolute and change from baseline for DAS28-CRP & ESR and CRP & ESR values will be provided.

For Treatment period 2 summary statistics of DAS28-CRP & ESR scores changes from Week 24 at Week 48 will be presented, in addition to incidence rates for ACR 20/50/70 at Week 48.

The quality of life assessments HAQ-DI and FACIT Fatigue Scale will be summarized for absolute values and change from baseline at Week 4, 12 and 24 and for change from Week 24 at Week 48. In addition incidence rates of patients achieving a HAQ-DI score of ≤ 0.5 and a score improvement of > 0.3 shall be presented.

9.5.3 Safety

All safety evaluations will be performed on the SAF analysis sets.

Adverse events

Treatment Emergent AEs (TEAE) defined as events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity, will be summarized. However all AEs recorded will be listed.

AEs will be summarized by primary system organ class and preferred term for:

- TEAEs
- TEAEs by maximum severity
- Treatment-related TEAEs
- SAEs
- TEAEs leading to dose adjustment/interruption
- TEAEs leading to premature discontinuation
- deaths

If a patient reported more than one adverse event within the same primary system organ class/preferred term, the patient will be counted only once with the greatest severity at the system organ class level/preferred term, where applicable.

Injection Site Reactions

ISRs will be summarized by presenting the number and percentage of patients experiencing any ISR and by category. Summaries will also be presented by severity and for treatment-related ISRs.

Laboratory data

Summary statistics for absolute and change from baseline by visit will be presented. In addition qualitative laboratory results will be summarized by visit. The incidence of patients with abnormal clinically notable laboratory values will be summarized.

Vital signs

Summary statistics of change from baseline for vital sign measurements by visit will be presented. Abnormal vital sign measurements shall be summarized.

Electrocardiogram

ECG will be summarized for ECG variables by visit and treatment group.

9.5.4 Immunogenicity

Full ADA formation data and the titer and neutralization potential (as assessed by a neutralizing antibody (NAb) assay) of all confirmed positive binding results will be reported in the study CSR.

9.5.5 Pharmacokinetics

No formal PK will be performed. Figures will be generated to illustrate the time course of adalimumab trough levels. The trough serum levels at selected visits will be evaluated using descriptive statistics.

[redacted]

9.6 Sample size calculation

The sample size for this study is based on an expected difference of zero and common SD of 1.30 for the DAS28-CRP change from baseline at Week 12 (ReAct study), an equivalence margin of 0.6and assumed loss of 20% patients from the per-protocol analysis set. A 0.6 change in DAS28-CRP score is considered as the minimum clinically meaningful difference by EULAR criteria and is therefore used as the equivalence margin limits [0.6,-0.6].

In order to fulfil FDA regulatory requirements for establishing therapeutic equivalence (e.g. using 90% confidence interval), a sample size of 154 patients per treatment group (to maintain

[redacted]

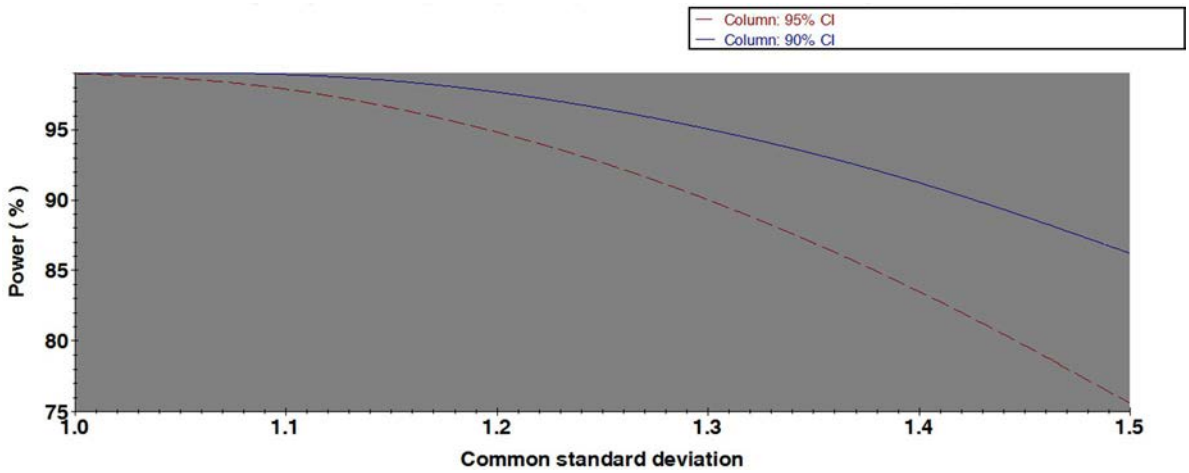
overall 246 evaluable patients for the primary endpoint analysis) will have 95% power to test the equivalence between GP2017 and US-licensed Humira®.

In order to fulfil EMA regulatory requirements for establishing therapeutic equivalence (e.g. using 95% confidence interval), a sample size of 154 patients per treatment group (to maintain overall 246 evaluable patients for the primary endpoint analysis) will have 90% power to test the equivalence between GP2017 and US-licensed Humira®.

9.7 Power for analysis of critical secondary variables

From Burmester et al (2014) the standard deviation at 6 months, i.e. roughly Week 24, was calculated as 1.5. This compares with the value of 1.3 found for the Week 12 assessment (see Section 9.6). However, it is difficult to estimate the common SD for the AUEC because this will depend on the correlation between the DAS28 values for the same subject at different visits. Assuming the correlation lies between 0 and 1, then common SD values between around 0.7 to 1.4 seem likely. Figure 9-1 below shows the resulting power for different values of the common SD with 246 evaluable patients when calculating both a 90% and 95% confidence interval. It is clear that there is always sufficient power (80%) to demonstrate equivalence using the 90% confidence interval, and that the power will also most likely be sufficient using the 95% confidence interval.

Figure 9-1 Power of AUEC analysis for various common standard deviations



9.8 Interim analysis

No interim analysis is planned.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. any of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

The sponsor will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by the sponsor before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the sponsor (or CRO working on behalf of the sponsor) after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study and up to 70 days after the end of study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

The "Information for female partners of male study participants" document should be given to male participants as part of the informed consent process with the request that they share it with their female partners. In case a partner of a male study participant becomes pregnant during the study, consent of the pregnant partner should be sought to collect information about the pregnancy, the birth and health of the baby.

10.3 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to the sponsor or delegated CRO before study initiation. Prior to study start, the investigator is

required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, other designated agents of the sponsor or CRO, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor or designated CRO immediately that this request has been made.

10.4 Publication of study protocol and results

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. Study results containing primary outcome measure will be published on clinicaltrials.gov within 12 months of primary completion date (defined as the date when all study patients have completed Week 12/ EoS (Visit 16) whichever is earlier). After finalization of the study report, the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted, except when necessary to eliminate immediate hazards to the subjects.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the Heath Authority where required, and the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to Health Authority and IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the applicable IRB/IEC/REB should be informed as required per local regulations.

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Appendix 1: Clinically notable laboratory values

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

Clinically notable values will be forwarded to the Sponsor at the same time that they are sent to investigators by Central Laboratory.

Clinically notable laboratory values should be documented as AE if the laboratory change has been confirmed by 3 repeated measurements at subsequent per-protocol visits. In subjects who already had abnormal laboratory parameters (eg CTC AE grade 1) at screening, laboratory change to CTC AE grade 2, confirmed by 3 repeated measurements should be considered clinical relevant and documented as AE. At the discretion of investigator, a laboratory change can be considered an AE already prior to confirmation by 3 repeated measurements.

Table 12-1 Notable laboratory values for subjects with value within limits of normal at baseline

Laboratory variable	Standard units	SI units
Aspartate aminotransferase	> 3 x ULN	> 3 x ULN
Alanine aminotransferase	> 3 x ULN	> 3 x ULN
Total Bilirubin	> 1.5 x ULN	> 1.5 x ULN
Alkaline Phosphatase	> 2.5 x ULN	> 2.5 x ULN
Creatinine (serum)	> 50% above baseline	> 50% above baseline
Potassium	< 3.0 mEq/L > 6.0 mEq/L	< 3.0 mmol/L > 6.0 mmol/L
Sodium	< 130 mEq/L > 150 mEq/L	< 130 mmol/L > 150 mmol/L
Calcium	<8 mg/dL	<2 mmol/L
	>11.5 mg/dL	>2.9 mmol/L
Hemoglobin	> 20 g/L decrease from baseline	> 20 g/L decrease from baseline
Red Blood Cell count	> 20% below baseline	> 20% below baseline
Platelet count	< LLN	< LLN
White Blood Cell count	< 0.8 x LLN	< 0.8 x LLN
Absolute Neutrophil count	< 0.9 x LLN	< 0.9 x LLN
Absolute Lymphocyte count	> 1.1 x ULN	> 1.1 x ULN
Total Cholesterol	≥ 350 mg/dL	≥ 9.1 mmol/L

Appendix 2: American College of Rheumatology (ACR) Measures

- The following 66/68 joints will be assessed for tenderness and swelling
- Number of tender joints:

The 68 joints to be examined for tenderness are: temporomandibular (2), sternoclavicular (2), acromioclavicular (2), shoulder (2), elbow (2), wrist (2), metacarpophalangeal (10), thumb interphalangeal (2), distal interphalangeal (8), proximal interphalangeal (8), hip (2), knee (2), ankle mortise (2), ankle tarsus (2), metatarsophalangeal (10), interphalangeal of great toe (2) and proximal/distal interphalangeal of the toes (8).

- Number of swollen joints:

The 66 joints to be examined for swelling are the same as those examined for tenderness, except the hip joints are not included.

- Patient's assessment of RA pain

On a 100 mm non-anchored visual analog scale, from no pain to unbearable pain.

- Patient's global assessment of disease activity

On a 100 mm non-anchored visual analog scale, from no arthritis activity to maximal arthritis activity, after the question "Considering all the ways your arthritis affects you, draw a line on the scale for how well you are doing".

- Physician's global assessment of disease activity

On a 100 mm non-anchored visual analog scale, from no arthritis activity to maximal arthritis activity.

- Health Assessment Questionnaire disability index – HAQ-DI©

Appendix 3: FACIT Fatigue Scale

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

FACIT-Fatigue Subscale Scoring Guidelines (Version 4)

Instructions:*

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?	Item response	Item Score
FATIGUE	HI7	4 -	___ _____	=_ _____
SUBSCALE	HI12	4 -		=___ _____
			___ _____	
	An1	4 -	___ _____	=___ _____
	An2	4 -	___ _____	=___ _____
	An3	4 -	___ _____	=___ _____
	An4	4 -	___ _____	=___ _____
	An5	0 +	___ _____	=___ _____
	An7	0 +	___ _____	=___ _____
	An8	4 -	___ _____	=___ _____
	An12	4 -	___ _____	=____ _____
	An14	4 -	___ _____	=____ _____
	An15	4 -	___ _____	=___ _____
	An16	4 -	___ _____	=____ _____
Sum individual item scores:				____ _____
Multiply by 13:				___ _____
Divide by number of items answered:				___ _____
Score range: 0-52 = Fatigue Subscale score				

[redacted]