CLINICAL PHARMACOLOGY REVIEW

BLA	761042
Submission Date:	07/30/2015
Proposed Brand Name:	ERELZI
Nonproprietary Name:	GP2015
Clinical Pharmacology Reviewer:	Yunzhao Ren, M.D., Ph.D.
Clinical Pharmacology Team Leader (Acting):	Ping Ji, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor:	Sandoz
Submission Type; Code:	351(k); standard review
Formulation; Strength(s)	0.5 mL or 1.0 mL of a 50 mg/mL solution in pre-filled syringe or autoinjector
Proposed Indications:	• Rheumatoid Arthritis (RA) • Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Plaque Psoriasis (PsO)
Proposed Dosage Regimens:	• Adult RA and PsA: 50 mg once weekly with or without methotrexate • AS: 50 mg once weekly • Adult PsO: 50 mg twice weekly for 3 months, followed by 50 mg once weekly • JIA: 0.8 mg/kg weekly, with a maximum of 50 mg per week

Note –

In this review, the term of "US-Enbrel" is interchangeable with "US-licensed Enbrel"; and the term "EU-Enbrel" is interchangeable with "EU-approved Enbrel".

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1. Executive Summary

Sandoz submitted a Biologic License Application (BLA) for GP2015, a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 tumor necrosis factor receptor (TNFR2) linked to the Fc portion of human immunoglobulin G1 (IgG1), under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for GP2015 as a biosimilar to US-licensed Enbrel (BLA 103795, US-Enbrel) and licensure for all the indications currently approved for US-Enbrel. GP2015 drug product is supplied as 1.0 mL or 0.5 mL of 50 mg/mL solution which is clear and colorless to slightly yellowish, sterile, preservative-free. The solution is packaged in the single-use prefilled syringe (PFS) or autoinjector for subcutaneous injection (b) (4)

The clinical development for GP2015 included four PK similarity studies (Studies 101, 102, 103, and 104) in healthy subjects, one cross-study PK comparison (Report 105) and one comparative clinical study (Study 302) in patients with chronic PsO.

Pharmacokinetic similarity was established between GP2015 and US-licensed Enbrel (Study 102). The clinical pharmacology program also provided PK bridging data, in addition to the analytical bridging data, to scientifically justify the relevance of the comparative data from the clinical development program with EU-approved Enbrel to support a demonstration of no clinically meaningful differences to US-licensed Enbrel.

In addition, similar steady state PK was demonstrated between GP2015 and EU-approved Enbrel with repeat dosing in the setting of treatment of patients with plaque psoriasis in Study 302.

PK is comparable between GP2015's pre-filled syringe and autoinjector as the 90% CIs for the geometric mean ratios (autoinjector/pre-filled syringe) of systemic exposure (i.e., AUC_{0-t}, AUC_{0-inf}, and C_{max}) are all within 80-125% (Study 103).

No confirmed positive ADA response was noted in any of the three healthy volunteer studies (Studies GP15-102, GP15-101 and GP15-103). A total of 5 patients (0.9%, all in the Enbrel/EU group) in study GP15-302) showed confirmed positive ADA responses during the first 12 weeks of the study

Overall, the GP2015 clinical pharmacology program supports the demonstration of PK similarity between GP2015 and US-licensed Enbrel, and the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel. The PK results add to the totality of evidence to support a demonstration of biosimilarity of GP2015 and US-licensed Enbrel.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that PK similarity has been established between GP2015 and US-licensed Enbrel, and the PK results support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

Labeling Recommendations

Please refer to Section 3 – Detailed Labeling Recommendations.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

The clinical pharmacology program of GP2015 to evaluate the pharmacokinetic (PK) similarity between GP2015 and US-licensed Enbrel and to assess the PK element of the scientific bridge between GP2015, US-licensed Enbrel and EU-approved Enbrel included three PK studies (Studies 101, 102, and 104) in healthy subjects, a cross-study PK comparison (Report 105), and steady state PK assessment in patients with chronic PsO (Study 302) (Table 1.1).

Table 1.1 Key Design Features of GP2015 Clinical Studies

Study ID	Design	Objectives	Subjects	Treatments	Endpoints
Clinical Pharmacology Studies					
Study 101	R, DB, 2-way cross-over	PK, safety, and immunogenicity	57 healthy subjects	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 102	R, DB, 2-way cross-over	PK, safety, and immunogenicity	54 healthy subjects	SD 50 mg SC: • GP2015 • US-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 104	R, DB, 2-way cross-over	PK, safety, and immunogenicity	54 healthy males	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Report 105	A cross-study comparison of studies 101 and 102				
Comparative Clinical Study					
Study 302	R, DB, PG TP1 (Wk 0-12)	Efficacy, safety, immunogenicity, PK	531 PsO patients	50 mg SC twice weekly: • GP2015 • EU-Enbrel	PASI 75
	R, DB, PG TP2 (switching) (Wk 12-30)	Safety, immunogenicity, PK	PsO patients re-randomized	50 mg SC Q weekly: • GP2015 cont • GP2015 switch • EU-Enbrel cont • EU-Enbrel switch	Safety, Immunogenicity

R=randomized, DB=double blind, PG=parallel group, TP=treatment period, SD=single dose, SC=subcutaneous

Each of the three PK studies was conducted as randomized, two-way crossover studies to assess PK, safety, and immunogenicity. In these studies, healthy subjects received one single dose of 50 mg subcutaneously (SC) of study drug followed by a washout period of at least 35 days and were then crossed over to receive another single dose of 50 mg SC of the comparator product. As described in the draft guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product,"[12] a single-dose, randomized study is generally the preferred design for PK similarity assessments. A cross-over design is appropriate for etanercept because it has a relatively short half-life and low immune response rate. Additionally, conducting the study in healthy subjects is reasonable as it is more sensitive in evaluating the product similarity due to lack of potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. The 50 mg SC dose is relevant as it is consistent with the approved dose of US-licensed Enbrel.

- Study 102 was the pivotal clinical pharmacology study designed to evaluate PK similarity, safety, and immunogenicity of GP2015 and US-licensed Enbrel.

- Both Study 101 and Study 104 were designed to compare the PK profiles of GP2015 and EU-approved Enbrel. Study 104 was conducted on request by the European Regulatory Authorities to

[12] Guidance for Industry "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product." May 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

support the demonstration of PK similarity of GP2015 to the EU-approved Enbrel, as in Study 101, the pre-specified acceptance criteria were met for C_{max} but not for AUC_{0-t} and AUC_{0-inf}.

- A pre-specified cross-study comparison was conducted to establish the PK bridge between US-licensed Enbrel (from Study 102) and EU-approved Enbrel (from Study 101) (Report 105). In addition to the analytical bridging data, the PK comparison provided in the report and the PK similarity data from Studies 101, 102, and 104 comprised the bridging data to scientifically justify the relevance of the comparative data from the clinical development program with EU-approved Enbrel. A cross-study comparison was justified because both Study 101 and 102 had identical study design, eligibility criteria, demographic and baseline characteristics of the study population, GP2015 product lot, and bioanalytical method. The two studies were performed during an overlapping time period.

- The supportive PK similarity assessment in the setting of repeat dosing was conducted in patients with moderate to severe chronic plaque-type psoriasis (Study 302). The Study 302 was designed as a multi-center, randomized, double-blind, parallel group, comparative clinical efficacy, safety, and immunogenicity study between GP2015 and EU-approved Enbrel. Sparse PK samples from 147 patients were collected for trough concentrations at Week 2, 4, 8, and 12.

The PK samples in the clinical pharmacology studies were analyzed with validated ELISA method. The bioanalytical assays used in the PK studies provided total protein concentration measurement and were not able to distinguish the disulfide bond correctly-bridged variant and wrongly-bridged variant. Of note, the Applicant submitted data from one additional PK study, Study 103, designed to assess PK similarity between two delivery devices following a single dose of GP2015. Because this study was not intended to assess similarity between GP2015 and the reference product, it is not discussed further in this briefing document.

Results of Clinical Pharmacology Studies

Study 102: GP2015 vs US-licensed Enbrel

Study 102 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and US-licensed Enbrel in 54 healthy subjects. The pairwise comparisons of GP2015 and US-licensed Enbrel met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUC_{0-inf}, $AUC_{0-tlast}$, and C_{max} within the interval of 80% to 125%) as summarized in Table1.2 and depicted in Figure1.1. The analytical data on glycan structure showed small differences in the levels of high mannose forms Man 5, Man 6 and Man8 (~2.2% for GP2015 and ~8% for US-licensed Enbrel and EU-approved Enbrel). High mannose glycan structures may alter the PK of a molecule though binding to cell surface mannose binding proteins. However, PK similarity was demonstrated for GP2015 and US-licensed Enbrel, which addresses the residual uncertainty in the differences in high mannose glycans between GP2015 and US-licensed Enbrel and which supports a demonstration of biosimilarity between GP2015 and US-licensed Enbrel.

Table 1.2 Statistical Analysis of the PK Parameters of GP2015 and US-Licensed Enbrel in Study 102

Parameter	N	GP2015	US-Enbrel	Ratio (GP2015/US-Enbrel)[2]
AUC_{0-t} (µg·h/mL)[1]	53	369.761	414.962	0.8911 (0.8308, 0.9557)
AUC_{0-inf} (µg·h/mL)[1]	54	390.286	439.656	0.8877 (0.8320, 0.9471)
C_{max} (µg/mL)[1]	54	2.028	2.146	0.9450 (0.8695, 1.0271)

Source: Table 4.12
[1] Least-squares geometric means
[2] Ratio (90% CI)

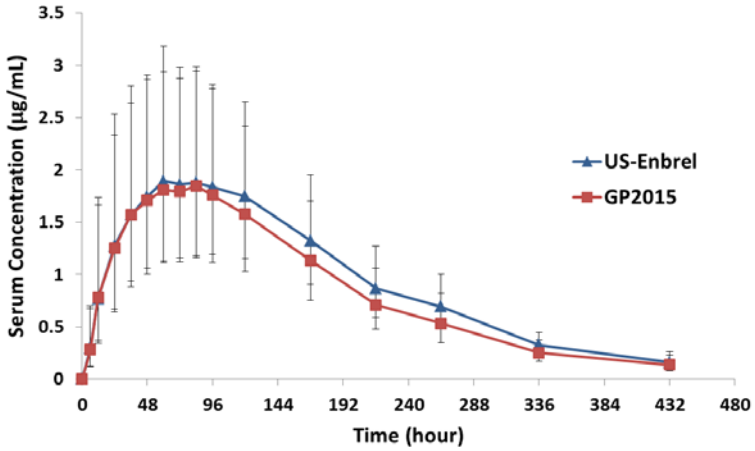

Figure 1.1 Geometric Mean Serum Concentration-time Profiles of GP2015 (red, N=54) and US-licensed Enbrel (blue, N=54) from Study 102 (Source: adapted from Figure 4.4)

Studies 101 and 104: GP2015 vs EU-approved Enbrel

Study 101 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and comparator EU-approved Enbrel in healthy subjects. The pairwise comparison of GP2015 and EU-approved Enbrel was within the pre-specified criteria for C_{max} but not for AUC_{0-t} and AUC_{0-inf} as summarized in Table1.3 and depicted in Figure1.2.

Table 1.3 Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 101

Parameter	N	GP2015	EU-Enbrel	Ratio (GP2015/EU-Enbrel)[2]
AUC_{0-t} (µg·h/mL)[1]	49	335.150	392.619	0.8536 (0.7830, 0.9307)
AUC_{0-inf} (µg·h/mL)[1]	49	353.338	416.506	0.8583 (0.7803, 0.9223)
C_{max} (µg/mL)[1]	50	1.808	1.982	0.9124 (0.8247, 1.0094)

Source: Table 4.6
[1] Least-squares geometric means
[2] Ratio (90% CI)

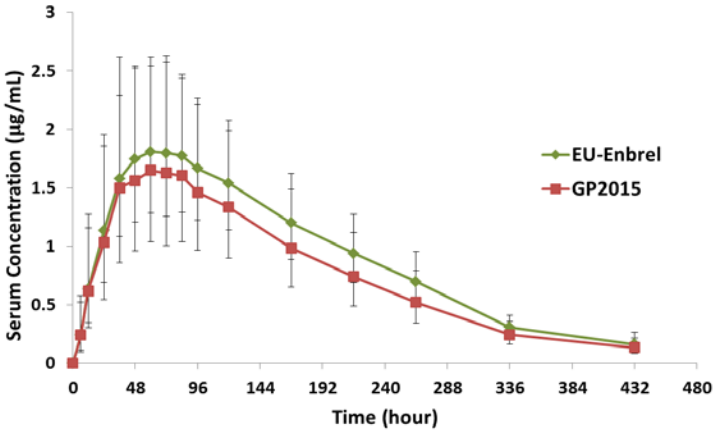

Figure 1.2 Geometric Mean Serum Concentration-Time Profiles of GP2015 (red, N=50) and EU-approved Enbrel (green, N=50) from Study 101 (Source: adapted from Figure 4.2)

Study 104 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and comparator EU-approved Enbrel in healthy males. It is a repeat study, on request by the European Regulatory Authorities, and has the same study design and methodology as Study 101. Notable differences include that only male subjects (n=54) were enrolled in Study 104 whereas both males (n=23) and females (n=23) were enrolled in the study 101; the batches of both GP2015 and EU-approved Enbrel were different between two studies; and the bioanalytical methods were different between two studies, although both methods were validated. The modifications implemented in Study 104 were intended to reduce the PK variability observed in Study 101. The pairwise comparisons of GP2015 and EU-approved Enbrel for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} met the pre-specified acceptance criteria for PK similarity as summarized in Table 1.4 and depicted in Figure1.3.

Table 1.4 Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 104

Parameter	N	GP2015	EU-Enbrel	Ratio (GP2015/EU-Enbrel)[2]
$AUC_{0\text{-}t}$ (µg·h/mL)[1]	54	632.662	644.007	0.9824 (0.9449, 1.0214)
$AUC_{0\text{-}inf}$ (µg·h/mL)[1]	54	680.945	706.883	0.9633 (0.9264, 1.0016)
C_{max} (µg/mL)[1]	54	3.416	3.087	1.1066 (1.0500, 1.1664)

Source: Table 4.25
[1] Least-squares geometric means
[2] Ratio (90% CI)

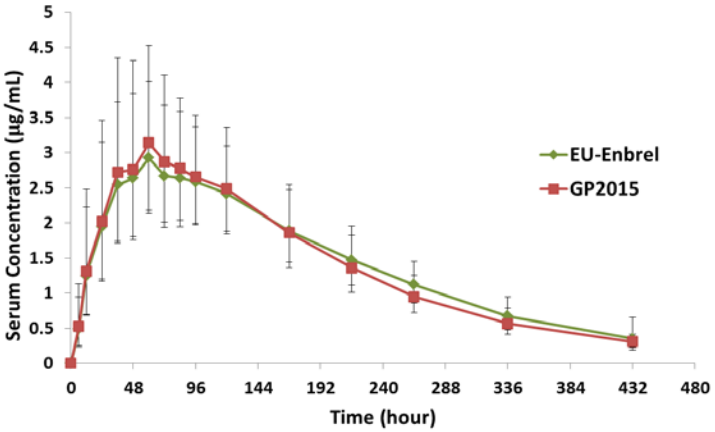

Figure 1.3 Geometric Mean Serum Concentration-time Profiles of GP2015 (red, N=54) and EU-approved Enbrel (green, N=54) from Study 104 (Source: Adapted from Figure 4.9)

The two-fold difference in exposure between Study 104 and Study 101 observed for GP2015 and EU-approved Enbrel could be due to different bioanalytical methods used in the two studies, however, other factors cannot be ruled out.

Report 105: EU-approved Enbrel and US-licensed Enbrel

The PK comparison between EU-licensed Enbrel from study 101 and US-licensed Enbrel from Study 102 was conducted and summarized in Report 105. This statistical comparison was pre-defined and outlined as a pre-specified objective of both protocols. The sample size used in the data analysis was pre-determined from the two study protocols 101 and 102 and appears sufficient to assess biosimilarity between these two products. The pairwise comparisons of EU-approved Enbrel and US-licensed Enbrel met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of $AUC_{0\text{-inf}}$, $AUC_{0\text{-tlast}}$, and C_{max} within the interval of 80% to 125%) as summarized in Table 1.5 and depicted in Figure1.4.

Table 1.5 Statistical Analysis of the PK Parameters of EU-approved Enbrel and US-Licensed Enbrel in Report 105

Parameter	EU-Enbrel	US-Enbrel	Ratio (EU-Enbrel/US-Enbrel)[2]
$AUC_{0\text{-t}}$ (µg·h/mL)[1]	392.632 (N=49)	415.237 (N=53)	0.9456 (0.8397, 1.0647)
$AUC_{0\text{-inf}}$ (µg·h/mL)[1]	416.484 (N=49)	439.738 (N=54)	0.9471 (0.8451, 1.0615)
C_{max} (µg/mL)[1]	1.980 (N=50)	2.146 (N=54)	0.9222 (0.8026, 1.0596)

Source: Table 4.31
[1] Least-squares geometric means
[2] Ratio (90% CI)

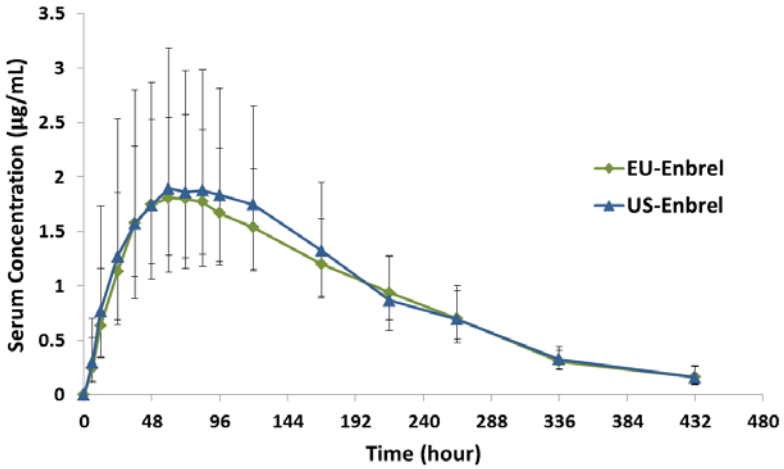

Figure 1.4 Geometric Mean Serum Concentration-time Profiles of EU-approved Enbrel (green, N=50) and US-licensed Enbrel (blue, N=54) from Report 105 (Source: Adapted from Figure 4.11)

Study 302: Supportive PK in patients after repeat dosing

In comparative clinical Study 302, pre-dose PK samples were collected from 147 patients at Day 1, and at Weeks 2, 4, 8, and 12 during treatment period 1. The mean trough serum concentrations were generally comparable at each time point between GP2015 and EU-approved Enbrel at steady state. The mean serum trough concentrations-time profiles indicate steady-state was reached from Week 2 for GP2015 and EU-approved Enbrel (Figure1.5).

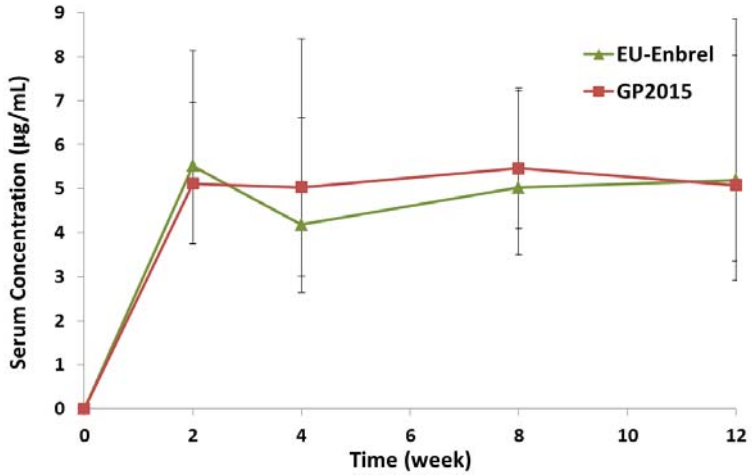

Figure 1.5 Geometric Mean Trough Serum Concentration-time Profiles of GP2015 (red, N=72) and EU-approved Enbrel (green, N=75) from Study 302 (Source: Adapted from Figure 4.15)

Extrapolation of the PK Data for GP2015

The pharmacokinetic parameters of etanercept in patients with PsO were similar to those seen in patients with RA.[1] The estimated half-life of etanercept was about 100 hours and comparable in healthy subjects, JIA and RA patients. As a fusion glycoprotein and consisting entirely of human protein components, etanercept is expected to undergo proteolysis in patients across different diseases. There are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between GP2015 and US-licensed Enbrel in the indications sought for licensure. Since similar PK was demonstrated between GP2015 and US-licensed Enbrel in healthy subjects and psoriasis, a similar PK profile would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, AS, and PsA.

Clinical Pharmacology Summary

Overall, the submitted clinical pharmacology studies are adequate to:

1) Demonstrate similarity of exposure between GP2015 and US-licensed Enbrel. The PK studies, conducted in healthy subjects, are considered sensitive to detect clinically significant differences in exposure among the products. Single-dose PK similarity pre-specified margins were met in comparison of GP2015 to US-licensed Enbrel, GP2015 to EU-approved Enbrel, and US-licensed Enbrel to EU-approved Enbrel. The demonstration of similar exposure supports a finding of biosimilarity between GP2015 and US-licensed Enbrel.

[1] FDA-approved Enbrel labeling

2) Establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of the biosimilarity of GP2015 to US-licensed Enbrel.

3) Together with the analytical similarity (discussed in the CMC section above), justify the relevance of the PK findings from the GP2015 clinical program to the indications that were not directly studied in the GP2015 clinical program, for which US-licensed Enbrel is licensed and for which the Applicant is seeking licensure.

In summary, the PK similarity has been demonstrated between GP2015 and US-licensed Enbrel, and the results from the PK studies add to the totality of evidence to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel. The PK studies have not raised any new uncertainties in the assessment of biosimilarity of GP2015 to US-licensed Enbrel.

2. Question Based Review

2.1 Regulatory History

GP2015 was developed by Sandoz as a biosimilar product to the US-licensed reference product Enbrel®, which is licensed in the US to Immunex Corp, Thousand Oaks, CA, and marketed by Amgen Inc and Pfizer Inc. In Europe, Enbrel® is authorized for Pfizer Limited, UK. Sandoz initiated the first clinical study (Study 101) in UK in June, 2010.

A pre-IND meeting request was submitted on 12/19/2011 and the meeting was held on 07/09/2012. The summary of clinical pharmacology-related questions and comments are listed as following:
Question 4: The sponsor is conducting a single dose, cross-over phase I study in healthy volunteers with GP2015 and the reference product Enbrel sourced from the US to demonstrate PK bioequivalence using conventional bioequivalence criteria. Does the Agency agree that the ongoing phase I study is appropriate to demonstrate a similar PK profile of GP2015 and the reference product Enbrel?

FDA Response: Yes, we agree. We recommend that you assess AUCt, AUCinf and Cmax for the purpose of establishing PK similarity. You stated that this is an ongoing study. We would expect that you conduct this assessment with the formulation you intend to commercialize.

Question 9: Regarding using non-US reference drug, the sponsor intensively analyzed and compared multiple batches of US and EU sourced reference product Enbrel at physicochemical and biological level and came to the conclusion that the products from both regions are indistinguishable. The sponsor considers therefore the similarity data from physicochemical and biological testing of the two products as an acceptable bridge to use data (e.g. nonclinical) generated with EU sourced Enbrel in a GP2015 351(k) application. Furthermore, the sponsor will gain data from two phase I studies in healthy volunteers using reference drug from the US and EU, respectively. The two phase I studies have an identical design and differ only in the reference product used. The sponsor will perform a side-by-side comparison of the relevant PK parameters (AUC, Cmax, t1/2) as well as of the incidence of related adverse events to compare the US and the EU licensed versions of Enbrel. In combination with the comprehensive similarity data available on a physico-chemical and biological/functional level, does the Agency agree that this approach is sufficient to demonstrate the scientific bridge between the US-licensed product and the EU-licensed product?

FDA Response: No, we do not agree. If you seek to use data from a nonclinical or clinical study comparing GP2015 to EU-approved etanercept to address, in part, the requirements under section 351(k) (2) (A) of the PHS Act, you should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and establish an acceptable scientific bridge to the US-licensed reference product. The type of bridging data that may be needed to provide adequate scientific justification for this approach would likely include a bridging clinical PK/PD study, as well as a direct physico-chemical comparison of all 3 products (US-licensed Enbrel, EU-approved etanercept, and GP2015). All three comparisons (US-licensed Enbrel to GP2015, EU-approved etanercept to GP2015, and EU-approved etanercept to US-licensed Enbrel) should meet the pre-specified acceptance criteria for analytical and PK similarity. The adequacy of this scientific justification and bridge to the US-licensed reference product would be a review issue. FDA refers the sponsor to the responses to Questions 1 and 3, and the Agency's draft guidance on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guiances/UCM273001.pdf), specifically Q&A.I.8, for additional information.

You have proposed two separate studies to demonstrate PK similarity between GP 2015 with US-licensed product (study GP15-102) and GP 2015 and EU-licensed product (study GP15-101). You have also proposed submitting only the safety data from study GP15-301, a comparative safety and efficacy trial of GP2015 and EU-approved etanercept in patients with RA.

If you wish to submit only GP2015 safety data from study GP15-301, and not comparative safety and/or efficacy data from both GP2015 and EU-approved etanercept, then it may be sufficient to conduct two separate PK trials as proposed, as you would not be relying on clinical data obtained with a non-US licensed comparator for approval. Please note, however, that if you are unable to scientifically justify extrapolating from psoriasis to RA and other rheumatologic indications, the two 2-way PK similarity studies would not be sufficient to bridge to the data obtained in Study GP15-301 and the RA indication. If you believe that is the likely scenario, it would be in your best interest to consider a 3-way PK similarity study.

The proposed 3-way analytical similarity assessment appears to be acceptable to support the use of the data from study #GP15-003, but this will ultimately be a review issue based on the data submitted.

The meeting adjourned after Sandoz summarized the following points:
Question 9: Sandoz acknowledged FDA's advice regarding conducting a 3-way PK similarity study with the EU-approved etanercept and US-licensed Enbrel. Sandoz stated that they would proceed with the 2 proposed PK similarity studies and acknowledged the risk to their program.

A PeRC meeting was held on 02/11/2015 and the Divisions (DDDP & DPARP) agreed that no additional pediatric studies would be required under PREA for the proposed biosimilar product. DPARP agreed that the Etanercept is fully assessed for pJIA down to two years of age and that studies were waived for pJIA less than two years of age, and ankylosing spondylitis and psoriatic arthritis. DDDP agreed that studies should be fully waived for this product for PsO because of the known safety signal (b) (4). No pre-BLA meeting was held before the submission of BLA 761042.

A different development approach was proposed for establishing the 3-way PK bridge for the proposed biosimilar to Enbrel than what is recommended in the guidance, and also different from the advice provided prior to submitting their BLA (FDA advised a 3-arm PK similarity study in a BPD meeting in July 2012). Sandoz conducted two independent 2-way comparative PK studies (i.e. Studies-101 and -102). To establish the third pairwise comparison of the bridge between US-licensed Enbrel and EU-approved Enbrel, Sandoz performed a pre-specified cross-study analysis (Report-105) of Studies-101 and -102. Sandoz justified this approach indicating that Studies -101 and -102 shared the same study unit, identical study design, identical inclusion/exclusion criteria, subjects with similar demographic and baseline characteristics, the same GP2015 product lot, identical bioanalytical method, and the studies were performed over an overlapping time period. Sandoz purports these factors reduce the weaknesses typically associated with cross-study comparisons. The biologic review committee (BRC) and the center director briefing concluded that this bridging approach is acceptable.

2.2 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the BLA

Four *in vivo* clinical pharmacology-related studies (Studies 101, 102, 103, and 302) and one cross-study report (Report 105) were originally submitted under BLA 761042 on 7/30/2015. The Sponsor submitted another PK study (Study 104) on 9/10/2015 after the filing meeting was held (09/02/2015).

Table 2.1 List of Clinical Studies/Report Containing PK Evaluation

Study ID	Study Location	Study Date	Study Objective(s)	Study Design	Subjects	Treatments
Study 101	UK	11/21/11 – 04/20/12	PK comparison	R, DB, SD, 2-way CO	54 HS enrolled with 51 completed	GP2015 50 mg EU-Enbrel 50 mg
Study 102	UK	02/28/2012 – 08/23/2012	PK comparison	R, DB, SD, 2-way CO	57 HS enrolled with 54 completed	GP2015 50 mg US-Enbrel 50 mg
Study 103	Netherlands	03/18/2014 – 06/25/2014	PK comparison	R, OL, SD, 2-way CO	57 HM randomized with 49 completed	GP2015 50 mg Autoinjector or pre-filled syringe
Study 104*	UK	06/30/2014 – 11/19/2014	PK comparison	R, DB, SD, 2-way CO	54 HM enrolled with 48 completed	GP2015 50 mg EU-Enbrel 50 mg
Study 302	Non-US Multi-center	06/24/2013 – 06/24/2014	Efficacy, Safety, PK, Immunogenicity	R, DB, MD, PG, up to 52 week	531 patients enrolled with 511 completed period 1	GP2015 50 mg EU-Enbrel 50 mg twice weekly for the first 12 weeks and once weekly thereafter
Report 105			Cross-study PK comparison			US-Enbrel 50 mg EU-Enbrel 50 mg

* Submitted after filing meeting
R=randomized, DB=double blind, SD=single dose, CO=cross-over, MD=multiple dose, PG=parallel group, HS=healthy subjects, HM=healthy males
Source: adapted from section 5.2 Tabular Listing of all Clinical Studies.pdf

2.3 General Attributes of the Drug

2.3.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

GP2015 drug substance is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 KD tumor necrosis factor receptor (TNFR2) linked to the Fc portion of human immunoglobulin G (IgG1). GP2015 contains 934 amino acids (homo-dimer: 467) and has an approximate molecular mass of 125 kD as determined by mass spectroscopy. GP2015 is glycosylated and contains 6 N-glycans and multiple O-glycans. These variants are sialylated as well. In addition, 29 disulfide bridges are present throughout the molecule. GP2015 drug substance is expressed in a Chinese hamster ovary cell line. GP2015 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection is provided as a colorless to slightly yellowish solution with pH approximately 6.3. The composition of GP2015 solution is listed in Table 2.2. The formulation of GP2015 solution is different from US-Enbrel.

Table 2.2 Composition of GP2015 25 mg/0.5 mL Solution for Injection

Component	Nominal amount per syringe	Amount per syringe [2]	Function	Reference to quality standards [3]
Active ingredient				
Etanercept [1]	25 mg	(b) (4) mg	Active substance	See [Module 3.2.S.4.1]
Other ingredients				
Citric acid anhydrous	0.393 mg	(b) (4) mg	Buffer	Ph. Eur., USP
Sodium citrate dihydrate	6.76 mg	mg	Buffer	Ph. Eur., USP/NF
Sodium chloride	0.750 mg	mg	(b) (4)	Ph. Eur., USP/NF
Sucrose	5.00 mg	mg		Ph. Eur., USP/NF
L-lysine HCl	2.300 mg	mg		Ph. Eur., USP
Sodium hydroxide	q.s. [4]	[4]	pH modifier	Ph. Eur., USP/NF
Hydrochloric acid 25%	q.s. [4]	[4]	pH modifier	Ph. Helv.
Water for injection	ad (b) (4) mg [5]	ad (b) (4) mg [5]	(b) (4)	Ph. Eur., USP
(b) (4)				

[3] The current edition of the pharmacopoeia is used

(b) (4)

Source: section 3.2.P.1 Page 9, Table 1-1

US-Enbrel is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNFR2 linked to the Fc portion of human IgG1. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 KD (via SDS-PAGE). US-Enbrel drug substance is expressed in a Chinese hamster ovary cell line. The solution of US-Enbrel in the single-use prefilled syringe and the single-use prefilled SureClick autoinjector is clear and colorless, sterile, preservative-free, and is formulated at pH 6.3 ± 0.2. US-Enbrel is also supplied in a multiple-use vial as a sterile, white, preservative-free, lyophilized powder. Reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colorless solution with a pH of 7.4 ± 0.3. The composition of US-Enbrel solution for prefilled syringe product is listed in Table 2.3:

Table 2.3 Composition of US-Enbrel 25 mg Prefilled Syringe Drug Product

Ingredient Name	Amount/mL	Test Requirements [a]
etanercept	50 mg/mL	In House
Sodium Phosphate, Dibasic, (b) (4)	(b) (4) mg/mL	USP, Ph Eur, JP
Sodium Phosphate, Monobasic, (b) (4)	mg/mL	USP, Ph Eur, JP
L-Arginine Hydrochloride, (b) (4)	5.3 mg/mL	USP, Ph Eur, JP
Sucrose, (b) (4)	10.0 mg/mL	NF/ Ph Eur
Sodium Chloride, (b) (4)	5.8 mg/mL	USP, Ph Eur, JP
(b) (4)	(b) (4)	USP, Ph Eur

[a] Quality assessment is in accordance with the current USP, N/F, JP and/or respective Ph Eur.
Source: BLA 103795 submission, section 3.2.P.1 Page 1, Table 1

2.3.2 What are the proposed mechanism of action and therapeutic indication(s)?

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.

Two distinct receptors for TNF (TNFRs), a 55 KD protein (p55, TNFR1) and a 75 KD protein (p75, TNFR2), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFRs.

GP2015 binds to TNF and blocks the binding between TNF-α/β to cell surface TNFRs, rendering TNF biologically inactive. In in vitro studies, large complexes of etanercept with TNF-α were not detected and cells expressing transmembrane TNF (that binds etanercept) are not lysed in the presence or absence of complement.

The therapeutic indications of GP2015 are: RA, Polyarticular JIA in patients aged 2 years or older, PsA, AS, and PsO.

2.3.3 What are the proposed dosages and routes of administration?

The proposed route of administration for GP2015 is subcutaneous injection. The proposed dosages for different indications are:

- Adult RA and PsA: 50 mg once weekly with or without methotrexate
- AS: 50 mg once weekly
- Adult PsO: 50 mg twice weekly for 3 months, followed by 50 mg once weekly
- JIA: 0.8 mg/kg weekly, with a maximum of 50 mg per week

2.3.4 What drugs (substances, products) indicated for the same indication are approved in the U.S.?

GP2015 is seeking the identical indications as covered by US-Enbrel. The proposed indications of US-Enbrel are unique and not identical to the other approved TNF antagonists (Table 2.4).

Table 2.4 Summary of Currently FDA-Approved TNF Antagonists

		Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
BLA#		103772	103795	125057	125160	125289
Original Approval Date		08/24/1998	11/02/1998	12/31/2002	4/22/2008	4/24/2009
Drug Substance		Chimeric anti-TNFα Ab	TNFR2-IgG1 fusion protein	Human anti-TNF IgG1 Ab	Anti-TNFα-polyethylene fusion protein	Human anti-TNFα IgG1 Ab
Clinical Indications	**Rheumatoid Arthritis**	X	X	X	X	X
	Juvenile chronic Arthritis		X	X		
	Ankylosing Spondylitis	X	X	X	X	X
	Crohn's Disease	X		X	X	
	Pediatric Crohn's Disease	X		X		
	Ulcerative Colitis	X		X		X
	Pediatric Ulcerative Colitis	X				
	Plaque Psoriasis	X	X	X		
	Psoriasis Arthritis	X	X	X	X	X
	Hidradenitis Suppurativa			X		

Source: Reviewer's summary, indications as listed in the labels of the above biological products on 12/16/2015

2.4 General Clinical Pharmacology

2.4.1 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The key endpoints of all the studies were listed in Table 2.5. The PK endpoints ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}) were measured by non-compartmental model.

Table 2.5 Summary of Endpoints of Studies Containing PK Evaluation

Study ID	PK Endpoints	Other Endpoints
Study 101	$AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, $\%AUC_{extrap}$, t_{max}, k_{el}, $t_{1/2}$, and CL/F	Safety
Study 102	$AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, $\%AUC_{extrap}$, t_{max}, k_{el}, t1/2, and CL/F	Safety
Study 103	$AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, $\%AUC_{extrap}$, t_{max}, k_{el}, $t_{1/2}$, and $CL_{0\text{-}last}$	Safety
Study 104	$AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, $\%AUC_{extrap}$, t_{max}, k_{el}, $t_{1/2}$, and $CL_{0\text{-}inf}$	Safety
Study 302	C_{trough} at Day 1 and at Weeks 2, 4, 8, and 12	Efficacy (primary): PASI 75 response rate at Week 12 Safety

Source: Reviewer's summary

For the primary efficacy endpoint psoriasis area and severity index (PASI) 75 response, it was defined as patients who achieved ⊪75% improvement (reduction) in PASI score compared to baseline. For PASI assessment, the head, trunk, upper limbs and lower limbs were to be assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation).

The average degree of severity of each sign in each of the 4 body regions was assigned a score of 0–4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0.

Both ECG and immunogenicity were monitored as safety variables during all the clinical studies.

2.4.2 Are the active moieties in serum and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters?

Serum concentration of GP2015 was measured to assess its pharmacokinetic parameters. The capture antibody (Peprotech 500-P168 rabbit polyclonal antibody), the detecting antibodies (R&D Systems BAF726 goat polyclonal antibody and Becton Dickenson monoclonal antibody for SOP PV05102 version 02 and version 03, respectively) of GP2015 used in ELISA were all raised against recombinant human TNFR2. Therefore, it's the TNFR2 moiety of the fusion protein product that was measured during ELISA.

2.5 Dose/Exposure response

2.5.1 What are the characteristics of the dose/exposure-response relationship for effectiveness and safety?

Due to the nature of 351(k) submission, the dose/exposure relationship for effectiveness and safety of GP2015 was not evaluated.

2.5.2 Does this drug prolong the QT or QTc interval?

There were no meaningful changes over time and no notable differences among treatments and treatment groups with respect to ECG in all the studies.

2.6 PK Characteristics of the Drug

2.6.1 What are the known PK characteristics of the reference product US-licensed Enbrel?

The PK and immunogenicity of etanercept (US-licensed Enbrel) described in product labeling from BLA103795 are summarized in Table 2.6.

Table 2.6 PK and immunogenicity summary of US-licensed Enbrel (BLA103795)

- PK following 25 mg s.c. administration:
  - Clearance: 160 ± 80 mL/hr
  - C_{max}: 1.1 ± 0.6 µg/mL following single dose of 25 mg
  - T_{max}: 69 ± 34 hr
  - $C_{max,ss}$: 2.4 ± 1.0 µg/mL following 25 mg twice weekly, 6 month treatment
  - $t_{1/2}$: 102 ± 30 hours
- Steady state PK following 25 mg s.c. twice weekly administration:
  - $C_{max,ss}$: 2.4 ± 1.5 µg/mL
  - $C_{min,ss}$: 1.2 ± 0.7 µg/mL
  - Partial AUC: 297 ± 166 µg•h/mL
- Steady state PK following 50 mg s.c. once weekly administration:
  - $C_{max,ss}$: 2.6 ± 1.2 µg/mL
  - $C_{min,ss}$: 1.4 ± 0.7 µg/mL
  - Partial AUC: 316 ± 135 µg•h/mL
- Specific population:
  - No different between men and women
  - PK did not vary with age in adult patients
  - PK unaltered by concomitant MTX in RA patients
  - No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on etanercept disposition
- Immunogenicity
  Antibodies to the TNF receptor portion or other protein components of the Enbrel drug product were detected at least once in sera of approximately 6% of adult patients with RA, PsA, AS or PsO. These antibodies were all non-neutralizing.

Source: adapted from product label of BLA103795, section 6 and section 12

The single-dose PK results of US-licensed Enbrel obtained under BLA761042 (Study 102) are summarized in Table 2.7. Following single dose of 50 mg subcutaneous injection, serum US-Enbrel concentrations increased slowly with maximum concentrations occurring at median t_{max} values of 84 hours. Thereafter, drug product concentrations declined a mean rate of 115 mL/h. Mean $t_{1/2}$ values was 87 hours. The steady state of US-licensed Enbrel was achieved no later than Week 2 in patients with chronic

PsO. The geometric mean PK profile of US-Enbrel following 50 mg single dose subcutaneous injection is presented in Figure 2.1.

The PK profile of US-licensed Enbrel following multiple-dose administration has not been studied under BLA 761042.

2.6.2 What are the PK characteristics of GP2015?

Single-Dose PK

GP2015 vs US-licensed Enbrel: Study 102

Study 102 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and US-licensed Enbrel in 54 healthy subjects. The single-dose PK results of GP2015 from Study 102 are summarized in Table 2.7. Following single dose of 50 mg subcutaneous injection, serum G2015 concentrations increased slowly with maximum concentrations occurring at median t_{max} values of 72 hours. Thereafter, drug product concentrations declined a mean rate of 129 mL/h. Mean $t_{1/2}$ values was 89 hours. The geometric mean PK profile of GP2015 following 50 mg single dose subcutaneous injection is presented in Figure 2.1.

Table 2.7 PK Summary of GP2015 and US-licensed Enbrel (BLA761042)*

		50 mg GP2015 N=54	50 mg Enbrel® N=54
	N	Geometric mean (CV%)	
$AUC_{0\text{-}tlast}$ (ng.h/mL)	53[a]	365745 (44.5)	410523 (42.7)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	54	386486 (43.7)	435143 (40.6)
C_{max} (ng/mL)	54	2028 (50.5)	2146 (51.5)
$t_{1/2}$ (h)	54	88.6 (13.7)	86.8 (21.7)
k_{el} (h^{-1})	54	0.00782 (13.7)	0.00798 (21.7)
CL/F (mL/h)	54	129 (43.7)	115 (40.6)
CL/F (mL/h)[b]	54	129 (43.7)	115 (40.3)
		Arithmetic mean (SD)	
$\%AUC_{extrap}$ (%)	54	4.95 (1.91)	5.42 (2.80)
		Median (min – max)	
t_{max} (h)	54	72.0 (24.0 – 120)	84.0 (24.0 – 120)

N = Number of subjects studied.
[a] Subject 016 was excluded because $AUC_{0\text{-}tlast}$ value could not be reliably calculated for Period II
[b] Parameter calculated based on the actual dose received.
* All the PK parameters are listed as geometric mean (CV%) except t_{max} as median (range)
Source: Table 4.8

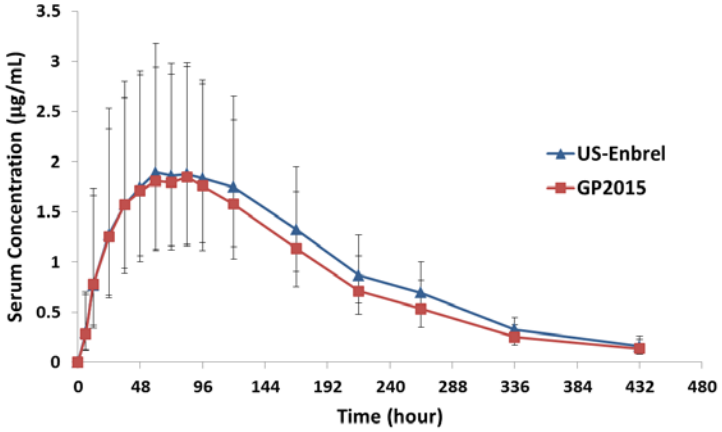

Figure 2.1 US-Enbrel (blue, N=54) and GP2015 (red, N=54) geometric serum concentration-time profile following 50 mg single dose subcutaneous injection in Study 102. The error bars represent SD. Source: Figure 4.4.

The statistical restuls of PK similarity analysis using operator as a fixed effect are listed in Table 1.1. The statistical restuls of PK similarity analysis without using operator as a fixed effect are listed in Table 4.12. The estimated ratio (GP2015/US-Enbrel) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} is 0.8911 (90% CI = 0.8308, 0.9557), 0.8877 (90% CI = 0.8320, 0.9471), and 0.9450 (90% CI = 0.8695, 1.0271), respectively. The PK similarity is established between GP2015 and US-licensed Enbrel as the 90% CI of all three ratios are within the goal post 80% -125%.

GP2015 vs EU-approved Enbrel: Studies 101 and 104

Study 101 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and comparator EU-approved Enbrel in healthy subjects. The single-dose PK results of GP2015 from Study 101 are summarized in Table 2.8. Following single dose of 50 mg subcutaneous injection, serum G2015 concentrations increased slowly with maximum concentrations occurring at median t_{max} values of 60 hours. Thereafter, drug product concentrations declined a mean rate of 143 mL/h. Mean $t_{1/2}$ values was 86 hours. The geometric mean PK profile of GP2015 following 50 mg single dose subcutaneous injection is presented in Figure 2.2.

Table 2.8 PK Summary of GP2015 and EU-Approved Enbrel*

		50 mg GP2015 N=50	50 mg Enbrel® N=50
	N	Geometric mean (CV%)	
$AUC_{0\text{-}tlast}$ (ng.h/mL)	49	331680 (43.1)[a]	388725 (30.0)[a]
$AUC_{0\text{-}tlast}$ (ng.h/mL)[b]	49	336759 (43.2)[a]	383984 (30.1)[a]
$AUC_{0\text{-}\infty}$ (ng.h/mL)	49	349383 (42.7)[a]	411692 (29.1)[a]
C_{max} (ng./mL)	50	1802 (49.3)	1980 (35.8)
C_{max} (ng./mL) (norm)[b]	50	1829 (49.3)	1955 (35.7)
$t_{1/2}$ (h)	49	85.9 (11.6)	84.4 (21.4)
k_{el} (h^{-1})	49	0.008 (11.6)	0.008 (21.4)
CL/F (mL/h)	49	143 (42.7)	121 (29.1)
CL/F (mL/h) (norm)[b]	49	141 (42.7)	123 (29.2)
		Arithmetic mean (SD)	
$\%AUC_{extrap}$ (%)	49	5.05 (1.63)[a]	5.55 (2.44)[a]
		Median (min – max)	
t_{max} (h)	50	60.0 (36.0 - 120)	72.0 (24.1 – 120)

N = Number of subjects studied; (norm) = normalized for actual dose administered.
[a] N = 49; Subject 43 was excluded as AUC values could not be calculated in Period II.
[b] Parameter calculated based on actual dose received.
* All the PK parameters are listed as geometric mean (CV%) except t_{max} as median (range)
Source: Table 4.2

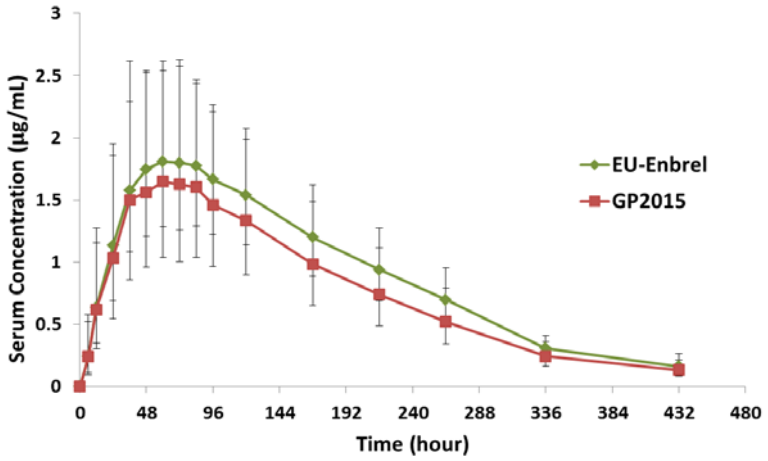

Figure 2.2 EU-Enbrel (green, N=50) and GP2015 (red, N=50) geometric serum concentration-time profile following 50 mg single dose subcutaneous injection in Study 101. The error bars represent SD. Source: Figure 4.2.

The statistical restuls of PK similarity analysis using operator as a fixed effect are listed in Table 2.9. The estimated ratio (GP2015/EU-Enbrel) of $AUC_{0\text{-}t}$ and C_{max} is 0.8757 (90% CI = 0.8130, 0.9432) and 0.9357 (90% CI = 0.8535, 1.0258), respectively.

Table 2.9 Statistical Analysis of the PK Parameters of GP2015/EU-Enbrel in Study 101 (Per-Protocol Set)*

		Geometric LS mean		Ratio of geometric LS mean	Within
	N	50 mg GP2015	50 mg Enbrel®	GP2015 : Enbrel® (90% CI)	subject CV%
$AUC_{0\text{-tlast}}$ (ng.h/mL)	49	272617	311318	0.8757 (0.8130, 0.9432)	21.41
C_{max} (ng./mL)	50	1466	1567	0.9357 (0.8535, 1.0258)	27.06

* The ANOVA model included sequence, treatment, period, and operator (person who performed the dosing) as fixed effects, and subject nested within sequence as a random effect.
Source: CSR 101, Page 37, Table 11-5

The statistical restuls of PK similarity analysis without using operator as a fixed effect are listed in Table 4.6. The estimated ratio (GP2015/EU-Enbrel) of AUC0-t, AUC0-inf, and Cmax is 0.8536 (90% CI = 0.7830, 0.9307), 0.8583 (90% CI = 0.7803, 0.9223), and 0.9124 (90% CI = 0.8247, 1.0094), respectively. Without operator, Study-101 failed to demonstrate the PK similarity between GP2015 and EU-approved Enbrel. Sandoz uses the term "operator effect" to describe consideration that the protocol allowed an alternate "operator" (i.e., the person administering the products). According to Sandoz, failure to meet the pre-specified criteria for PK similarity was observed when the product was administered by the alternate operator. Sandoz reported that when the operator effect was taken into account, the pre-specified criteria for PK similarity were met. As such, Sandoz concluded, "that different operators were a relevant source of variation and possibly the main reason for not meeting formal bioequivalence."

Based on feedback from EMA regarding the failure of Study-101 to meet the pre-specified criteria for PK similarity, Sandoz conducted a second PK similarity study (Study-104) comparing GP2015 and EU-approved Enbrel to support approval in the EU. Study-104 met the pre-specified criteria for PK similarity.

Sandoz submitted the results from Study-104 as an amendment to their BLA on September 10, 2015. Relevant differences between Studies-101 and -104 are as follows:

- Study-104 was conducted three years after Study-101 using different GP2015 and EU-approved Enbrel lots.
- The population studied in Study 104 was composed of 100% male subjects, while Study-101 population included 39% female subjects.
- Although both studies were conducted in the United Kingdom, the clinical sites were different.
- Different bioanalytical methods were used in Study-101 and -104:
  - The key reagents were different between two studies: Study 101 used goat anti-human polyclonal antibody whereas study 104 used rat anti-human monoclonal antibody.
  - The dilution factor of PK samples, the range of the calibration curve, and the lower limit of quantitation were all very different between two methods (Table 2.11).

The statistical restuls of PK similarity comparison between GP2015 and EU-approved Enbrel from Study 104 are listed in Table 2.10. The estimated ratio (GP2015/EU-Enbrel) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} is 0.98 (90% CI = 0.94, 1.02), 0.96 (90% CI = 0.93, 1.00), and 1.11 (90% CI = 1.05, 1.17), respectively. The PK bridge is established between GP2015 and EU-approved Enbrel as the 90% CI of all three ratios are within the goal post 80% -125%.

Table 2.10 Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 104

Parameter (unit)	LS Mean		Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	GP2015 N=54	Enbrel N=54			
C_{max} (ng/mL)	3416.22	3087.00	1.11	1.05 - 1.17	16.4
$AUC_{0\text{-tlast}}$ (h*ng/mL)	630363.18	642235.26	0.98	0.94 - 1.02	12.1
$AUC_{0\text{-inf}}$ (h*ng/mL)	678786.96	705159.10	0.96	0.93 - 1.00	12.3

Source: from Table 4.22

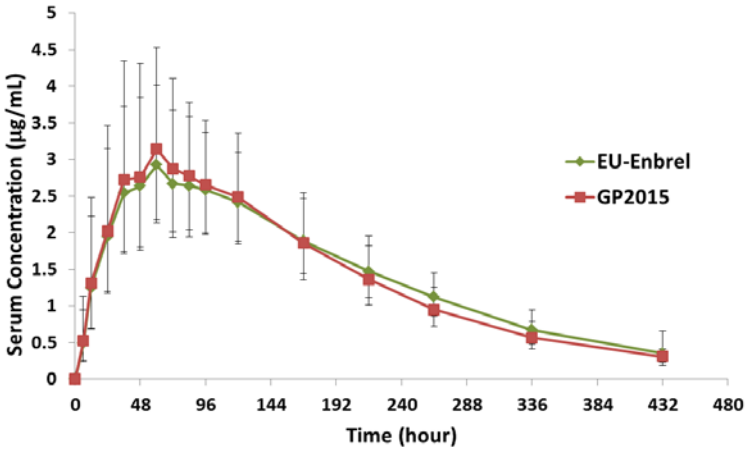

Figure 2.3 EU-Enbrel (green, N=50) and GP2015 (red, N=50) geometric serum concentration-time profile following 50 mg single dose subcutaneous injection in Study 104. The error bars represent SD. Source: Figure 4.9.

Of note, the exposures of both GP2015 and EU-approved Enbrel were about two-fold higher in Study 104 than in Study 101. The Clinical Pharmacology reviewers have noted that a cross-study comparison of Studies-102 and -104 would not meet the pre-specified criteria for PK similarity due to the exposure differences driven by the different bioanalytical methods.

EU-approved Enbrel and US-licensed Enbrel: Report 105

The PK comparison between EU-licensed Enbrel from study 101 and US-licensed Enbrel from Study 102 was conducted and summarized in Report 105. This statistical comparison was pre-defined and outlined as a pre-specified objective of both protocols. The sample size used in the data analysis was pre-determined from the two study protocols 101 and 102 and appears sufficient to assess biosimilarity between these two products. The pairwise comparisons of EU-approved Enbrel and US-licensed Enbrel met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of $AUC_{0\text{-inf}}$, $AUC_{0\text{-tlast}}$, and C_{max} within the interval of 80% to 125%) as summarized in Table2.11 and depicted in Figure2.4.

Table 2.11. Statistical Analysis of the PK Parameters of EU-approved Enbrel and US-Licensed Enbrel in Report 105

				Enbrel EU / Enbrel US 90% CI			Between subject CV%
	Enbrel	N	Geometric LS mean	Ratio	Lower	Upper	
$AUC_{0\text{-tlast}}$ (ng.h/mL)	EU	49	388578	0.9469	0.8412	1.0658	37.16
	US	53	410380				
C_{max} (ng/mL)	EU	50	1979	0.9222	0.8026	1.0596	44.62
	US	54	2146				
$AUC_{0\text{-}\infty}$ (ng.h/mL)	EU	49	411530	0.9457	0.8445	1.0591	35.62
	US	54	435143				

Source: from Table 4.28

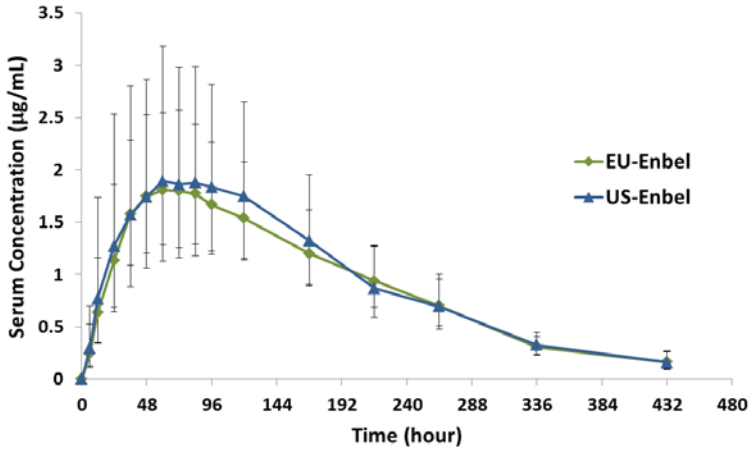

Figure 2.4. EU-Enbrel (green, N=50) and US-Enbrel (blue, N=54) geometric serum concentration-time profile from Report 105 (per-protocol set). The error bars represent SD. Source: Figure 4.11

Multiple-Dose PK

The C_{trough} following twice weekly multiple-dose administration of GP2015 and EU-Enbrel from Study 302 are summarized in Table 2.12. The geometric mean pre-dose concentrations at Weeks 2, 4, 8 and 12 are comparable between GP2015 and EU-Enbrel. The differences of point estimate are less than 20%. The steady-state appeared established no later than Week 2 and was maintained throughout the 12-week treatment period 1 (Figure 2.5), which is consistent with the drug's half-life of 4-5 days.

Table 2.12 Geometric mean (CV%) Trough Serum Concentration of GP2015/EU-Enbrel during Treatment Period 1 (PK set)

Time Points	EU-Enbrel		GP2015	
	N	geoMean (CV%) (µg/mL)	N	geoMean (CV%) (µg/mL)
Week 2	59	5.51 (41%)	59	5.12 (31%)
Week 4	56	4.18 (48%)	56	5.03 (55%)
Week 8	63	5.02 (38%)	63	5.46 (30%)
Week 12	61	5.20 (46%)	61	5.08 (56%)

Source: adapted from Figure 4.8

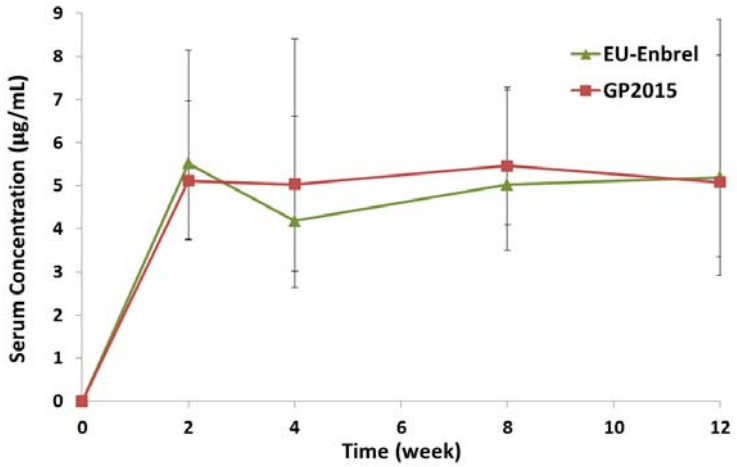

Figure 2.5 EU-Enbrel (green, N=75) and GP2015 (red, N=72) geometric trough concentration-time profile following 50 mg subcutaneous injection twice a week. The error bars represent SD. Source: Figure 4.8

2.6.3 How does the PK of GP2015 in healthy adults compare to that in patients with the target disease?

The PK of GP2015 in healthy adults and patients with PsO were not directly compared under BLA 761042.

A cross-study comparison on two studies (Studies 104 and 302) sharing the same version (version 03) of bioanalytical method was roughly evaluated:

- The geometric mean serum concentration of GP2015 at 84 hour post-dose following 50 mg s.c. single dose administration was 2.90 µg/mL in healthy males (Study 104).
- The geometric mean pre-dose serum concentration of GP2015 from Week 2 to Week 12 following 50 mg s.c. twice weekly administration ranged 5.03 to 5.46 µg/mL in patients with PsO.
- Thus an accumulation ratio approximately 1.7 to 1.9-fold was estimated by this cross-study

comparison.

- Meanwhile, an accumulation ratio of approximate 2-fold is expected by a twice weekly dosing regimen on GP2015 with elimination half-life about 89 hours.
- Therefore, the PK of patients with PsO is not expected to deviate aberrantly from that of healthy subjects.

2.7 Intrinsic Factors

2.7.1 Body Weight

Body weight was identified as a statistically significant covariate ($p<0.001$) for all three PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}) when body weight was used as covariate in ANCOVA analysis in Study 103.

The systemic exposure decreases when body weight increases (Figure 2.6). The geometric mean of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} decreased 42%, 41%, and 48% from low body weight group (<80 kg, N=17) to high body weight group (≥100 kg, N=17).

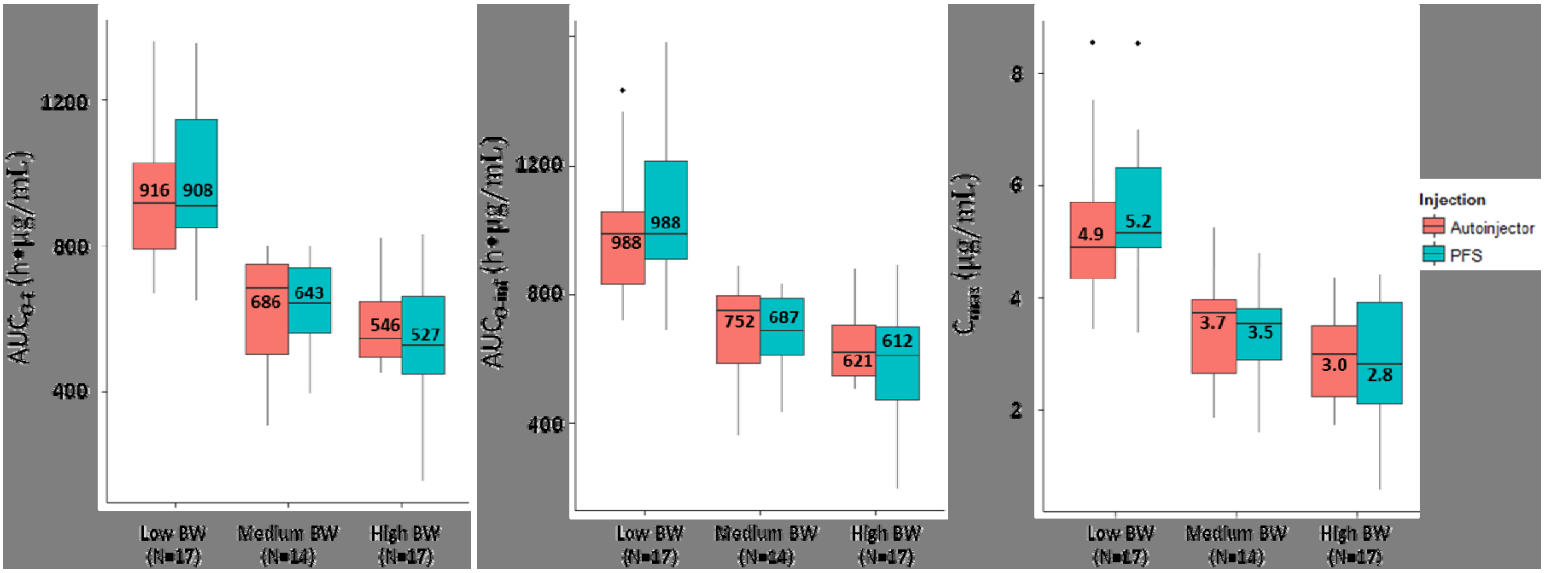

Figure 2.6 Boxplot of GP2015 $AUC_{0\text{-}t}$ (A), $AUC_{0\text{-}inf}$ (B), and C_{max} (C) comparison by body weight group following administration via an autoinjector (red) or a PFS (blue) from Study 103. Low body weight < 80 kg, 80 kg ≤ Medium body weight < 100 kg, 100 kg ≤ High body weight. Source: Figure 4.6

2.7.2 Immunogenicity

2.7.2.1 How was the immunogenicity assessed and what was the incidence of the formation of the anti-drug antibody (ADA)?

Immunogenicity was assessed using a validated ELISA method. The incidence of ADA positivity is 0 for GP2015 in both healthy subjects (up to Day 28) and patients with PsO (up to 42 weeks).

All samples were first analyzed in a screening assay. Study samples with a result below the validated screening cut-point were reported negative for ADAs. In the event of a positive result, the sample was to

be additionally analyzed in a secondary confirmatory assay (specificity assay). In case the assay signal could be reduced after addition of excess of etanercept beyond the validated confirmatory assay cut-point, a sample was to be reported as confirmed binding positive. In contrast, samples were to be reported as negative.

The ADA of GP2015 was negative in any healthy subjects from PK similarity studies and in any patients with chronic PsO from comparative clinical study. Similarly, ADA of EU-Enbrel or US-Enbrel was negative in any healthy subjects from PK similarity studies. The incidence of EU-Enbrel ADA positivity was 1.9% (5/266) during the treatment period 1 (Week 1 to Week 12) of comparative clinical Study 302. All the ADA-positive incidences occurred during Week 2 and Week 4. Four of five ADA-positive patients only had one sample showed positive result. All five ADA-positive patients changed to ADA-negative after Week 4 (including some samples up to week 42).

2.7.2.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

The impact of ADA on GP2015 PK and/or PD was not evaluated as the ADA incidence is 0 in both healthy subjects and patients with PsO.

The impact of ADA on PK of EU-Enbrel could not be statistically evaluated. At each time point (Week 2, 4, 8, and 12), there were only two ADA-positive patients having PK samples available.

The PD marker, plasma high sensitivity C-reactive protein (hsCRP) geometric baseline concentration in ADA-positive patients (N=5) was 2.4-fold as high as that of ADA-negative patients (N=261). However, the hsCRP concentration reduced proportionally to the respective baseline level in ADA-positive or ADA-negative patients following 4-week and 12-week EU-Enbrel treatment (Figure 2.7).

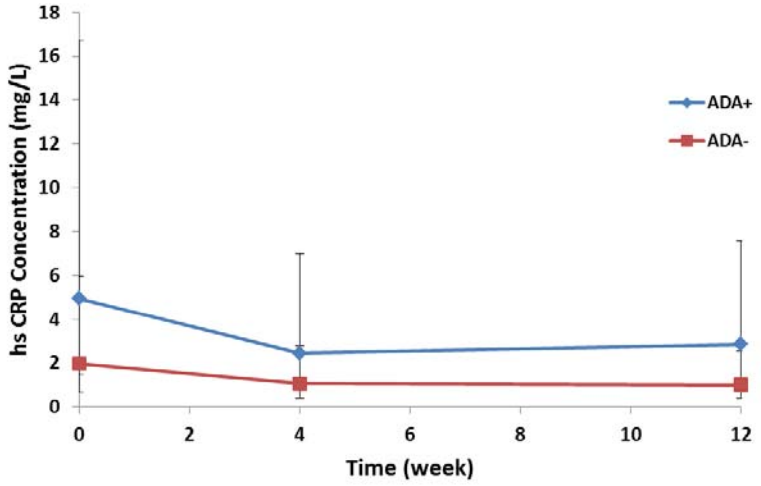

Figure 2.7 hsCRP geometric mean plasma concentration-time profile in ADA-positive patients (blue, N=5) and ADA-negative patients (red, N=261) following 50 mg EU-Enbrel treatment during PT1 in Study 302. The error bars represent SD. Source: reviewer's analysis.

TNF-α, the therapeutic protein of GP2015, was not measured under BLA 761042.

2.7.2.3 Do the anti-drug antibodies have neutralizing activities?

All ADA-positive samples following EU-Enbrel treatment in Study 302 were tested negative for

neutralizing antibodies.

2.7.2.4 What is the impact of ADA on clinical efficacy?

The impact of ADA on GP2015 efficacy in PsO patients was not evaluated as the ADA incidence is 0 in both healthy subjects and patients with PsO.

The impact of ADA on EU-Enbrel efficacy in PsO patients was not evaluated by the Sponsor.

2.7.2.5 What is the impact of ADA on clinical safety?

The impact of ADA on GP2015 safety in PsO patients was not evaluated as the ADA incidence is 0 in both healthy subjects and patients with PsO.

The impact of ADA on EU-Enbrel safety in PsO patients was not evaluated by the Sponsor.

2.8 General Biopharmaceutics

2.8.1 How is the proposed to-be-marketed formulation/device linked to the clinical development formulation/device?

The proposed to-be marketed formulation is the same as the clinical development formulation. The proposed to-be-marketed s.c. injection devices are single-use prefilled syringe and autoinjector. Only PFS was used in the comparative clinical Study 302. However, the PK similarity was established for GP2015 between administrations using an autoinjector and a PFS in Study 103.

Following a single dose of GP2015 50 mg administered by an autoinjector or by a PFS, the mean PK parameters were similar between two injection devices (Figure 2.8). The estimated ratio (autoinjector/PFS) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} is 1.01 (90% CI = 0.95, 1.07), 1.01 (90% CI = 0.96, 1.07), and 1.01 (90% CI = 0.94, 1.08), respectively (Table 2.13).

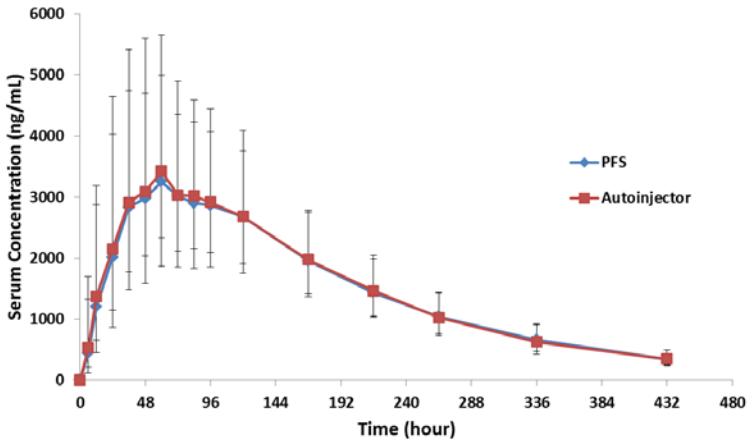

Figure 2.8 GP2015 serum concentration-time profile following 50 mg single dose subcutaneous injection via autoinjector (red, N=48) and PFS (blue, N=48) in Study 103. Source: Figure 4.5.

Table 2.13 Statistical Analysis of the PK Parameters of GP2015 following Autoinjector or PFS Administration in Study 103 (Per-Protocol Set)

	Geometric LS means		Ratio (b) (4) GP2015_50/GP2015-PFS 90% Confidence interval		
PK parameter	(b) (4) GP2015_50	GP2015-PFS	Estimate	Lower	Upper
C_{max} (µg/mL)	3.7	3.6	1.01	0.94	1.08
$AUC_{0\text{-last}}$ (h*µg/mL)	684.1	678.4	1.01	0.95	1.07
$AUC_{0\text{-inf}}$ (h*µg/mL)	745.2	737.4	1.01	0.96	1.07

Source: Table 4.15

2.9 Analytical Section

2.9.1 What are the analytical methods used to measure GP2015 or Enbrel in serum?

Two versions of analytical methods were developed to measure GP2015, US-Enbrel, and EU-Enbrel. Method SOP PV05102, version 02 was used in Study 101 and 102. Method SOP PV05102, version 03 was used in Study 103, 104, and 302. The serum concentrations of GP2015, US-Enbrel, and EU-Enbrel were all quantified by validated ELISA method. Based on the submitted bioanalytical reports and validation reports, the bioanalytical portions of BLA 761042 are acceptable.

For the determination of concentrations of total GP2015, US-Enbrel, or EU-Enbrel in human healthy serum, an ELISA method was used. A microtiter plate was first coated with a rabbit polyclonal anti-human soluble TNFR2 capture antibody and afterwards nonspecific binding sites were blocked. A mixture of serum samples (e.g. standards, quality controls (QCs) or study samples) was then added to the coated microtiter plate. The detection was done by a biotinylated anti-human TNFR2 antibody. After a further incubation with streptavidin-conjugated horseradish peroxidase (HRP) which bound to the biotinylated goat anti-human TNFR2 antibody, a chromogen was added to the wells and was oxidized by HRP to form a blue colored complex. After stopping the reaction with acid, the optical density was measured at 450 nm/620 nm using a microplate reader. The concentrations of the quality control and study samples were interpolated using a standard curve from known concentrations of etanercept that were similarly processed as the QCs or study samples.

Some critical assay reagents, i.e. reference standard used for the generation of the calibration curve, and detection reagents and buffer solutions, were different between SOP PV05102, version 02 and version 03 (Table 2.14).

Table 2.14 Some Critical Assay Reagents/Process of Bioanalytical Method SOP PV05102, Version 02 and Version 03

	Version 02	Version 03
Applied Clinical Studies	Studies 101 and 102	Studies 103, 104, and 302
Capture Antibody	Peprotech 500-P168 rabbit anti-human soluble TNFR II polyclonal antibody	
Detection Antibody	R&D Systems BAF726 biotinylated goat anti-human	Becton Dickenson 552477 biotinylated rat anti-human TNFR II

	TNFR II polyclonal antibody	monoclonal antibody	
Streptavidin-HRP	Invitrogen SNN4004		
Quality Control	Sandoz GP2015.01REF 9.59 mg/mL	Sandoz GP2015.02REF 9.7 mg/mL	
Minimal Required Dilution in Blocking Buffer	1:3	Study 103/104: 1:20	Study 302: 1:100
Quantification range of the calibration curve (ng/mL)	1.0 to 120.0	Study 103/104: 6.7 to 800.0	Study 302: 33.3 to 4000.0
Lower Limit of Quantitation of Sample (ng/mL)	8.0	Study 103/104: 6.7	Study 302: 33.3

Source: reviewer's summary from bioanalytical study validation reports 12008, 14011, 12012, and 13005.

2.9.2 Which moiety of the product does the assay detect? Does the assay detect all forms of fusion protein, i.e., folded and mis-folded protein?

The TNFR moiety was detected during the assay. The assay detected both folded and mis-folded variants (due to wrongly bridged disulfide-bond).

Both the capture antibody and the detection antibody used in the ELISA method were raised against human TNFR p75. Therefore, it's the TNFR moiety of GP2015 and Enbrel that was detected in the assay. Four variants of the fusion protein resulted from wrongly formed disulfide-bond were detected in the drug substance. The reverse-phase chromatography detected the AUC of the major peak represented 89% of the total AUC, which was numerically higher than US-Enbrel (84%) and EU-Enbrel (82%), indicating the composition of mis-folded protein is higher in Enbrel than GP2015. In a response to FDA's Information Request dated on 12/04/2015, the Sponsor stated that
"The applied etanercept PK methods laid down in the two versions of SOP PV05102 follow the same assay principle capturing total levels of Enbrel and GP2015 identically including their wrongly bridged variants."

Based on the totality of the product composition, the potency (tier 1) of GP2015 is estimated to be 10% higher than US- and EU-Enbrel. For details, refer to primary review by Product Quality Reviewer Dr. Peter Adams. Combination of this potency difference and the PK profile comparison between GP2015 and US/EU-Enbrel, the clinical meaning is unclear.

2.9.3 For all moieties measured, is free, bound, or total measured?

The total amount of etanercept in a sample (irrespective of the status of bound TNF) was measured.

2.9.4 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?
The range of the standard curves and the limit of quantitation from Study 101, 102, 103, 104, and 302 were listed in Table 11. The coefficient of variance of precision was ≤ 20% (≤ 25% at LLOQ or ULOQ) for both methods (Table 2.15). The accuracy was within 80% to 120% (80% to 120% at LLOQ or ULOQ) for both methods. The samples were stable in room temperature for at least 4 hours. The samples could sustain at least five freeze/thaw cycles (except three-cycles for US-Enbrel QC3). The samples were stable at ⩽ -70 °C for at least 6 months. The samples were stable at ⩽ -20 °C for at least 6 months (except three months for US-Enbrel QC3).

Table 2.15 Summary of ELISA Validation Results of Bioanalytical Method SOP PV05102, Version 02 (BA 12008) and Version 03 (BA 14011, BA14020, and BA13005)

	BA12008	BA14011 BA14020	BA13005
Calibration range (ng/mL)	1.0 to 120.0	6.7 to 800.0	33.0 to 4000.0
Matrix QC Concentrations (ng/mL, Low, Mid, and High)	3.0, 22.5, and 90.0	20, 150, and 600	100, 750, 3000
Intra-assay Precision	4% - 13%	3% - 9%	3% - 7%
Inter-assay Precision	3% - 14%	4% - 15%	7% - 12%
Intra-assay Accuracy	84% - 105%	82% - 101%	94% - 105%
Inter-assay Accuracy	89% - 109%	97% - 105%	93% - 102%
Intra-assay Precision at LLOQ	6% - 22%	4% - 7%	3% - 5%
Inter-assay Precision at LLOQ	8% - 16%	10% - 12%	13%
Intra-assay Accuracy at LLOQ	75% - 94%	95% - 113%	100% - 105%
Inter-assay Accuracy at LLOQ	83% - 102%	99% - 107%	102% - 109%
Intra-assay Precision at ULOQ	4% - 12%	3% - 18%	11% - 12%
Inter-assay Precision at ULOQ	11% - 21%	17% - 22%	12% - 14%
Intra-assay Accuracy at ULOQ	78% - 102%	87% - 105%	90% - 105%
Inter-assay Accuracy at ULOQ	85% - 115%	101% - 105%	90% - 102%
Room Temperature Stability	4 hours	4 hours	20 hours
Freeze/thaw Stability	Up to five cycles[1]	five cycles	five cycles
Long Term Stability at ≤ -70 °C	6 months	6 months	13 months
Long Term Stability at ≤ -20 °C	Up to 6 months[2]	6 months	8 months

Assay BA12008 was used for Study 101/102; Assay BA14011 was used for Study 103; Assay 14020 was used for Study 104; Assay BA13005 was used for Study 302.
Precision (CV) acceptance criteria are ≤ 25% for LLOQ and ULOQ samples, and ≤ 20% for other samples.
Accuracy acceptance criteria are within 75 – 125% for LLOQ and ULOQ samples, and 80 – 120%for other samples.
[1] Except for US-Enbrel QC3, stable up to three freeze/thaw cycles.
[2] Except for US-Enbrel QC3, stable up to three months.
Source:
Section 2.7.1, Summary of Biopharmaceutical Studies and Associated Analytical Methods.pdf, Page 9-16, Table 1-6
Section 5.3.1.4, BA14011-R validation report, Page 14-17, Table 3-1
Section 5.3.1.4, BA13005-R validation report, Page 13-19, Table 3-1

2.9.5 What is the matrix selectivity of the Assay?

- SOP PV05102, Version 02 for Study 101/102 (BA12008-R)

After performance of the selectivity testing the results indicated an impact of the single sera on the detection of the fusion protein. Therefore it was decided to spike Etanercept at higher concentrations in 100 % serum and to include further dilution steps using 1:3 diluted human serum pool to eliminate the effect of the single sera. During the assay, the individual serum samples were diluted 1:3 in SD2 buffer and spiked with GP2015.01REF validation samples 1 (VS1, 30 ng/ml) and VS3 (1 ng/ml) or further diluted in 1:3 diluted human serum pool (additional dilution factors: 1:4 or 1:8) and spiked afterwards with the same concentration three times independently.

An additional 1:8 dilution of the single sera using 1:3 diluted human serum pool as diluent was sufficient to meet the acceptance criteria for 80% of 12 individual tested sera (precision CV ⩽ 25%, accuracy between 75% and 125%). Therefore, the minimal dilution for serum samples analysis is 1:3 in SD2 buffer followed by a 1:8 dilution in 1:3 diluted human serum pool. Taking this additional dilution into account, the LLOQ of this assay is 8 ng/ml.

- SOP PV05102, Version 03 for Study 103 and 104 (BA14011-R, BA 14020-R)

The potential matrix-related interferences were evaluated using 10 individual human serum samples of healthy volunteers. Pre-dilution GP2015 VS (GP2015-S0014) was diluted 1:20 in blocking buffer to 600 ng/mL VS1 and the LLOQ-VS was prepared by a further dilution step to 6.7 ng/mL. The samples were analyzed in duplicate against a calibration curve prepared in 1:20 diluted human serum pool healthy volunteers on one day. 100% of sera met the acceptance criteria for precision [⩽ 20% (CV ⩽ 25% at LLOQ)] and 90% of the individual sera met the acceptance criteria for accuracy [between 80% and 120% (between 75% and 125% at LLOQ)].

- SOP PV05102, Version 03 for Study 302 (BA13005-R)

The potential matrix-related interferences were evaluated using 10 individual human sera of patients with psoriasis. The 1:100 diluted individual serum samples were spiked with the test items at two concentrations (VS1 = 3,000 ng/ml and LLOQ = 33 ng/ml in 100% serum) of the test items three times independently and were analyzed in duplicate against a calibration curve prepared in 1:100 diluted (b) (4) human serum pool on one day. For GP2015, 80% of the individual sera met the acceptance criteria. For EU-Enbrel, 100% of the individual sera met the acceptance criteria [precision⩽ 20% (CV ⩽ 25% at LLOQ), accuracy between 80% and 120% (between 75% and 125% at LLOQ)].

2.9.6 What is the dilution integrity of the Assay?

- SOP PV05102, Version 02 for Study 101/102 (BA-12008-R)

A dilution series in 1:3 diluted human serum pool starting from a GP2015.01REF concentration of 3000 ng/ml in 100 % human serum pool was prepared. For analysis, the samples were diluted 1:3 in SD2 buffer. Final concentrations of GP2015.01REF (30 ng/mL, 15 ng/mL, 7.5 ng/mL, and 3.75 ng/mL, or 100×, 200×, 400×, and 800× from 3000 ng/mL, respectively) were diluted in 1:3 diluted human serum pool before analysis. Each dilution series was prepared three times. The precision CV ranged 2% – 7%; and the accuracy ranged 81% – 97% for all the diluted concentrations. The results meet the acceptance criteria (precision CV ⩽ 20%, accuracy between 80% and 120%).

- SOP PV05102, Version 03 for Study 103 and 104 (BA14011-R, BA 14020-R)

Reference item GP2015.02REF in 1:20 diluted human serum pool HV was prepared starting from an concentration of 4000 ng/ml. Final concentrations of GP2015.02REF (2000 ng/mL, 400 ng/mL, 200 ng/mL, 100 ng/mL, and 50 ng/mL, or 2×, 10×, 20×, 40×, and 80× from 4000 ng/mL, respectively) were diluted in 1:20 diluted human serum pool. The precision CV ranged 4% – 14%; and the accuracy ranged 80% – 100% for all the diluted concentrations. The results meet the acceptance criteria (precision CV ≤ 20%, accuracy between 80% and 120%).

- SOP PV05102, Version 03 for Study 302 (BA13005-R)

To test the impact of the dilution medium, a dilution series of the test item no. 1 (GP2015) and no. 2 (EU-Enbrel) in 1:100 diluted (b) (4) serum pool was prepared starting with a concentration of 200 ng/ml in 1:100 diluted psoriatic serum pool. The following dilution series, prepared in 1:100 diluted (b) (4) serum pool was analyzed:
100 ng/ml (2×, test of prozone effect), 20 ng/ml (10×,), 10 ng/ml (20×), 5 ng/ml (40×), and 2.5 ng/ml (80×)

The precision CV ranged 3% – 8%; and the accuracy ranged 80% – 82% for all the diluted concentrations beyond 10×. The results meet the acceptance criteria (precision CV ≤ 20%, accuracy between 80% and 120%).

2.9.7 What bioanalytical methods are used to assess the anti-drug antibodies?

Two versions of bioanalytical methods were used to assess the immunogenicity. Version 1 was used in Studies 101, 102, 103, and 104 for assessing immunogenicity in healthy subjects. Version 2 was used in Study 302 for assessing immunogenicity in patient with PsO. The immune response was evaluated by a three-step procedure comprising a validated screening and confirmatory ECL and a validated neutralization antibody assay. The used positive control was a polyclonal rabbit anti-etanercept antibody generated by hyperimmunization using GP2015. In addition, a commercial available monoclonal neutralizing anti-etanercept antibody was used within the validation of the neutralizing antibody assay.

- Screening ECL assay

Serum samples were screened for antibodies capable of binding GP2015/Enbrel in a screening ECL assay. First, complexes of ADA and GP2015/Enbrel in the serum were dissociated by an acid treatment. In a subsequent step ADAs were bound to a plate pre-coated with GP2015/Enbrel. After over-night incubation, residual GP2015/Enbrel was removed by a washing step. Afterwards the ADAs were dissociated from the plate by a second acid treatment. Neutralization was carried out in the presence of two differently labeled etanercept molecules (biotin or sulfotag labelled). Consequently, the ADA established a bridge between the two labeled the immune complex biotin-etanercept-ADA – sulfotag-etanercept was bound to a streptavidin plate. The readout was then achieved by an ECL reaction and was measured with the respective device (Sector imager from MSD).

- Confirmatory ECL assay (Specific of the binding)

Samples with assay signal binding results above the calculated cut-point in the screening assay were reanalyzed in a confirmatory ECL assay. After the second acid treatment, serum samples would have been neutralized in the presence of both solid-phase and high concentrations of soluble drug (GP2015.02REF, 10 µg/ml) and analyzed together with unspiked samples. Specific ADAs would have bound to the soluble drug and would have led to a reduction in the assay read-out (counts) compared to the unspiked samples. Specificity of the binding was confirmed if the reduction of the obtained signal was above the specificity/confirmatory cut-point when unlabeled GP2015 was added to serum.

The differences between two versions of ADA bioanalytical methods are listed in Table 2.16. The major difference is the different cut-offs applied in two versions.

Table 2.16 Comparison of Two Versions of Bioanalytical Methods for Immunogenicity Assessment

		Version 1	Version 2
Applied Clinical Studies		Studies 101, 102, 103, and 104	Study 302
Screening Assay	**Labeling Antibody**	Biotin GP2015 and Sulfo-GP2015 from Hexal AG	
	Quantification range of the calibration curve (µg/mL)	0.1 to 20	0.15 to 24
	LLOQ (µg/mL)	0.2	0.15
	Quality Control (µg/mL)	0.6, 2.4, 15	0.9, 2.7, 18
	Cut-point	Blank + 86 counts	Blank + 12.8 counts
Confirmatory Assay	**Inhibition signal cut-point**	18%	23%

Source: reviewer's summary from bioanalytical study validation reports 12017, 12025, 14017, 14021, and 14001.

2.9.8 What bioanalytical methods are used to assess the neutralizing antibodies?

The coefficient of variance of precision was ≤ 20% (≤ 25% at LLOQ or ULOQ) for both methods (Table 2.17). The accuracy was within 80% to 120% (80% to 120% at LLOQ or ULOQ) for both methods. The samples were stable in room temperature for 4 hours and 22.5 hours for version 1 and 2, respectively. The samples could sustain up to five freeze/thaw cycles for both versions. The samples were stable at 2 - 8 °C for 1-3 days. The samples were stable at ⩽ -70 °C for up to 6 months and 12 months for version 1 and 2, respectively.

Table 2.17 Performance of Two Versions of ADA Assays

	Version 1	Version 2
Applied Clinical Studies	Studies 101, 102, 103, and 104	Study 302
Quantification range of the calibration curve (µg/mL)	0.1 to 20	0.15 to 24
Intra-assay Precision	3% - 6%	3% - 7%
Inter-assay Precision	2% - 6%	4% - 7%
Intra-assay Accuracy	94% - 114%	87% - 101%
Inter-assay Accuracy	88% - 104%	92% - 103%
Intra-assay Precision at LLOQ	12%	8%
Inter-assay Precision at LLOQ	11%	8%
Intra-assay Accuracy at LLOQ	123%	125%
Inter-assay Accuracy at LLOQ	102%	110%
Intra-assay Precision at ULOQ	2%	7%
Inter-assay Precision at ULOQ	4%	6%
Intra-assay Accuracy at ULOQ	90%	91%
Inter-assay Accuracy at ULOQ	97%	99%
Limit of Detection (ng/mL)	21	116.5
Room Temperature Stability	4 hours	22.5 hours
2 - 8 °C Stability	3 days	1-3 days
Freeze/thaw Stability	5 cycles	Up to 5 cycles
Long Term Stability at ≤ -70 °C	Up to 6 months	Up to 12 months

Source: reviewer's summary from section 2.7.1, page 37-38, Table 1-14 and page 43-45, Table 1-17

2.9.9 What is the performance of the neutralizing assay?

Samples positive for binding ADAs in the confirmatory ECL assay (only available from Study 302) were further evaluated for neutralizing antibodies in a competitive ligand binding assay. The first step was an acid treatment of serum samples in order to dissociate complexes of ADAs and GP2015/Enbrel. In the subsequent neutralization step, free ADAs were bound to immobilized GP2015 and concomitantly, excess of drug remaining in the supernatant was washed away. After a second acid treatment ADAs were removed from immobilized GP2015. Afterwards, the ADAs were neutralized and incubated with GP2015. Afterwards, this solution was transferred to a TNF coated plate (Peprotech 300-01A). Neutralizing ADAs formed a complex with GP2015 and therefore the binding of GP2015 to TNF was inhibited. In this case, ADAs were characterized as neutralizing antibodies. The detection of GP2015 was done by a biotinylated goat antihuman TNFR2 antibody (R & D Systems BAF726). The goat antibody was further bound by streptavidin-HRP (Invitrogen SNN4004), which catalyzed chromogen for color change. The optical density was measured at 450 nm/620 nm using a microplate reader. The cut-point for neutralization

antibody positivity was 20% reduction of the optic density signal. The rabbit anti-etanercept polyclonal antibody (BioGenes 140809-05) was used as a positive control in the neutralizing assay.

The range of the calibration curve was 500.0 ng/mL – 10000.0 ng/mL. The sera from psoriasis patients were all diluted 1:3 before the analysis. The coefficient of variance of precision was ≤ 20% (Table 2.18). The accuracy was within 80% to 120%. The LLOQ and ULOQ were not determined as the method is not used for the quantification of the neutralizing anti-etanercept antibodies. For the stability of the test samples, refer to section 2.9.8.

Table 2.18 Validation Summary of Neutralizing Antibody Assays

Validation Parameter	Validation Results
Selectivity/Specificity	80% of sera spiked with LPC[1] resulted in inhibition of 32 – 54%
Intra-assay Precision	2% - 9%
Inter-assay Precision	13% - 15%
Intra-assay Accuracy	83% - 92%
Inter-assay Accuracy	89% - 94%
Cut-point	≥ 20% Inhibition[2]

[1] LPC: low positive control (1852.7 ng/mL)
[2] Interpolated as 935.4 ng/mL
Source: reviewer's summary from section 2.7.1, page 51, Table 1-20

3. Detailed Labeling Recommendations

None

Appendix

4.1 Appendix – Individual Study Review

4.1.1 Study 101

Study Type: single dose, crossover, PK comparison study in healthy adults
Study Dates: 11/21/2011 – 04/20/2012
Study Center: Covance Clinical Research Unit Ltd., Leeds, United Kingdom
Drug Products Batch: GP2015 (batch no. 2G27062011) and EU-Enbrel (batch no. E88057)

Title:
A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel® (EU-licensed) following a single subcutaneous injection in healthy subjects

Objective:

- The primary objective was to determine bioequivalence between GP2015 and EU-Enbrel in terms of the PK parameters $AUC_{0\text{-}tlast}$ and C_{max} following a single subcutaneous injection of 50 mg.

- The secondary objectives were to further compare GP2015 and EU-Enbrel with respect to the following criteria:
  - Remaining PK parameters ($AUC_{0\text{-}\infty}$, t_{max}, k_{el}, and $t_{½}$)
  - Immunogenicity of both products
  - Overall safety and local tolerance.

Study Design and Method:
This study was a single center, randomized, double-blind, single-dose, two-way cross-over study with two treatment periods to evaluate the PK and the safety profile of GP2015 and EU-Enbrel in 54 healthy male and female adults. Subjects were randomly assigned in a 1:1 ratio to one of the following treatment sequences:

- 50 mg GP2015 in Period I and 50 mg EU-Enbrel in Period II
- 50 mg EU-Enbrel in Period I and 50 mg GP2015 in Period II

The wash-out period between two dose administrations was at least 35 days.

Noteworthy inclusion criteria included:

- Male or female subjects aged 18 to 49 years inclusive.
- Body weight between 50 to 99.9 kg and body mass index (BMI) between 19.0 to 29.9 kg/m^2 inclusively.

Noteworthy exclusion criteria included:

- Any exposure to any recombinant human anti-TNFα inhibitor in the past.
- Abnormal vital signs or abnormal 12-lead ECG results, e.g. long QT syndrome or a QT interval corrected using Bazett's formula (QTcB) > 450 msec for males and > 470 msec for females at screening, that are judged by the Investigator to be clinically significant as confirmed by two repeat measurements.
- Use of any prescription medication or over-the-counter medicines that might have an effect on the objectives of the study, within 14 days prior to dosing. Hormonal contraceptives, hormonal

replacement therapy, vitamins, minerals and nutritional supplements may be taken at the discretion of the Investigator.

Blood samples (3.5 mL) for PK evaluation were collected from a forearm vein (direct venipuncture or from an indwelling cannula) into a serum tube at each time point (predose and 6, 12, 24, 36, 48, 60, 72, 84, 96, 120, 168, 216, 264, 336, and 432 hours postdose in each period).

In total 1682 serum samples from clinical Study 101 were analyzed by ELISA to determine the concentration of GP2015/EU-Enbrel in human serum. The samples were stored until analysis at -70 °C. Considering the results of the corresponding validation study BA12008, all study samples were analyzed in a minimal dilution of 1:3 (diluent: SD2 buffer) and in addition in a minimum of 1:8 (prepared in 1:3 diluted human serum pool or in a higher dilution, if appropriate). All samples were measured against a calibration curve of the reference item prepared in 1:3 diluted human serum pool (diluent: SD2 buffer). All samples were analyzed in duplicate. For details of ELISA bioanalytical method, refer to section 2.5.

The PK parameters were determined in serum using non-compartmental methods. All BLQ values in the absorption phase, prior to the first quantifiable concentration, as well as BLQ values between evaluable concentrations were substituted by the half value of LLOQ. The terminal BLQ values were treated as missing for the PK evaluation and as ½ LLOQ for descriptive statistics purposes. ANOVA was performed on the log-transformed PK parameters $AUC_{0\text{-tlast}}$ and C_{max} separately. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The power of enrolling 54 subjects (including 10% dropout rate) to demonstrate PK similarity 90% CI boundary within 80% to 125% was estimated to be 90%.

Blood samples for detecting ADA were collected at pre-dose (Day1) and at follow-up visit (Day 29).

Criteria for evaluation:

- PK: GP2015/EU-Enbrel serum concentrations, and the following associated parameters were, where possible, determined for each subject: $AUC_{0\text{-tlast}}$, C_{max}, $AUC_{0\text{-}\infty}$, $\%AUC_{extrap}$, t_{max}, k_{el}, $t_{½}$, and CL/F.
- Safety: Adverse events, clinical laboratory evaluations, ECG, vital signs, physical examination, assessment of local tolerance (injection site reaction scores and visual analogue scales for pain), and immunogenicity.

Results:

- PK
  - Analyzed dataset

    The PK analyses were based on the per-protocol analysis set population. This included the 50 subjects who completed the study without major protocol violation. Subjects 3, 9, and 37 withdrew from the study, and thus were excluded from the per-protocol population. Subject 30 was excluded from the per-protocol population due to a major protocol violation in Period II. The calculated dose for this subject in Period II (when taking GP2015) was 67.2 mg which was technically impossible as this corresponded to a volume which was greater than the dosing syringe. Subject 43 was excluded from the PK summary statistics and statistical analysis (with the exception of C_{max} and t_{max}) because two samples for this subject in Period II (when taking EU-Enbrel) were labelled 336 hours and, as a result, there was no PK blood sample for this subject at the 432 hours postdose time point. It could not be confirmed to which time point the samples belonged and the subject was consequently excluded from the analysis of AUCs.

Carryover concentrations from Period I, defined as predose serum concentrations greater than the LLOQ (>8 ng/mL) at Period II, were noted in the pre-dose samples for 12 subjects: 8 subjects with carryover from GP2015 and 4 subjects with carryover from EU-Enbrel. Since the positive pre-dose concentrations were less than 5% (with the exception of Subject 3 who was excluded from the per-protocol population) of their respective C_{max}, their pre-dose concentrations in Period II were set as 0 during the analysis.

- Demographic characteristics

All subjects satisfied the inclusion and exclusion criteria prior to entry into the study (Table 4.1).

Table 4.1 Demographic Summary by Study Sequence in Study 101

		Sequence AB N=27	Sequence BA N=27	Overall N=54
Age (years)	Mean	38	37	38
	SD	9.6	9.8	9.6
	Median	39	40	40
	Range	21 – 49	19 – 49	19 – 49
Gender – n (%)	Male	16 (59%)	17 (63%)	33 (61%)
	Female	11 (41%)	10 (37%)	21 (39%)
Race – n (%)	Asian	1 (3.7%)	2 (7.4%)	3 (5.6%)
	Black	1 (3.7%)	0 (0%)	1 (1.9%)
	White	24 (88.9%)	25 (92.6%)	49 (90.7%)
	Other	1 (3.7%)	0 (0%)	1 (1.9%)
BMI (kg/m^2)	Mean	25	26	25
	SD	2.46	3.08	2.78
	Median	24.7	26.0	25.2
	Range	20.4 – 28.9	20.0 – 29.6	20.0 – 29.6

Treatment A: 50 mg GP2015; Treatment B: 50 mg EU-Enbrel
Source: CSR 101, Page 32, Table 11-1

- PK results

The arithmetic mean PK profiles of GP2015 and EU-Enbrel following 50 mg single dose subcutaneous injection are presented in Figure 4.1.

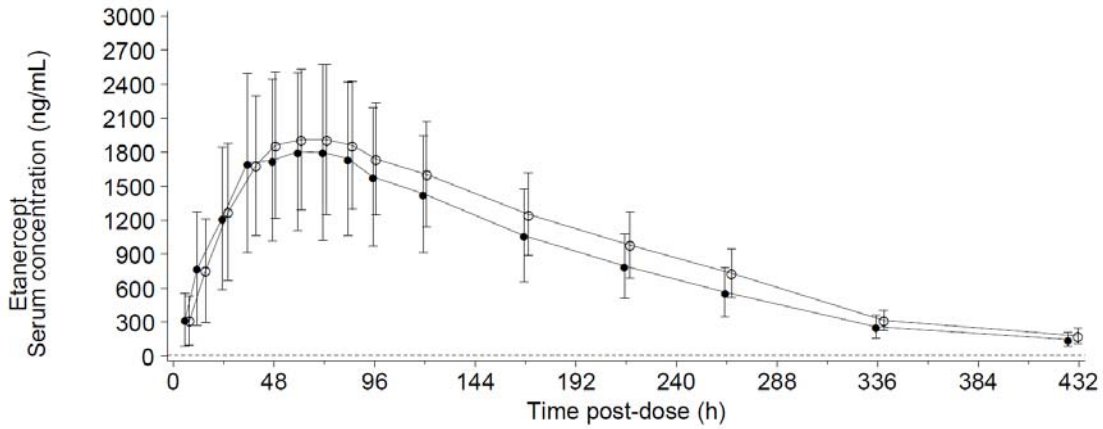

Figure 4.1 EU-Enbrel (circle, N=49) and GP2015 (dot, N=49) arithmetic serum concentration-time profile from Study 101. The error bars represent SD. Source: CSR101, page 34, Figure 11-1.

Following single dose of 50 mg subcutaneous injection, serum drug product concentrations increased slowly with maximum concentrations occurring at median t_{max} values of 60.0 and 72.0 hours for GP2015 and EU-Enbrel, respectively. Thereafter, drug product concentrations declined a mean rate of 141 mL/h and 123 mL/h for GP2015 and EU-Enbrel, respectively. Mean $t_{1/2}$ values were 86 and 84 hours for GP2015 and EU-Enbrel, respectively (Table 4.2).

Table 4.2 Summary of PK Parameters of GP2015 and EU-Enbrel in Study 101 (Per-Protocol Set)

		50 mg GP2015 N=50	50 mg Enbrel® N=50
	N	Geometric mean (CV%)	
$AUC_{0\text{-tlast}}$ (ng.h/mL)	49	331680 (43.1)[a]	388725 (30.0)[a]
$AUC_{0\text{-tlast}}$ (ng.h/mL)[b]	49	336759 (43.2)[a]	383984 (30.1)[a]
$AUC_{0\text{-}\infty}$ (ng.h/mL)	49	349383 (42.7)[a]	411692 (29.1)[a]
C_{max} (ng./mL)	50	1802 (49.3)	1980 (35.8)
C_{max} (ng./mL) (norm)[b]	50	1829 (49.3)	1955 (35.7)
$t_{1/2}$ (h)	49	85.9 (11.6)	84.4 (21.4)
k_{el} (h^{-1})	49	0.008 (11.6)	0.008 (21.4)
CL/F (mL/h)	49	143 (42.7)	121 (29.1)
CL/F (mL/h) (norm)[b]	49	141 (42.7)	123 (29.2)
		Arithmetic mean (SD)	
$\%AUC_{extrap}$ (%)	49	5.05 (1.63)[a]	5.55 (2.44)[a]
		Median (min – max)	
t_{max} (h)	50	60.0 (36.0 - 120)	72.0 (24.1 – 120)

N = Number of subjects studied; (norm) = normalized for actual dose administered.
[a] N = 49; Subject 43 was excluded as AUC values could not be calculated in Period II.
[b] Parameter calculated based on actual dose received.

Source: CSR 101, Page 35, Table 11-3

The primary statistical analysis comparing the PK parameters between GP2015 and EU-Enbrel are presented in Table 4.3. The estimated ratio (GP2015/EU-Enbrel) of $AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$, and C_{max} is 0.8540 (90% CI = 0.7835, 0.9039), 0.8494 (90% CI = 0.7815, 0.9233), and 0.9124 (90% CI = 0.8247, 1.0094), respectively.

Table 4.3 Statistical Analysis of the PK Parameters of GP2015/EU-Enbrel in Study 101 (Per-Protocol Set)

		Geometric LS mean		Ratio of geometric LS mean	Within
	N	50 mg GP2015	50 mg Enbrel®	GP2015 : Enbrel® (90% CI)	subject CV%
$AUC_{0\text{-tlast}}$ (ng.h/mL)	49	331961	388708	0.8540 (0.7835, 0.9309)	25.84
C_{max} (ng./mL)	50	1808	1982	0.9124 (0.8247, 1.0094)	30.80
$AUC_{0\text{-}\infty}$ (ng.h/mL)	49	349647	411634	0.8494 (0.7815, 0.9233)	24.97

Source: CSR 101, Page 36, Table 11-4

- Safety

The safety analyses were based on the safety set population which included all 54 subjects who were dosed at least once with study medication. Among 54 subjects, 51 subjects received a second dose.

There were no deaths reported during the study. Two subjects were withdrawn from the study due to AEs; one subject (Subject 3) due to neutropenia following administration of GP2015 which was considered to be possibly related to study drug, and one subject (Subject 9) due to body tinea following administration of EU-Enbrel which was also considered to be possibly related to study drug.

During the course of this study, 145 treatment-emergent AEs were reported by 48 (88.9%) subjects, of which, 70 were reported by 31 (58.5%) subjects following administration of 50 mg GP2015, and 75 were reported by 35 (66.0%) of subjects following treatment with EU-Enbrel (Table 4.4). One severe AE was reported during the study, though it was not considered to have a suspected relationship to study drug. Subject 42 experienced an episode of vasovagal syncope in Period I 2 minutes after receiving 50 mg GP2015 and was treated with 0.9% intravenous saline solution (750 mL); the AE resolved after 14 minutes.

Table 4.4 Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	50 mg GP2015 (N=53) Subjects	Adverse Events	50 mg Enbrel® (N=53) Subjects	Adverse Events
Total number	31 (58.5%)	70	35 (66.0%)	75
Relation to IMP				
Unsuspected	13 (24.5%)	22	22 (41.5%)	28
Suspected	26 (49.1%)	48	29 (54.7%)	47
Intensity				
Mild	29 (54.7%)	62	30 (56.6%)	59
Moderate	6 (11.3%)	7	12 (22.6%)	16
Severe	1 (1.9%)	1	-	-

Source: CSR 101, Page 39, Table 12-1

The overall incidence of AEs and AEs by primary system organ class was generally comparable between GP2015 and EU-Enbrel treatment groups (Table 4.5). The most commonly affected system organ classes were infections and infestations (primarily nasopharyngitis).

Table 4.5 Incidence of Adverse Events by Primary System Organ Class (Safety Analysis Set)

	50 mg GP2015 N=53 n (%)	50 mg Enbrel® N=53 n (%)
Subjects with at least one adverse event	31 (58.5%)	35 (66.0%)
Primary system organ class		
Infections & infestations	11 (20.8%)	14 (26.4%)
Nervous system disorders	6 (11.3%)	11 (20.8%)
General disorders & administration site conditions	8 (15.1%)	8 (15.1%)
Respiratory, thoracic & mediastinal disorders	9 (17.0%)	7 (13.2%)
Musculoskeletal & connective tissue disorders	4 (7.5%)	8 (15.1%)
Gastrointestinal disorders	8 (15.1%)	3 (5.7%)
Skin & subcutaneous tissue disorders	2 (3.8%)	6 (11.3%)
Blood & lymphatic system disorders	4 (7.5%)	4 (7.5%)
Investigations	2 (3.8%)	2 (3.8%)
Injury, poisoning and procedural complications	1 (1.9%)	3 (5.7%)
Psychiatric disorders	2 (3.8%)	1 (1.9%)
Reproductive system & breast disorders	2 (3.8%)	0 (0%)
Metabolism & nutrition disorders	1 (1.9%)	0 (0%)

Source: CSR 101, Page 40, Table 12-2

There were no clinically important findings in the morphology of the 12-lead ECGs, heart rate or ECG intervals for individual subjects following dosing with 50 mg GP2015 or EU-Enbrel.

The anti-drug antibody results were negative prior to the first dose, prior to the second dose and at the follow-up visit (28 days after the last dose) for all individual subjects.

Conclusions:

- The PK similarity was not established between GP2015 and EU-Enbrel in Study 101 as the lower boundary of 90% CI of the ratios (GP2015/EU-Enbrel) of AUC_{0-t} (0.7835) and AUC_{0-inf} (0.7815) are lower than the goal post 80% - 125%.
- There was no evidence of anti-drug antibody production against GP2015 or EU-Enbrel.
- The safety profiles are comparable between GP2015 and EU-Enbrel.

Reviewer's Analysis:

Reviewer's independent analysis showed similar results, which are in agreement with the Sponsor's analysis: the lower boundary of 90% CI of the ratio (GP2015/EU-Enbrel) of AUC_{0-t} (0.7830) and AUC_{0-inf} (0.7803) are lower than the goal post 80% - 125% (Table 4.6).

Table 4.6 Comparison of PK Parameters of GP2015/EU-Enbrel in Study 101 (Per-Protocol Set)

Parameter	N	GP2015	EU-Enbrel	Ratio (GP2015/EU-Enbrel)[3]
AUC_{0-t} (µg·h/mL)[1]	49	335.150	392.619	0.8536 (0.7830, 0.9307)
AUC_{0-inf} (µg·h/mL)[1]	49	353.338	416.506	0.8583 (0.7803, 0.9223)
C_{max} (µg/mL)[1]	50	1.808	1.982	0.9124 (0.8247, 1.0094)
T_{max} (hour)[2]	50	60 (36-120)	72 (24-120)	-

[1] Least-squares geometric means
[2] Median (range)
[3] Ratio (90% CI)
Source: Reviewer's analysis, the ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect.

The geometric mean PK profiles of GP2015 and US-Enbrel following 50 mg single dose subcutaneous injection are presented in Figure 4.2.

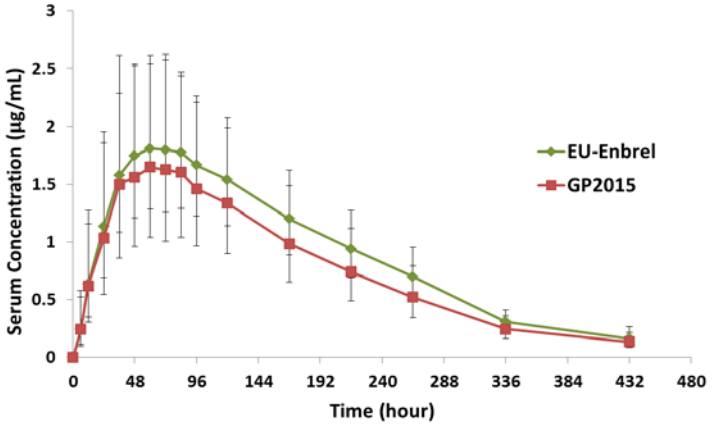

Figure 4.2 EU-Enbrel (green, N=50) and GP2015 (red, N=50) geometric serum concentration-time profile from Study 101. The error bars represent SD. Source: Reviewer's analysis.

4.1.2 Study 102

Study Type: single dose, crossover, PK comparison study in healthy males
Study Dates: 02/28/2012 – 08/23/2012
Study Center: Covance Clinical Research Unit Ltd., Leeds, United Kingdom
Drug Products Batch: GP2015 (batch no. 2G27062011) and US-Enbrel (batch no. 1026663)

Title:
A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel® (US-licensed) following a single subcutaneous injection in healthy subjects

Objective:

- The primary objective was to determine bioequivalence between GP2015 and US-Enbrel in terms of the PK parameters $AUC_{0\text{-}tlast}$ and C_{max} following a single subcutaneous injection of 50 mg.

- The secondary objectives were to further compare GP2015 and US-Enbrel with respect to the following criteria:
  - Remaining PK parameters ($AUC_{0\text{-}\infty}$, t_{max}, k_{el}, and $t_{½}$)
  - Immunogenicity of both products
  - Overall safety and local tolerance.

Study Design and Method:
This study was a single center, randomized, double-blind, single-dose, two-way cross-over study with two treatment periods to evaluate the PK and the safety profile of GP2015 and US-Enbrel in 57 healthy male and female adults. Subjects were randomly assigned in a 1:1 ratio to one of the following treatment sequences:

- 50 mg GP2015 in Period I and 50 mg US-Enbrel in Period II
- 50 mg US-Enbrel in Period I and 50 mg GP2015 in Period II

The wash-out period between two dose administrations was at least 35 days.

Noteworthy inclusion criteria included:

- Male or female subjects aged 18 to 49 years inclusive.
- Body weight between 50 to 99.9 kg and body mass index (BMI) between 19.0 to 29.9 kg/m^2 inclusively.

Noteworthy exclusion criteria included:

- Any exposure to any recombinant human anti-TNFα inhibitor in the past.
- Abnormal vital signs or abnormal 12-lead ECG results, e.g. long QT syndrome or a QT interval corrected using Bazett's formula (QTcB) > 450 msec for males and > 470 msec for females at screening, that are judged by the Investigator to be clinically significant as confirmed by two repeat measurements.
- Use of any prescription medication or over-the-counter medicines that might have an effect on the objectives of the study, within 14 days prior to dosing. Hormonal contraceptives, hormonal replacement therapy, vitamins, minerals and nutritional supplements may be taken at the discretion of the Investigator.

Blood samples (3.5 mL) for PK evaluation were collected from a forearm vein (direct venipuncture or

from an indwelling cannula) into a serum tube at each time point (predose and 6, 12, 24, 36, 48, 60, 72, 84, 96, 120, 168, 216, 264, 336, and 432 hours postdose in each period).

In total 1774 serum samples from clinical Study 102 were analyzed by ELISA to determine the concentration of GP2015/US-Enbrel in human serum. The samples were stored until analysis at -70 °C. Considering the results of the corresponding validation study BA12008, all study samples were analyzed in a minimal dilution of 1:3 (diluent: SD2 buffer) and in addition in a minimum of 1:8 (prepared in 1:3 diluted human serum pool or in a higher dilution, if appropriate). All samples were measured against a calibration curve of the reference item prepared in 1:3 diluted human serum pool (diluent: SD2 buffer). All samples were analyzed in duplicate. For details of ELISA bioanalytical method, refer to section 2.5.

The PK parameters were determined in serum using non-compartmental methods. All BLQ values in the absorption phase, prior to the first quantifiable concentration, as well as BLQ values between evaluable concentrations were substituted by the half value of LLOQ. The terminal BLQ values were treated as missing for the PK evaluation and as ½ LLOQ for descriptive statistics purposes. ANOVA was performed on the log-transformed PK parameters $AUC_{0\text{-tlast}}$ and C_{max} separately. The ANOVA model included sequence, treatment, operator (person who performed the dosing), and period as fixed effects, and subject nested within sequence as a random effect. The power of enrolling 54 subjects (including 10% dropout rate) to demonstrate PK similarity 90% CI boundary within 80% to 125% was estimated to be 90%.

Blood samples for detecting ADA were collected at pre-dose (Day1) and at follow-up visit (Day 29).

Criteria for evaluation:

- PK: GP2015/US-Enbrel serum concentrations, and the following associated parameters were, where possible, determined for each subject: $AUC_{0\text{-tlast}}$, C_{max}, $AUC_{0\text{-}\infty}$, $\%AUC_{extrap}$, t_{max}, k_{el}, $t_{½}$, and CL/F.
- Safety: Adverse events, clinical laboratory evaluations, ECG, vital signs, physical examination, assessment of local tolerance (injection site reaction scores and visual analogue scales for pain), and immunogenicity.

Results:

- PK
  - Analyzed dataset

    The PK analyses were based on the per-protocol analysis set population. 57 subjects (including 3 replacement subjects) were enrolled and 54 subjects completed the study. Three subjects (Subject 13, 30, 43) were withdrawn from the study after completing one treatment period and before dosing in the second period. Subject 16 was excluded from the PK summary statistics and statistical analysis of $AUC_{0\text{-t}}$ because the sample taken at 432 hours postdose in Period II was not analyzed.

    Carryover concentrations from Period I, defined as predose serum concentrations greater than the LLOQ (>8 ng/mL) at Period II, were noted in the pre-dose samples for 22 subjects: 14 subjects with carryover from GP2015 and 8 subjects with carryover from US-Enbrel. Since the positive pre-dose concentrations were less than 2% of their respective C_{max}, their pre-dose concentrations in Period II were set as 0 during the analysis.

  - Demographic characteristics

    All subjects satisfied the inclusion and exclusion criteria prior to entry into the study (Table 4.7).

Table 4.7 Demographic Summary by Study Sequence in Study 102

		Sequence AB N=28	Sequence BA N=29	Overall N=57
Age (years)	Mean	31	29	30
	SD	9.7	8.8	9.3
	Median	32	25	28
	Range	19 – 48	18 – 49	18 – 49
Gender – n (%)	Male	21 (75%)	21 (72%)	42 (74%)
	Female	7 (25%)	8 (28%)	15 (26%)
Race – n (%)	Asian		2 (6.9%)	2 (3.5%)
	Black	1 (3.6%)	1 (3.4%)	2 (3.5%)
	White	27 (96.4%)	24 (82.8%)	51 (89.5%)
	Other		2 (6.9%)	2 (3.5%)
BMI (kg/m^2)	Mean	25	25	25
	SD	2.93	2.91	2.89
	Median	25	24.6	24.7
	Range	19.4 – 29.7	19.6 – 28.8	19.4 – 29.7

Treatment A: 50 mg GP2015; Treatment B: 50 mg US-Enbrel
Source: CSR 102, Page 31, Table 11-1

- PK results

The arithmetic mean PK profiles of GP2015 and US-Enbrel following 50 mg single dose subcutaneous injection are presented in Figure 4.3.

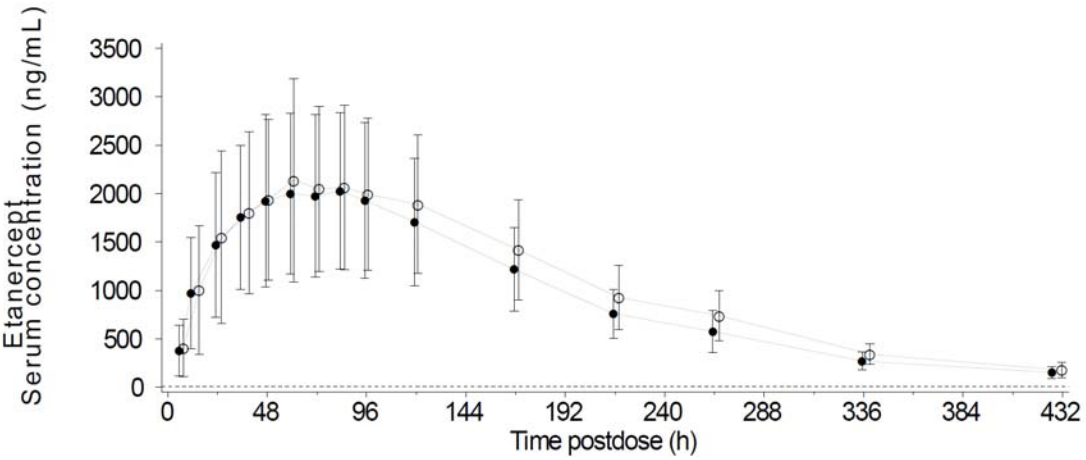

Figure 4.3 US-Enbrel (circle, N=53) and GP2015 (dot, N=53) serum concentration-time profile from Study 102. Source: CSR102, page 33, Figure 11-1.

Following single dose of 50 mg subcutaneous injection, serum drug product concentrations increased slowly with maximum concentrations occurring at median t_{max} values of 72.0 and 84.0 hours for GP2015 and US-Enbrel, respectively. Thereafter, drug product concentrations declined a mean rate of 129 mL/h and 115 mL/h for GP2015 and US-Enbrel, respectively. Mean $t_{1/2}$ values were 89 and 87 hours for GP2015 and US-Enbrel, respectively (Table 4.8).

Table 4.8 Summary of PK Parameters of GP2015 and US-Enbrel in Study 102 (Per-Protocol Set)

		50 mg GP2015 N=54	50 mg Enbrel® N=54
	N	Geometric mean (CV%)	
$AUC_{0\text{-tlast}}$ (ng.h/mL)	53[a]	365745 (44.5)	410523 (42.7)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	54	386486 (43.7)	435143 (40.6)
C_{max} (ng/mL)	54	2028 (50.5)	2146 (51.5)
$t_{1/2}$ (h)	54	88.6 (13.7)	86.8 (21.7)
k_{el} (h^{-1})	54	0.00782 (13.7)	0.00798 (21.7)
CL/F (mL/h)	54	129 (43.7)	115 (40.6)
CL/F (mL/h)[b]	54	129 (43.7)	115 (40.3)
		Arithmetic mean (SD)	
$\%AUC_{extrap}$ (%)	54	4.95 (1.91)	5.42 (2.80)
		Median (min – max)	
t_{max} (h)	54	72.0 (24.0 – 120)	84.0 (24.0 – 120)

N = Number of subjects studied.
[a] Subject 016 was excluded because $AUC_{0\text{-tlast}}$ value could not be reliably calculated for Period II
[b] Parameter calculated based on the actual dose received.
Source: CSR 102, Page 34, Table 11-3

The primary statistical analysis comparing the PK parameters between GP2015 and US-Enbrel are presented in Table 4.9. The estimated ratio (GP2015/US-Enbrel) of $AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$, and C_{max} is0.8985 (90% CI = 0.8422, 0.9586), 0.8924 (90% CI = 0.8401, 0.9481), and 0.9500 (90% CI = 0.8797, 1.0260), respectively.

Table 4.9 Statistical Analysis of the PK Parameters of GP2015/US-Enbrel in Study 102 (Per-Protocol Set)

		Geometric LS mean		Ratio of geometric LS mean GP2015 : Enbrel® (90% CI)	Within subject CV%
	N	50 mg GP2015	50 mg Enbrel®		
$AUC_{0\text{-tlast}}$ (ng.h/mL)	53	376279	418797	0.8985 (0.8422, 0.9586)	19.88
C_{max} (ng/mL)	54	2055	2163	0.9500 (0.8797, 1.0260)	23.97
$AUC_{0\text{-}\infty}$ (ng.h/mL)	54	397239	445118	0.8924 (0.8401, 0.9481)	18.75

Source: CSR 102, Page 35, Table 11-4

- Safety

The safety analyses were based on the safety analysis set which included all 57 subjects who were dosed at least once with study medication. Among 57 subjects, 54 subjects received a second dose. Three subjects were withdrawn from the study prior to dosing in Period II: Subject 043 withdrew consent, Subject 013 was withdrawn due to an AE (rash) and Subject 030 violated the protocol (tested positive for drugs of abuse). There were no deaths or SAEs reported during the study, and none of the AEs reported were considered to be severe.

During the course of this study, 112 treatment-emergent AEs were reported by 40 subjects (70.2%), of which, 60 AEs (54%) were reported by 33 subjects following GP2015 treatment, and 52 (46%) AEs were reported by 28 subjects following US-Enbrel treatment (Table 4.10).

Table 4.10 Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	50 mg GP2015 (N=55)	Adverse Events	50 mg Enbrel® (N=56)	Adverse Events
Total number	33 (60.0%)	60	28 (50.0%)	52
Relation to IMP				
Unsuspected	14 (25.5%)	18	14 (25.0%)	21
Suspected	27 (49.1%)	42	19 (33.9%)	31
Intensity				
Mild	32 (58.2%)	50	27 (48.2%)	44
Moderate	8 (14.5%)	10	6 (10.7%)	8
Severe	–	–	–	–

Source: CSR 102, Page 39, Table 12-1

The overall incidence of AEs and AEs by primary system organ class was generally comparable between GP2015 and US-Enbrel treatment groups (Table 4.11). The most commonly affected primary system organ classes were, respiratory, thoracic and mediastinal disorders (primarily oropharyngeal pain and nasal congestion), nervous system disorders (primarily headache and dizziness), and infections and infestations (primarily nasopharyngitis).

Table 4.11 Incidence of Adverse Events by Primary System Organ Class (Safety Analysis Set)

	50 mg GP2015 N=55 n (%)	50 mg Enbrel® N=56 n (%)	Overall N=57 n (%)
Subjects with at least one adverse event	33 (60.0%)	28 (50.0%)	40 (70.2%)
Primary system organ class			
Respiratory, thoracic and mediastinal disorders	6 (10.9%)	10 (17.9%)	15 (26.3%)
Nervous system disorders	9 (16.4%)	8 (14.3%)	13 (22.8%)
Infections and infestations	8 (14.5%)	7 (12.5%)	13 (22.8%)
Gastrointestinal disorders	7 (12.7%)	5 (8.9%)	10 (17.5%)
General disorders and administration site conditions	4 (7.3%)	6 (10.7%)	10 (17.5%)
Injury, poisoning and procedural complications	6 (10.9%)	1 (1.8%)	7 (12.3%)
Skin and subcutaneous disorders	3 (5.5%)	4 (7.1%)	7 (12.3%)
Blood and lymphatic system disorders	2 (3.6%)	3 (5.4%)	5 (8.8%)
Musculoskeletal and connective tissue disorders	1 (1.8%)	1 (1.8%)	2 (3.5%)
Eye disorders	1 (1.8%)	1 (1.8%)	1 (1.8%)
Investigations	1 (1.8%)	0 (0%)	1 (1.8%)
Ear and labyrinth disorders	1 (1.8%)	0 (0%)	1 (1.8%)
Metabolism and nutrition disorders	1 (1.8%)	0 (0%)	1 (1.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0%)	1 (1.8%)	1 (1.8%)

Source: CSR 102, Page 40, Table 12-2

There were no clinically important findings in the morphology of the 12-lead ECGs, heart rate or ECG intervals for individual subjects following dosing with 50 mg GP2015 or US-Enbrel.
The anti-drug antibody results were negative prior to the first dose, prior to the second dose and at the follow-up visit (28 days after the last dose) for all individual subjects.

Conclusions:

- The PK similarity was established between GP2015 and US-Enbrel in Study 102 as the 90% CIs of the ratios (GP2015/US-Enbrel) of $AUC_{0\text{-}t}$, $AUC0_{\text{-}inf}$, and C_{max} are all within the goal post 80% - 125%.
- There was no evidence of anti-drug antibody production against GP2015 or US-Enbrel.
- The safety profiles are comparable between GP2015 and US-Enbrel.

Reviewer's Analysis:

Reviewer's independent analysis used ANOVA method without inclusion of the operator factor as a fixed effect. The results are similar, which is in agreement with the Sponsor's analysis: 90% CI of the ratios (GP2015/US-Enbrel) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} are all within the goal post 80% - 125% (Table 4.12).

Table 4.12 Comparison of PK Parameters of GP2015/US-Enbrel in Study 102 (Per-Protocol Set)

Parameter	N	GP2015	US-Enbrel	Ratio (GP2015/US-Enbrel)[3]
$AUC_{0\text{-}t}$ (µg·h/mL)[1]	53	369.761	414.962	0.8911 (0.8308, 0.9557)
$AUC_{0\text{-}inf}$ (µg·h/mL)[1]	54	390.286	439.656	0.8877 (0.8320, 0.9471)
C_{max} (µg/mL)[1]	54	2.028	2.146	0.9450 (0.8695, 1.0271)
T_{max} (hour)[2]	54	72 (24-120)	84 (24-120)	-

[1] Least-squares geometric means
[2] Median (range)
[3] Ratio (90% CI)
Source: Reviewer's analysis, the ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect.

The geometric mean PK profiles of GP2015 and US-Enbrel following 50 mg single dose subcutaneous injection are presented in Figure 4.4.

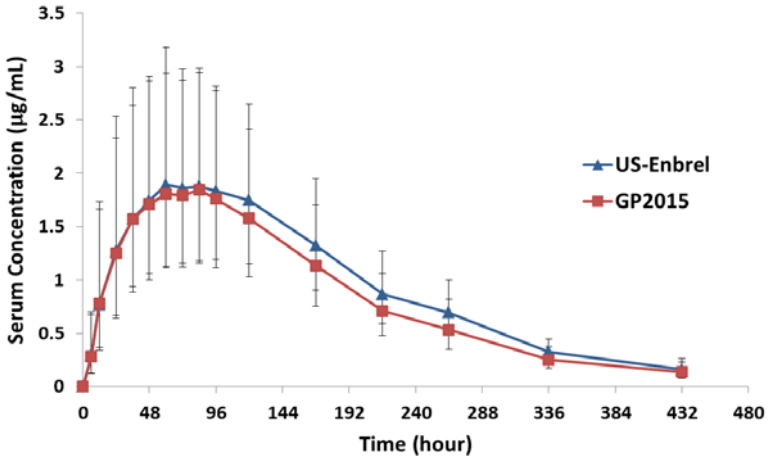

Figure 4.4 US-Enbrel (blue, N=54) and GP2015 (red, N=54) geometric serum concentration-time profile from Study 102. The error bars represent SD. Source: Reviewer's analysis.

4.1.3 Study 103

Study Type: single dose, crossover, PK comparison study in healthy adults
Study Dates: 03/18/2014 – 06/25/2014
Study Center: PRA, Stationsweg 163, 9471 GP, Zuidlaren, Netherlands
Drug Products Batch: GP2015 [batch no. DR0919 (S0016)]

Title:
A randomized, open label, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 following a single subcutaneous injection by an autoinjector and by a pre-filled syringe in healthy male subjects

Objective:

- The primary objective was to demonstrate bioequivalence of GP2015 administered by an autoinjector ((b) (4) GP2015_50) and a pre-filled syringe (PFS) as single subcutaneous injection of 50 mg to healthy adult male subjects in terms of the PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}

- The secondary objectives were:
  - To study and compare the primary PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}, by weight category (low: 50.0-79.9 kg, medium: 80.0-99.9 kg, and high: 100.0-140.0 kg) between autoinjector and PFS, when GP2015 was administered as a single subcutaneous injection of 50 mg
  - To compare remaining PK parameters t_{max}, k_{el}, $t_{1/2}$ between autoinjector and PFS, both administered GP2015 as a single subcutaneous injection of 50 mg, across the total population as well as by weight categories
  - To evaluate and compare the overall safety, tolerability and local tolerance of GP2015 administered by autoinjector and PFS as a single subcutaneous injection of 50 mg

Study Design and Method:
This study was a single center, randomized, open-label, single-dose, two-way cross-over study with two treatment periods to evaluate the PK and the safety profile of GP2015 administered by autoinjector and by PFS in 51 healthy male adults. Subjects were randomly assigned in a 1:1 ratio to one of the following treatment sequences:

- 50 mg GP2015 administered by autoinjector in Period I and administered by PFS in Period II
- 50 mg GP2015 administered by PFS in Period I and administered by autoinjector in Period II

The wash-out period between two dose administrations was at least 35 days.

Noteworthy inclusion criteria included:

- Male subjects aged 18 to 55 years inclusive.
- Body weight between 50 to 140 kg and body mass index (BMI) between 18.5 to 49.9 kg/m^2 inclusively.

Noteworthy exclusion criteria included:

- Any exposure to any recombinant human anti-TNFα inhibitor in the past.
- Abnormal vital signs or abnormal 12-lead ECG results, e.g. long QT syndrome or QTcF > 450 msec for males at screening, that were judged by the principal investigator to be clinically significant as confirmed by 2 repeat measurements.

- Use of any prescription medication or over-the-counter medicines that might have an effect on the objectives of the study, within 14 days prior to dosing. Hormonal contraceptives, hormonal replacement therapy, vitamins, minerals and nutritional supplements may be taken at the discretion of the Investigator.

Blood samples (3.5 mL) for PK evaluation were collected from a forearm vein (direct venipuncture or from an indwelling cannula) into a serum tube at each time point (predose and 6, 12, 24, 36, 48, 60, 72, 84, 96, 120, 168, 216, 264, 336, and 432 hours postdose in each period).

In total 1589 serum samples from clinical Study 103 were analyzed by ELISA to determine the concentration of GP2015 in human serum. The samples were stored until analysis at -70 °C. The minimum required dilution in blocking buffer of the study samples is 1:20. An additional dilution in 1:20 diluted human serum pool from healthy volunteers was carried out if the analyzed concentration of a sample was above the highest standard. All samples were measured against a calibration curve of the reference item prepared in 1:20 diluted human serum pool healthy volunteers (diluent: blocking buffer). All samples were analyzed in duplicate. The test method was validated during study BA14011 and BA12008. For details of ELISA bioanalytical method, refer to section 2.5.

The PK parameters were determined in serum using non-compartmental methods. All BLQ values in the absorption phase, prior to the first quantifiable concentration, as well as BLQ values between evaluable concentrations were substituted by the half value of LLOQ. The terminal BLQ values were treated as missing for the PK evaluation and as ½ LLOQ for descriptive statistics purposes. ANCOVA were performed on the ln-transformed PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} separately. The ANCOVA model included treatment administration, sequence and period as fixed effects and subject nested within sequence as a random effect. Subject's weight was included in the model as covariate. The power of enrolling 51 subjects (including 15% dropout rate) to demonstrate PK similarity 90% CI boundary within 80% to 125% was estimated to be 90%.

Blood samples for detecting ADA were collected at pre-dose (Day1) and at follow-up visit (Day 29).

Criteria for evaluation:

- PK: The following PK parameters were determined from individual serum concentration time profiles of GP2015: $AUC_{0\text{-last}}$, C_{max}, $AUC_{0\text{-inf}}$, t_{max}, k_{el}, $t_{½}$, and $CL_{0\text{-last}}$
- Safety: Adverse events, clinical laboratory evaluations, ECG, vital signs, physical examination, assessment of local tolerance (injection site reaction scores and visual analogue scales for pain), and immunogenicity.

Results:

- PK
  - Analyzed dataset

    The PK analyses were based on the per-protocol analysis set population. 51 subjects were enrolled and 49 subjects completed the study. Two subjects (Subject 212, 306) were withdrawn from the study after completing one treatment period and before dosing in the second period.

    Carryover concentrations from Period I, defined as predose serum concentrations greater than the LLOQ (>6.7 ng/mL) at Period II, were noted in the pre-dose samples for 47 subjects: 24 subjects with carryover from autoinjector administration and 23 subjects with carryover from PFS. Only Subject 114 was found to have a pre-dose PK concentration of >5% of C_{max} in Period II. This subject did meet the pre-defined criteria for exclusion from PK analysis and was therefore not

included in the PK analysis set. Carryover pre-dose concentrations of other subjects in Period II were kept as is during the analysis.

- Demographic characteristics

All subjects met the eligibility criteria, except Subject 212 due to previous medical history.

The majority of subjects were White, and the median age was 32 years (range: 18 to 53 years) with 33.0% each in all three weight categories i.e. 50-79.9, 80-99.9 kg and 100.0-140.0 kg (Table 4.13). The median BMI was 27.7 kg/m^2 (range: 19.3 to 39.0 kg/m^2).

Table 4.13 Demographic Summary by Study Sequence in Study 103

		(b) (4) GP2015_50/ GP2015-PFS N=25	GP2015-PFS/ (b) (4) GP2015_50 N=26	Total N=51
Gender – n (%)	Male	25 (100)	26 (100)	51 (100)
Race – n (%)	American Indian or Alaska native	0	1 (4)	1 (2)
	Black	3 (12)	6 (23)	9 (18)
	Other	0	1 (4)	1 (2)
	White	22 (88)	18 (69)	40 (78)
Body weight group – n (%)	50-58.9 kg	1 (4)	2 (8)	3 (6)
	59-79.9 kg	8 (32)	6 (23)	14 (27)
	80-99.9 kg	8 (32)	9 (35)	17 (33)
	100-125.9 kg	5 (20)	8 (31)	13 (25)
	126-140 kg	3 (12)	1 (4)	4 (8)
Age (years)	Mean	33.8	34.3	34.1
	SD	10.02	10.29	10.06
	Median	32	34	32
	Range	18-50	18-53	18-53
Weight (kg)	Mean	91.16	91.83	91.50
	SD	20.291	19.635	19.761
	Median	87.8	95.2	92.3
	Range	57.8-126.9	54.5-133.7	54.5-133.7
BMI (kg/m^2)	Mean	27.20	28.22	27.72
	SD	5.304	4.468	4.873
	Median	26.0	28.1	27.7
	Range	19.3-39.0	20.1-37.0	19.3-39.0

Source: CSR 103, Page 41-42, Table 11-2

- PK results

The arithmetic mean PK profiles of GP2015 following 50 mg single dose subcutaneous injection via autoinjector and PFS are presented in Figure 4.5.

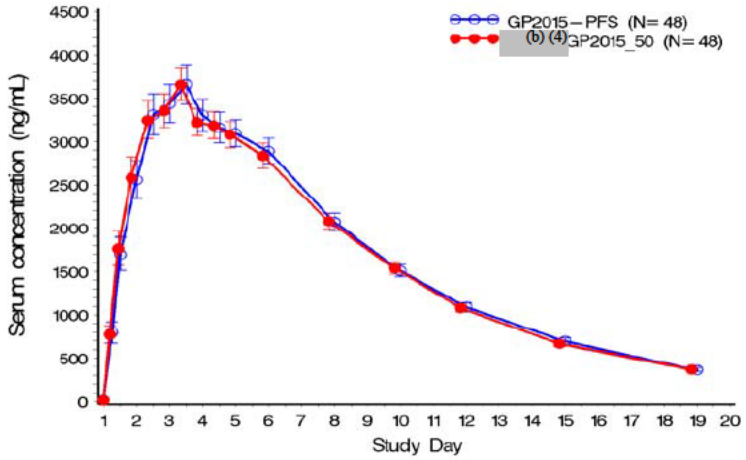

Figure 4.5 GP2015 serum concentration-time profile following 50 mg single dose subcutaneous injection via autoinjector (red, N=48) and PFS (blue, N=48) in Study 103. Source: CSR103, page 44, Figure 11-1.

Following a single dose of GP2015 50 mg administered by an autoinjector or by a PFS, the concentrations of GP2015 in serum increased slowly, with maximum concentrations reached on average at approximately 60 hours post-dose. The shape of the serum concentration profiles of GP2015 was similar for both treatment administrations. The mean PK parameters were similar between the autoinjector and the PFS treatment administrations (Table 4.14).

Table 4.14 Summary of PK Parameters of GP2015 following Subcutaneous Injection via autoinjector and PFS in Study 103 (Per-Protocol Set)

Parameter	Statistic	(b) (4)GP2015_50	GP2015-PFS
C_{max} (µg/mL)	N	48	48
	Geometric mean	3.67	3.63
	Mean (SD)	3.92 (1.47)	3.99 (1.62)
	Range	1.73-8.54	0.597-8.53
t_{max} (h)	N	48	48
	Median	60.00	60.00
	Mean (SD)	62.51 (19.34)	63.55 (25.77)
	Range	24.00-120.20	36.00-170.00
$AUC_{0\text{-last}}$ (h*µg/mL)	N	48	48
	Geometric mean	684	678
	Mean (SD)	719 (231)	725 (253)
	Range	308-1357	156-1359
$AUC_{0\text{-inf}}$ (h*µg/mL)	N	48	48
	geometric mean	745	737
	Mean (SD)	779 (238)	784 (269)
	Range	367-1431	199-1564
AUC_{extra} (%)	N	48	48
	Geometric mean	7.3	7.1
	Mean (SD)	8.1 (4.0)	7.9 (4.2)
	Range	2.7-22.7	3.1-24.7
CL/F (mL/h)	N	48	48
	geometric mean	73.1	73.7
	Mean (SD)	76.9 (25.8)	80.3 (42.9)
	Range	36.8-162	36.8-320
$t_{1/2}$ (h)	N	48	48
	Geometric mean	108	107
	Mean (SD)	109 (23.2)	109 (23.8)
	Range	71.6-228	81.2-228

Source: CSR 103, Page 45, Table 11-3

The primary statistical analysis comparing the PK parameters of GP2015 administered via an autoinjector or via a PFS is presented in Table 4.15. The estimated ratio (autoinjector/PFS) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} is 1.01 (90% CI = 0.95, 1.07), 1.01 (90% CI = 0.96, 1.07), and 1.01 (90% CI = 0.94, 1.08), respectively.

Table 4.15 Statistical Analysis of the PK Parameters of GP2015 following Autoinjector or PFS Administration in Study 103 (Per-Protocol Set)

	Geometric LS means		Ratio (b) (4) GP2015_50/GP2015-PFS 90% Confidence interval		
PK parameter	(b) (4) GP2015_50	GP2015-PFS	Estimate	Lower	Upper
C_{max} (µg/mL)	3.7	3.6	1.01	0.94	1.08
$AUC_{0\text{-}last}$ (h*µg/mL)	684.1	678.4	1.01	0.95	1.07
$AUC_{0\text{-}inf}$ (h*µg/mL)	745.2	737.4	1.01	0.96	1.07

Source: CSR 103, Page 46, Table 11-4

The secondary statistical analysis compared the PK parameters of GP2015 administered via an autoinjector or via a PFS in three different body weight categories (Table 4.16). There were 17, 14, and 17 subjects in low, medium, and high body weight categories. The 90% CIs of the ratio (autoinjector/PFS) for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} in the low and medium body weight categories (50.0-99.9 kg) were within the goal post 80% - 125%. However, the upper boundaries of 90% CI for the ratio (autoinjector/PFS) for $AUC_{0\text{-}t}$, and C_{max} in the high body weight category were higher than 125%. Nevertheless, Study 103 was not powered to show PK similarity of autoinjector and PFS for this body weight based sub-group analysis.

Table 4.16 Statistical Analysis of the PK Parameters of GP2015 following Autoinjector or PFS Administration by Body Weight Category in Study 103 (Per-Protocol Set)

		Geometric LS means		Ratio (b) (4) GP2015_50/GP2015-PFS 90% Confidence interval		
Body weight category	PK parameter	(b) (4) GP2015_50	GP2015-PFS	Estimate	Lower	Upper
Low (50.0-79.9 kg)	C_{max} (µg/mL)	5.1	5.4	0.94	0.86	1.02
	$AUC_{0\text{-}last}$ (h*µg/mL)	923.6	959.8	0.96	0.90	1.02
	$AUC_{0\text{-}inf}$ (h*µg/mL)	986.6	1030.5	0.96	0.90	1.02
Medium (80.0-99.9 kg)	C_{max} (µg/mL)	3.4	3.4	1.00	0.89	1.12
	$AUC_{0\text{-}last}$ (h*µg/mL)	602.3	635.7	0.95	0.86	1.05
	$AUC_{0\text{-}inf}$ (h*µg/mL)	660.0	684.5	0.96	0.89	1.05
High (100.0-140.0 kg)	C_{max} (µg/mL)	2.9	2.6	1.10	0.95	1.29
	$AUC_{0\text{-}last}$ (h*µg/mL)	564.0	509.0	1.11	0.97	1.26
	$AUC_{0\text{-}inf}$ (h*µg/mL)	623.0	564.0	1.10	0.98	1.24

Source: CSR 103, Page 48, Table 11-5

The secondary PK endpoints $t_{1/2}$ and t_{max} were similar between two administration methods for total and by body weight category.

- Safety

The safety analyses were based on the safety analysis set which included all 51 subjects who were dosed at least once with study medication. Among 51 subjects, 49 subjects received a second dose. Subject 212 was withdrawn on the day after PFS administration in the Period I, a letter was received from the general practitioner explaining that the subject had a melanoma in situ in his medical history, which the subject did not report to the physician before inclusion into the study. This was considered a protocol violation. Subject 306 was withdrawn on the 32 days after autoinjector administration because the pain associated with an animal (cat) bite in the left hand (moderate severity). There were no deaths or SAEs reported during the study, and none of the AEs reported were considered to be severe.

During the course of this study, the overall incidence of AEs was generally comparable between two administration methods. 110 treatment-emergent AEs were reported by 32 subjects (63.0%), of which, 55 AEs (50%) was reported by 25 subjects following each administration method (Table 4.18).

Table 4.17 Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

Category	Level	(b) (4)GP2015-50 (N=50) e	n	%	GP2015-PFS (N=50) e	n	%	Total (N=51) e	n	%
Any		55	25	50	55	25	50	110	32	63
Relationship to study drug	Not Suspected	43	20	40	45	20	40	88	28	55
	Suspected	12	11	22	10	9	18	22	14	27
Intensity	Mild	49	24	48	51	25	50	100	32	63
	Moderate	6	5	10	4	2	4	10	7	14
	Severe									
Outcome	Ongoing				1	1	2	1	1	2
	Resolved	55	25	50	54	25	50	109	32	63

Source: CSR 103, Page 240, Table 14.3.1-7

The incidences of AEs were different in some primary system organ classes. There were more incidences of AEs in nervous system and gastrointestinal disorder following autoinjector administration (Table 4.18). There were more incidences of AEs in skin and subcutaneous tissue and psychiatric disorders following PFS administration.

Table 4.18 Incidence of Adverse Events by Primary System Organ Class (Safety Analysis Set)

System organ class	(b) (4)GP2015_50 N=50 n (%)	GP2015-PFS N=50 n (%)	Overall N=51 n (%)
Subjects with at least one TEAE	25 (50)	25 (50)	32 (63)
Nervous system disorders	10 (20)	6 (12)	13 (25)
Musculoskeletal and connective tissue disorders	5 (10)	7 (14)	11 (22)
Gastrointestinal disorders	8 (16)	4 (8)	9 (18)
General disorders and administration site conditions	5 (10)	4 (8)	9 (18)
Infections and infestations	4 (8)	4 (8)	8 (16)

Blood and lymphatic system disorders	5 (10)	5 (10)	6 (12)
Respiratory, thoracic and mediastinal disorders	3 (6)	3 (6)	5 (10)
Skin and subcutaneous tissue disorders	0	5 (10)	5 (10)
Vascular disorders	1 (2)	3 (6)	4 (8)
Renal and urinary disorders	2 (4)	3 (6)	3 (6)
Investigations	1 (2)	1 (2)	2 (4)
Psychiatric disorders	0	2 (4)	2 (4)
Immune system disorders	1 (2)	0	1 (2)
Injury, poisoning and procedural complications	1 (2)	0	1 (2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (2)	1 (2)
Reproductive system and breast disorders	1 (2)		1 (2)

Source: CSR 103, Page 54-55, Table 12-3

All ECG evaluations were recorded as normal or as not clinically significant. No changes or trends of clinical significance were seen for the heart rate, PR-interval, QRS-duration, QT interval or QTcF-interval.

All subjects had negative ADA results on Day 1 of both treatment periods and at follow-up (28 days after the last dose) for all individual subjects.

Conclusions:

- The PK similarity of GP2015 50 mg was established between administrations using an autoinjector and a PFS in Study 103 as the 90% CIs of the ratios (autoinjector/PFS) of AUC_{0-t}, $AUC0_{-inf}$, and C_{max} are all within the goal post 80% - 125%.
- The secondary PK endpoints $t_{1/2}$ and t_{max} were similar between the autoinjector and PFS, for total and by body weight category. In addition, the 90% CIs of the ratios (autoinjector/PFS) of AUC_{0-last}, AUC_{0-inf} and C_{max} are all within the goal post 80% - 125% in low (50.0-79.9 kg) and medium (80.0-99.9 kg) body weight categories.
- The overall safety profile was generally comparable between autoinjector and PFS. There were no notable trends or clinically relevant changes observed in the clinical laboratory parameters, vital signs, ECGs or local tolerance at injection site.

Reviewer's Analysis:

Reviewer's independent analysis used ANOVA method showed similar results, which is in agreement with the Sponsor's analysis: 90% CI of the ratios (autoinjector/PFS) of AUC_{0-t}, AUC_{0-inf}, and C_{max} are all within the goal post 80% - 125% (Table 4.19).

Table 4.19 Comparison of PK Parameters of GP2015 following Autoinjector or PFS Administration in Study 103 (Per-Protocol Set)

Parameter	N	Autoinjector	PFS	Ratio (Autoinjector/PFS)[3]
AUC_{0-t} (µg·h/mL)[1]	48	686.004	679.934	1.0089 (0.9520, 1.0692)
AUC_{0-inf} (µg·h/mL)[1]	48	746.245	738.814	1.0101 (0.9577, 1.0653)
C_{max} (µg/mL)[1]	48	3.666	3.627	1.0108 (0.9431, 1.0832)
T_{max} (hour)[2]	48	60 (24-120)	60 (36-168)	-

[1] Least-squares geometric means
[2] Median (range)
[3] Ratio (90% CI)

Source: Reviewer's analysis, the ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect.

The geometric mean PK profiles of single dose 50 mg GP2015 subcutaneous administration using an autoinjector or a PFS injection are presented in Figure 4.6.

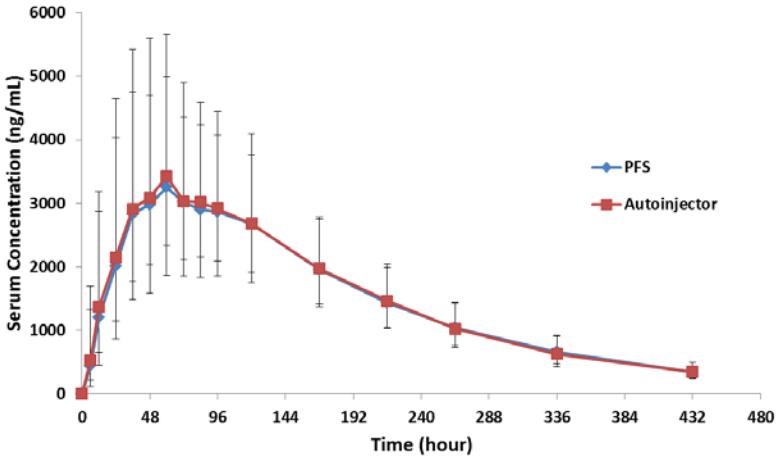

Figure 4.6 Geometric mean PK profiles of single dose 50 mg GP2015 subcutaneous administration using an autoinjector (red, N=48) or a PFS (blue, N=48) injection from Study 103. The error bars represent SD. During the Period II, the pre-dose carryover concentrations from Period I were set at 0. One post-dose BLQ value during absorption phase was substituted by the half value of LLOQ (6.7 ng/mL). Source: Reviewer's analysis.

The comparison of geometric mean $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of GP2015 following an autoinjector or a PFS injection are presented in Figure 4.7

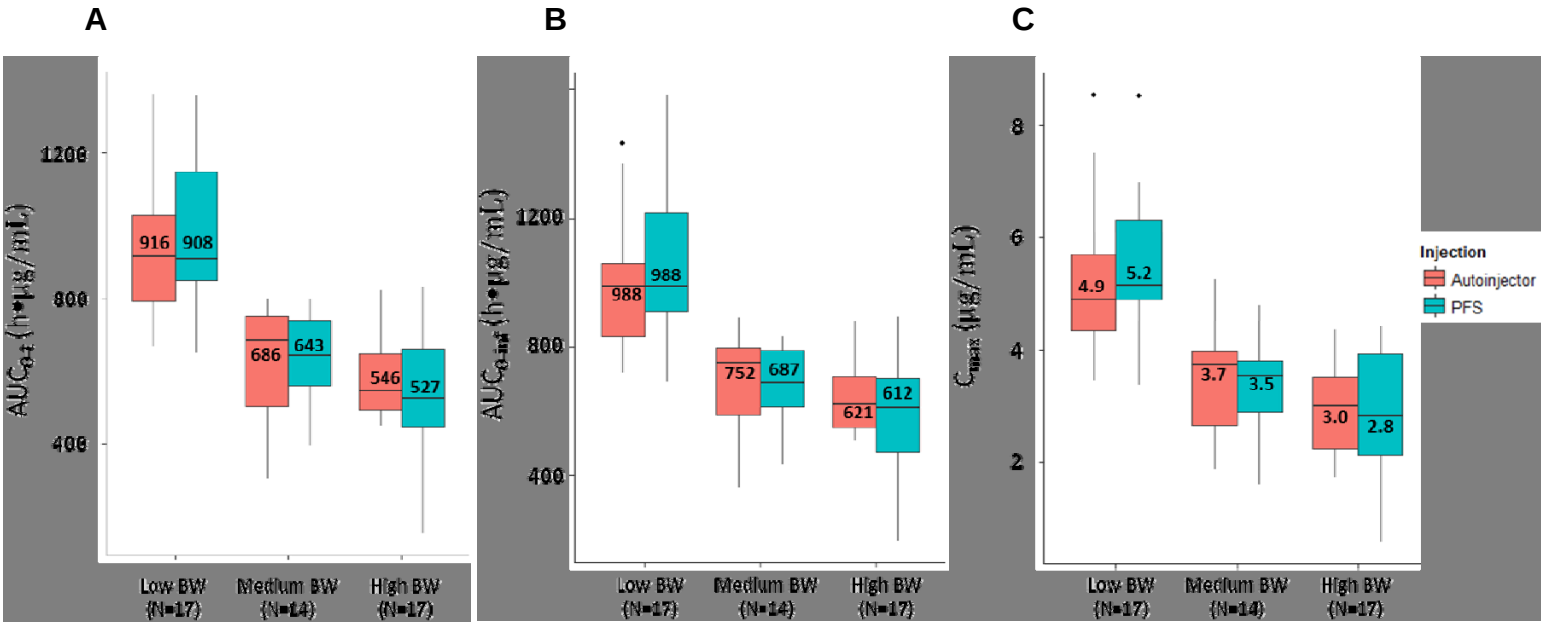

Figure 4.7 Boxplot of GP2015 $AUC_{0\text{-}t}$ (A), $AUC_{0\text{-}inf}$ (B), and C_{max} (C) comparison following administration via an autoinjector (red) or a PFS (blue) from Study 103. Low body weight < 80 kg, 80 kg ≤ Medium body weight < 100 kg, 100 kg ≤ High body weight. Source: Reviewer's analysis.

4.1.4 Study 104

Study Type: single dose, crossover, PK comparison study in healthy males
Study Dates: 06/30/2014 – 11/19/2014
Study Center: PAREXEL Early Phase Clinical Unit; Northwick Park Hospital; Harrow; United Kingdom
Drug Products Batch: GP2015 (batch no. S0014) and EU-Enbrel (batch no. H76640)

Title:
A randomized, double blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel (EU-licensed) following a single dose of 50 mg subcutaneous injection in healthy male subjects

Objective:

- The primary objective was to determine bioequivalence between GP2015 and EU-Enbrel in terms of the PK parameters $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, and C_{max} following a single subcutaneous injection of 50 mg.

- The secondary objectives were to further compare GP2015 and EU-Enbrel with respect to the following criteria:
  - Remaining PK parameters (t_{max}, k_{el}, and $t_{½}$)
  - Immunogenicity of both products
  - Overall safety, tolerability, and local tolerance.

Study Design and Method:
This study was a single center, randomized, double-blind, single-dose, two-way cross-over study with two treatment periods to evaluate the PK and the safety profile of GP2015 and EU-Enbrel in 54 healthy male adults. Subjects were randomly assigned in a 1:1 ratio to one of the following treatment sequences:

- 50 mg GP2015 in Period I and 50 mg EU-Enbrel in Period II
- 50 mg EU-Enbrel in Period I and 50 mg GP2015 in Period II

The wash-out period between two dose administrations was at least 35 days.

Noteworthy inclusion criteria included:

- Male subjects aged 18 to 49 years inclusive.
- Body weight between 50 to 99.9 kg and body mass index (BMI) between 19.0 to 29.9 kg/m^2 inclusively.

Noteworthy exclusion criteria included:

- Any exposure to any recombinant human anti-TNFα inhibitor in the past.
- Abnormal vital signs or abnormal 12-lead electrocardiogram (ECG) results e.g., long QT syndrome or QTcF > 450 msec at screening, as confirmed by two repeat measurements.
- Use of any prescription medication or over-the-counter medicines that might have an effect on the objectives of the study, within 14 days prior to dosing. Hormonal contraceptives, hormonal replacement therapy, vitamins, minerals and nutritional supplements may be taken at the discretion of the Investigator.

Blood samples (3.5 mL) for PK evaluation were taken by either direct venipuncture or indwelling cannula inserted in a forearm vein. at each time point (predose and 6, 12, 24, 36, 48, 60, 72, 84, 96, 120, 168, 216,

264, 336, and 432 hours postdose in each period).

Two aliquots were prepared for each sample of the 54 subjects (aliquot 1 for analysis and aliquot 2 as back-up sample for long term storage). In total, 3537 serum samples (both aliquots) of 54 subjects were analyzed by ELISA to determine the concentration of GP2015/EU-Enbrel in human serum. The samples were stored until analysis at -70 °C. The minimum required dilution in blocking buffer of the study samples is 1:20. An additional dilution in 1:20 diluted human serum pool from healthy volunteers was carried out if the analyzed concentration of a sample was above the highest standard. All samples were measured against a calibration curve of the reference item prepared in 1:20 diluted human serum pool HV (diluent: blocking buffer). For details of ELISA bioanalytical method, refer to section 2.5.

The PK parameters were determined in serum using non-compartmental methods. All BLQ values in the absorption phase, prior to the first quantifiable concentration, as well as BLQ values between evaluable concentrations were substituted by the half value of LLOQ. The terminal BLQ values were treated as missing for the PK evaluation and as ½ LLOQ for descriptive statistics purposes. Pre-treatment BLQ values were treated as zeros. ANOVA was performed on the log-transformed PK parameters $AUC_{0\text{-tlast}}$, $AUC_{0\text{-inf}}$, and C_{max} separately. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The power of enrolling 54 subjects (including 10% dropout rate) to demonstrate PK similarity 90% CI boundary within 80% to 125% was estimated to be 90%.

Blood samples for detecting ADA were collected at pre-dose (Day1) and at follow-up visit (Day 29).

Criteria for evaluation:

- Primary PK parameters: C_{max}, $AUC_{0\text{-tlast}}$, and $AUC_{0\text{-}\infty}$
- Second PK parameters: $\%AUC_{ex}$, $CL_{0\text{-inf}}$, t_{max}, k_{el}, and $t_{½}$
- Safety: Adverse events, clinical laboratory evaluations, ECG, vital signs, physical examination, and immunogenicity.

Results:

- PK
  - Analyzed dataset

    A total of 54 subjects were randomized: 27 subjects into the treatment sequence of GP2015/EU-Enbrel and 27 subjects into EU-Enbrel/GP2015 (Table 4.20). All subjects received study medication and completed the study. All 54 randomized subjects received study medication in both treatment periods and were included in the PK analysis set. There were no major protocol deviations all of these subjects were included in the PK analysis set.

    Carryover concentrations from Period I, defined as predose serum concentrations greater than the LLOQ (>6.7 ng/mL) at Period II, were noted in the pre-dose samples for 45 subjects: 20 subjects with carryover from GP2015 and 25 subjects with carryover from EU-Enbrel. Since the positive pre-dose concentrations were all less than 2% of their respective C_{max}, their pre-dose concentrations in Period II were kept as is during the analysis.

    The dose of etanercept delivered by each injection of GP2015 or EU-Enbrel was calculated by using the pre- and post-injection PFS weight differences, and the respective batch solution densities and protein concentrations. The EU-Enbrel batch PFS were found to consistently deliver approximately 5% less protein content than the nominal dose of 50 mg.

o Demographic characteristics

The majority of the healthy males were White (53.7%) followed by Asians (24.1%), Black or African American (14.8%), and others (7.4%). Overall, the mean (SD) age of subjects was 32.9 (8.27) years with a mean BMI (SD) of 24.85 (2.645) kg/m^2 (Table 4.20).

Table 4.20 Demographic Summary by Study Sequence in Study 104

Demographic variables	GP2015/Enbrel N=27	Enbrel/GP2015 N=27	Total N=54
Age (years)			
Mean (SD)	35.2 (8.45)	30.6 (7.55)	32.9 (8.27)
Median	36.0	30.0	32.0
Range	20 - 48	22 - 46	20 – 48
Race, n (%)			
White	15 (55.6)	14 (51.9)	29 (53.7)
Asian	7 (25.9)	6 (22.2)	13 (24.1)
Black or African American	3 (11.1)	5 (18.5)	8 (14.8)
Other	2 (7.4)	2 (7.4)	4 (7.4)
Ethnic, n (%)			
Not Hispanic or Latino	27 (100)	26 (96.3)	53 (98.1)
Hispanic or Latino	0	1 (3.7)	1 (1.9)
Height (cm)			
Mean (SD)	175.2 (7.60)	174.7 (5.55)	174.9 (6.60)
Median	177	174	175
Range	160 - 189	163 - 185	160 - 189
Weight (kg)			
Mean (SD)	75.51 (10.078)	76.71 (9.480)	76.11 (9.710)
Median	75.10	75.90	75.40
Range	52.2 - 91.8	63.1 - 97.9	52.2 - 97.9
BMI (kg/m^2)			
Mean (SD)	24.58 (2.727)	25.11 (2.583)	24.85 (2.645)
Median	24.30	25.20	25.20
Range	19.0 - 29.4	20.5 - 29.4	19.0 - 29.4

Source: CSR 104, Page 48, Table 11-2

o PK results

The arithmetic mean PK profiles of GP2015 and EU-Enbrel following 50 mg single dose subcutaneous injection are presented in Figure 4.8.

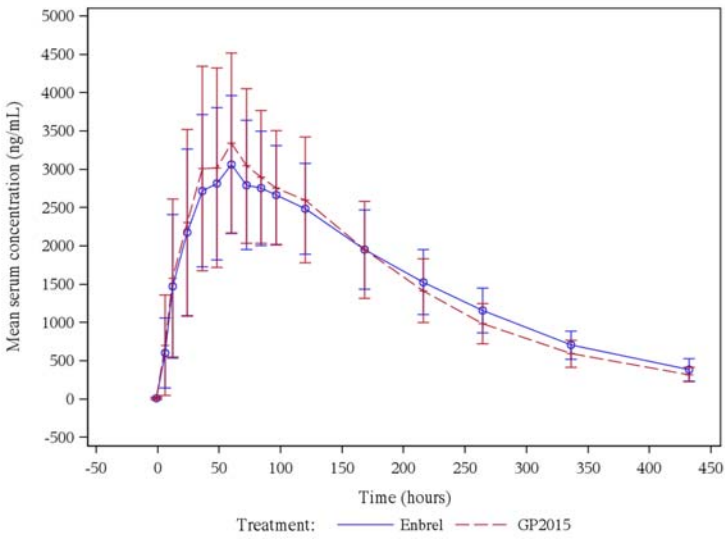

Figure 4.8 EU-Enbrel (blue, N=54) and GP2015 (red, N=54) arithmetic serum concentration-time profile from Study 104. The error bars represent SD. Source: CSR104, page 53, Figure 11-2.

Following single dose of 50 mg subcutaneous injection, serum drug product concentrations increased slowly with maximum concentrations occurring at median t_{max} values of 58 and 60 hours for GP2015 and EU-Enbrel, respectively. Thereafter, drug product concentrations declined a mean rate of 75 mL/h and 67 mL/h for GP2015 and EU-Enbrel, respectively. Mean $t_{1/2}$ values were 104 and 108 hours for GP2015 and EU-Enbrel, respectively (Table 4.21).

Table 4.21 Summary of PK Parameters of GP2015 and EU-Enbrel in Study 104

Parameter	Statistic	GP2015 N=54	Enbrel N=54
C_{max} (ng/mL)	Geometric mean	3416.22	3087.00
	Mean (SD)	3633.05 (1321.66)	3233.98 (980.26)
	Range	1463.10 – 7611.00	1391.10 – 5716.60
$AUC_{0\text{-tlast}}$ (h*ng/mL)	Geometric mean	630363.18	642235.26
	Mean (SD)	657012.54 (189664.79)	662364.08 (158901.07)
	Range	299620.76 - 1186213.25	325198.63 - 965979.97
$AUC_{0\text{-inf}}$ (h*ng/mL)	Geometric mean	678786.96	705159.10
	Mean (SD)	706159.33 (199223.51)	727205.09 (173879.56)
	Range	325659.69 - 1260373.35	363959.39 - 1094618.36
t_{max} (h)	Median	58.34	59.87
	Mean (SD)	60.21 (21.52)	64.77 (22.16)
	Range	23.00 – 121.20	24.20 – 119.90
AUC_{extra} (%)	Geometric mean	6.8526	7.6410
	Mean (SD)	7.1119 (2.01965)	8.8529 (3.60855)
	Range	3.691 - 14.733	0.139 - 18.913
$CL_{0\text{-inf}}$ (mL/h)	Geometric mean	74.9973	67.4917
	Mean (SD)	78.1229 (23.29331)	69.8956 (20.08147)
	Range	40.486 - 156.841	43.588 - 131.221
$t_{1/2}$ (h)	Geometric mean	104.17544	107.90857
	Mean (SD)	104.75574 (11.290552)	110.73040 (23.031779)
	Range	80.7365 - 142.4322	44.3111 - 169.0990
K_{el}	Geometric mean	0.00665	0.00642
	Mean (SD)	0.00669 (0.000702)	0.00664 (0.002026)
	Range	0.0049 - 0.0086	0.0041 - 0.0156

Source: CSR 104, Page 51, Table 11-4 and Page 54, Table 11-6

The primary statistical analysis comparing the PK parameters between GP2015 and EU-Enbrel are presented in Table 4.22. The estimated ratio (GP2015/EU-Enbrel) of $AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$, and C_{max} is 0.98 (90% CI = 0.94, 1.02), 0.96 (90% CI = 0.93, 1.00), and 1.11 (90% CI = 1.05, 1.17), respectively.

Table 4.22 Statistical Analysis of the PK Parameters of GP2015/EU-Enbrel in Study 104

Parameter (unit)	LS Mean		Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	GP2015 N=54	Enbrel N=54			
C_{max} (ng/mL)	3416.22	3087.00	1.11	1.05 - 1.17	16.4
$AUC_{0\text{-tlast}}$ (h*ng/mL)	630363.18	642235.26	0.98	0.94 - 1.02	12.1
$AUC_{0\text{-inf}}$ (h*ng/mL)	678786.96	705159.10	0.96	0.93 - 1.00	12.3

Source: CSR 104, Page 54, Table 11-7

- Safety

All 54 randomized subjects received study medication in both treatment periods and were included in the safety analysis set. Overall, there was no notable difference between treatments for both suspected and not suspected TEAEs. A total of 23 subject (38 events) and 20 subjects (43 events) had experienced TEAEs following GP2015 and EU-Enbrel treatments, respectively (Table 4.23). No deaths, SAEs or severe AEs were reported during this study.

Table 4.23 Summary of Treatment-Emergent Adverse Events in Study 104

	GP2015 N=54 n (%)	Enbrel N=54 n (%)
Subjects dosed	54 (100)	54 (100)
Subjects with at least one TEAE	23 (42.6)	20 (37.0)
Subjects with SAE	0	0
Subjects discontinued with TEAE	0	0
Relation to IMP		
Not suspected	15 (27.8)	13 (24.1)
Suspected	10 (18.5)	13 (24.1)
Severity		
Mild	20 (37.0)	18 (33.3)
Moderate	7 (13.0)	5 (9.3)
Severe	0	0

Source: CSR 104, Page 56, Table 12-1

The overall incidence of AEs and AEs by primary system organ class was generally comparable between GP2015 and EU-Enbrel treatment groups (Table 4.24). Most reported TEAEs regardless of relationship were observed in the SOCs of blood and lymphatic system disorders, nervous system disorders and respiratory, thoracic and mediastinal disorders with no notable differences between treatments at SOC level.

Table 4.24 Incidence of TEAE by Primary System Organ Class in Study 104

System Organ Class	GP2015 (N=54) N (%)	EU-Enbrel (N=54) N (%)
Subjects with at least one TEAE	23 (42.6%)	20 (37.0%)
Blood and Lymphatic System Disorders (Neutropenia)	7 (13%)	8 (14.8%)
Gastrointestinal Disorders	2 (3.7%)	3 (5.6%)
Nervous System Disorders	5 (9.3%)	6 (11.1%)
Respiratory, Thoracic, and Mediastinal Disorders	6 (11.1%)	4 (7.4%)
Vascular Disorders (Phlebitis)	0	1 (1.9%)
Infections and Infestations	5 (9.3%)	4 (7.4%)
General Disorders and Administration Site Conditions	1 (1.9%)	4 (7.4%)
Injury, Poisoning and Procedural Complications	2 (3.7%)	1 (1.9%)
Musculoskeletal and Connective Tissue Disorders	3 (5.6%)	2 (3.7%)

Source: adapted from CSR 104, Page 57, Table 12-2

No clinically significant abnormal 12-lead ECG results were reported for any of the subjects and none of the ECG abnormalities were reported as AEs.
All samples from the pre-dose (Day 1) of each period were ADA negative. A total of 3 subjects (Subject 10027, Subject 10037 and Subject 10053) had confirmed binding ADA at the follow-up visit (Day 65), however the concentrations were below the LLOQ (i.e. 200 ng/mL; concentration was determined by using a rabbit polyclonal anti-etanercept antibody as a positive control). All of these 3 subjects were treated with a treatment sequence of GP2015/Enbrel and accordingly Enbrel was administered in Period 2.

Conclusions:

- The PK similarity was established between GP2015 and EU-Enbrel in Study 104 as the 90% CI of the ratios (GP2015/EU-Enbrel) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} are all within the goal post 80% - 125%.
- All subjects had negative anti-drug antibody (ADA) results on Day 1 of both treatment periods. A total of 3 subjects had confirmed binding ADAs at the follow-up visit with titers near the detection limit.
- The safety profiles are comparable between GP2015 and EU-Enbrel.

Reviewer's Analysis:
Reviewer's independent analysis showed similar results, which are in agreement with the Sponsor's analysis: 90% CI of the ratios (GP2015/EU-Enbrel) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} are all within the goal post 80% - 125% (Table 4.25).

Table 4.25 Comparison of PK Parameters of GP2015/EU-Enbrel in Study 104

Parameter	N	GP2015	EU-Enbrel	Ratio (GP2015/EU-Enbrel)[3]
$AUC_{0\text{-}t}$ (µg·h/mL)[1]	54	632.662	644.007	0.9824 (0.9449, 1.0214)
$AUC_{0\text{-}inf}$ (µg·h/mL)[1]	54	680.945	706.883	0.9633 (0.9264, 1.0016)
C_{max} (µg/mL)[1]	54	3.416	3.087	1.1066 (1.0500, 1.1664)
T_{max} (hour)[2]	54	60 (24-120)	24 (24-120)	-

[1] Least-squares geometric means

[2] Median (range)
[3] Ratio (90% CI)
Source: Reviewer's analysis, the ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect.

The geometric mean PK profiles of GP2015 and EU-Enbrel following 50 mg single dose subcutaneous injection are presented in Figure 4.9.

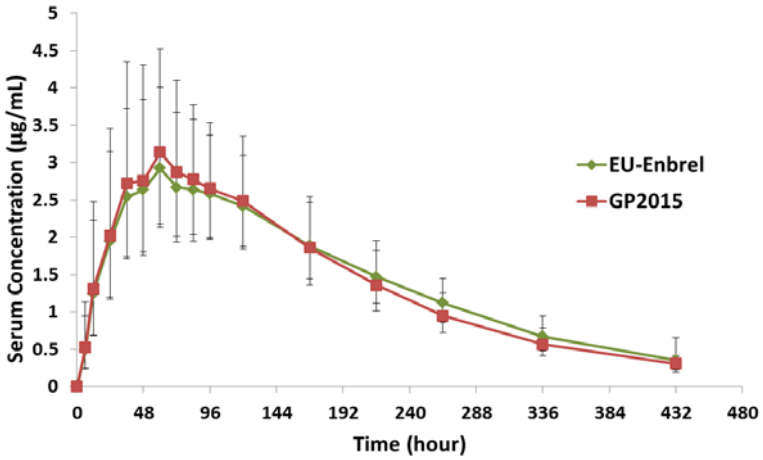

Figure 4.9 EU-Enbrel (green, N=54) and GP2015 (red, N=54) geometric serum concentration-time profile from Study 104. The error bars represent SD. During the Period II, the pre-dose carryover concentrations from Period I were set at 0. One terminal BLQ value was treated as missing. Source: Reviewer's analysis.

4.1.5 Report 105

Report Type: Cross study PK comparison report
Compared Studies: Study 101 and Study 102
Compared Treatments: Single dose of EU-Enbrel and US-Enbrel
Drug Products Batch: EU-Enbrel (batch no. E88057) and US-Enbrel (batch no. 1026663)

Title:
A cross-study comparison of Enbrel® (EU-licensed) and Enbrel® (US-licensed) to determine the pharmacokinetics and safety following a single subcutaneous injection in healthy subjects

Objective:
The protocols of studies 101 and 102 contained already the across-study comparison between the two reference products as a predefined secondary objective: PK and safety data on EU-Enbrel collected in Study101 were to be compared with the data on US- Enbrel collected in Study GP15-102. The objectives are:

- To compare EU-Enbrel andUS-Enbrel in terms of the PK parameters $AUC_{0\text{-}tlast}$ and C_{max}
- To compare the PK parameters $AUC_{0\text{-}inf}$, $\%AUC_{extrap}$, t_{max}, $t_{½}$, and k_{el}
- Immunogenicity
- Overall safety and local tolerance

Study Design and Method:
The study design and method of Studies 101 and 102 have been summarized in section 4.1.1 and 4.1.2.

Safety set: all subjects received EU-Enbrel in Study 101 and all subjects received US-Enbrel were assigned to the safety data set in the blind data review meeting of the respective is study.

Per-protocol set: all subjects assigned to the per-protocol set in the blind data review meeting of the respective study

ANOVA was performed on the log-transformed PK parameters $AUC_{0\text{-}tlast}$ and C_{max} separately. The ANOVA model included treatment and period as fixed effects. The across-study comparison of Enbrel EU and Enbrel US was not a powered objective of the studies, but the sample size is considered sufficient to assess the biosimilarity between these two products and it was outlined as a pre-specified objective of both protocols.

Results:

- PK
  - Per-protocol set

    54 healthy subjects were randomized in Study 101. Among them, 53 subjects received EU-Enbrel treatment (Subject 3 only received GP2015 treatment). Subject 9 and 37 were excluded from the per-protocol set in Study 101 because they did not receive GP2015 treatment. Subject 30 was further excluded from the per-protocol set because the calculated dose for this subject in Period II (when taking GP2015) was 67.2 mg which was technically impossible. Therefore 50 subjects from Study 101 were included in the per-protocol set of Report 105.

    57 healthy subjects were randomized in Study 102. Among them, 56 subjects received US-Enbrel treatment (Subject 13 only received GP2015 treatment). Subject 30 and 43 were excluded from the

per-protocol set in Study 102 because they did not receive GP2015 treatment. Therefore 54 subjects from Study 102 were included in the per-protocol set of Report 105.

Among those 104 per-protocol subjects, Subject 43 in Study 101 was excluded from $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-inf}}$ analysis because two samples were incorrectly labeled as taken at"336 hours"; Subject 16 in Study 102 was excluded from $AUC_{0\text{-tlast}}$ analysis because the last PK measurement (432 hours) was missing.

- Demographic characteristics

All subjects satisfied the inclusion and exclusion criteria prior to entry into the study. Overall, the demographics were comparable between subjects receiving EU-Enbrel and subjects receiving US-Enbrel. However, subjects receiving EU-Enbrel tended to be older and there was a slightly higher proportion of males compared with the subjects receiving US-Enbrel (Table 4.26).

Table 4.26 Demographic Summary by Treatment in Report 105

		Enbrel EU N=53	Enbrel US N=56	Overall N=109
Age (years)	Mean	38	30	34
	SD	9.7	9.3	10.1
	Median	40	28	34
	Range	19–49	18–49	18–49
Gender – n (%)	Male	32 (60%)	41 (73%)	73 (67%)
	Female	21 (40%)	15 (27%)	36 (33%)
Race – n (%)	Asian	3 (5.7%)	2 (3.6%)	5 (4.6%)
	Black	1 (1.9%)	1 (1.8%)	2 (1.8%)
	White	48 (90.6%)	51 (91.1%)	99 (90.8%)
	Other	1 (1.9%)	2 (3.6%)	3 (2.8%)
Body weight (kg)	Mean	75	76	76
	SD	12.38	12.63	12.45
	Median	76.1	77.2	76.6
	Range	52.6–99.3	51.5–98.5	51.5–99.3

Source: Report 105, Page 25, Table 11-2

- PK results

The arithmetic mean PK profiles of EU-Enbrel and US-Enbrel following 50 mg single dose subcutaneous injection are presented in Figure 4.10.

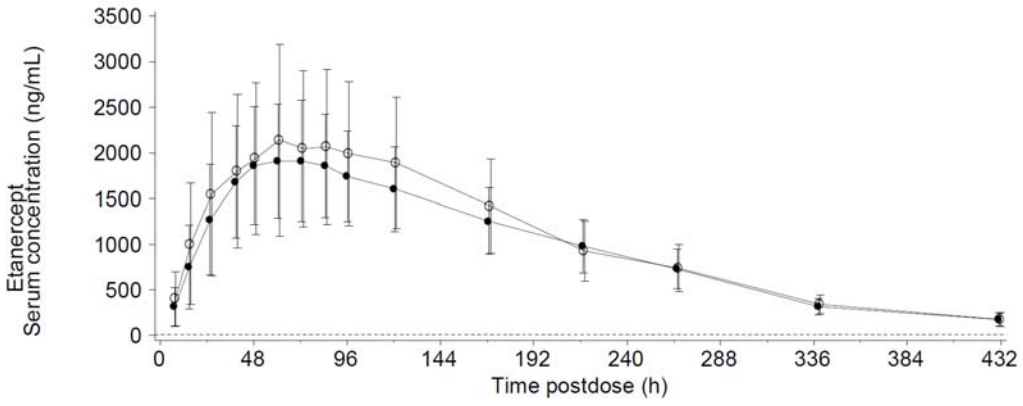

Figure 4.10 EU-Enbrel (dot, N=50) and US-Enbrel (circle, N=54) arithmetic serum concentration-time profile from Report 105. The error bars represent SD. Source: Report 105, page 27, Figure 11-2.

The primary statistical analysis comparing the PK parameters between GP2015 and EU-Enbrel per-protocol set are presented in Table 4.27. The estimated ratio (EU-Enbrel/US-Enbrel) of AUC_{0-t}, AUC_{0-inf}, and C_{max} is 0.9469 (90% CI = 0.8412, 1.0658), 0.9457 (90% CI = 0.8445, 1.0591), and 0.9222 (90% CI = 0.8026, 1.0596), respectively. The summary of other PK endpoints are listed in Table 4.28.

Table 4.27 Statistical Analysis of the PK Parameters of EU-Enbrel/US-Enbrel in Report 105 (Per-Protocol Set, N=104)

				Enbrel EU / Enbrel US			Between subject CV%
			Geometric LS mean		90% CI		
	Enbrel	N		Ratio	Lower	Upper	
$AUC_{0-tlast}$ (ng.h/mL)	EU	49	388578	0.9469	0.8412	1.0658	37.16
	US	53	410380				
C_{max} (ng/mL)	EU	50	1979	0.9222	0.8026	1.0596	44.62
	US	54	2146				
$AUC_{0-\infty}$ (ng.h/mL)	EU	49	411530	0.9457	0.8445	1.0591	35.62
	US	54	435143				

Source: Report 105, Page 28, Table 11-4

Table 4.28 Summary of Other PK Parameters of Enbrel (Per-Protocol Set, N=104)

Parameter	EU-Enbrel (N=50)	US-Enbrel (N=54)
t_{max} (hr) [1]	72.0 (24.1 – 120)	84.0 (24.0 – 120)
$t_{1/2}$ (hr) [2]	84.4 (21.4%)	86.8 (21.7%)
K_{el} (hr^{-1}) [2]	0.00822 (21.4%)	0.00798 (21.7%)
$\%AUC_{extrap}$	5.55 (44%)	5.42 (51.6%)

[1] median (range)
[2] geometric mean (CV%)
[3] arithmetic mean (CV%)
Source: Report 105, Page 54-58, Table 14.2-2

- Safety

A total of 53 subjects in Study 101 received one dose of EU-Enbrel and a total of 56 subjects in Study 102 received one dose of US-Enbrel. Thus, the safety set for the present cross-study analysis comprised 109 subjects.

Overall, 75 adverse events were reported in 35 (66.0%) subjects following administration of 50 mg EU-Enbrel, and 52 adverse events were reported in 28 (50.0%) subjects following administration of 50 mg US-Enbrel. There were no serious adverse events and no adverse events were of severe intensity (Table 4.29). Most adverse events had a mild intensity, and most adverse events were suspected by the investigator to be related to study medication. The overall incidence of adverse events and the incidence of adverse events with a suspected relationship to study medication appeared to be slightly

numerically higher in subjects receiving EU-Enbrel compared with subjects receiving US-Enbrel. One subject (Subject 9 in Study 101) discontinued the study prematurely due to body tinea approximately 49 days postdose following administration of EU-Enbrel, which was considered to be possibly related to study drug.

Table 4.29 General Summary of Adverse Events in Report 105 (Safety Set, N=109)

	Enbrel EU N=53		Enbrel US N=56	
Adverse events	Subjects (%)	Number of AEs	Subjects (%)	Number of AEs
Intensity				
Mild	25 (47.2)	40	17 (30.4)	24
Moderate	6 (11.3)	7	5 (8.9)	7
Severe	0	0	0	0
Relation to IMP				
Unsuspected	22 (41.5)	28	14 (25.0)	21
Suspected	29 (54.7)	47	19 (33.9)	31
AE leading to withdrawal	1	1	0	0

Source: Report 105, Page 30, Table 12-1

There were more incidences of AEs in musculoskeletal and connective tissue disorders and infections/infestations following administration of EU-Enbrel comparing to US-Enbrel. The most frequent preferred terms were nasopharyngitis, headache, and oropharyngeal pain (Table 4.30).

Table 4.30 Incidence of AE by Primary System Organ Class in Report 105 (Safety Set, N=109)

System Organ Class	EU-Enbrel (N=53) N (%), Events	US-Enbrel (N=56) N (%), Events
Overall	35 (66.0%), 75	28 (50.0%), 52
Infections and Infestations	14 (26.4%), 14	7 (12.5%), 7
Nervous System Disorders	11 (20.8%), 14	8 (14.3%), 11
Respiratory, Thoracic, and Mediastinal Disorders	7 (13.2%), 7	10 (17.9%), 11
General Disorders and Administration Site Conditions	8 (15.1%), 9	6 (10.7%),6
Skin and Subcutaneous Tissue Disorders	6 (11.3%), 8	4 (7.1%), 4
Musculoskeletal and Connective Tissue Disorders	8 (15.1%), 9	1 (1.8%), 1
Gastrointestinal Disorders	3 (5.7%), 3	5 (8.9%), 5
Blood and Lymphatic System Disorders (Neutropenia)	4 (7.5%), 4	3 (5.4%), 3
Injury, Poisoning and Procedural Complications	3 (5.7%), 3	1 (1.8%), 1
Eye Disorders (Eye Pain)	0	1 (1.8%), 2
Neoplasms Benign, Malignant and Unspecified (Neurofibroma)	0	1 (1.8%), 1
Psychiatric Disorders (Panic Attack)	1 (1.9%), 1	
Laboratory Investigations	2 (3.8%), 3	

Source: adapted from CSR 104, Page 57, Table 12-2

There were no clinically important findings in the morphology of the 12-lead ECG for individual subjects.

The antibody results were negative prior to the first dose, prior to the second dose and at the follow-up visit for all subjects.

Conclusions:

- Although this cross-study comparison was not a powered objective of the two studies, the main analysis showed that nominal doses of 50 mg of either EU-Enbrel or US-Enbrel resulted in similar etanercept exposure as the ratios (EU-Enbrel/US-Enbrel) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} are all within the goal post 80% - 125%.
- The nature of reported adverse events was similar for EU-Enbrel and US-Enbrel. However, the overall incidence was slightly numerically higher in subjects receiving EU-Enbrel than in subjects receiving US-Enbrel.

Reviewer's Analysis:

Reviewer's independent analysis on per-protocol set showed similar results, which are in agreement with the Sponsor's analysis: 90% CI of the ratios (EU-Enbrel/US-Enbrel) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} are all within the goal post 80% - 125% (Table 4.31).

Table 4.31 Comparison of PK Parameters of EU-Enbrel/US-Enbrel in Report 105 (Per-Protocol Set, N=104)

Parameter	EU-Enbrel	US-Enbrel	Ratio (EU-Enbrel/US-Enbrel)[3]
$AUC_{0\text{-}t}$ (µg·h/mL)[1]	392.632 (N=49)	415.237 (N=53)	0.9456 (0.8397, 1.0647)
$AUC_{0\text{-}inf}$ (µg·h/mL)[1]	416.484 (N=49)	439.738 (N=54)	0.9471 (0.8451, 1.0615)
C_{max} (µg/mL)[1]	1.980 (N=50)	2.146 (N=54)	0.9222 (0.8026, 1.0596)
T_{max} (hour)[2]	72 (24 – 120)	84 (24 – 120)	-

[1] Least-squares geometric means (N)
[2] Median (range)
[3] Ratio (90% CI)
Source: Reviewer's analysis, the ANOVA model included treatment and period as fixed effects.

Sensitivity analysis: In total 53 subjects received EU-Enbrel treatment and 56 subjects received US-Enbrel treatment; all these 109 subjects were included in the safety set of Report 105. The 5 subjects excluded from the per-protocol set were due to withdrawal or protocol deviation from GP2015 treatment period. Therefore, an ANOVA model was carried out by using this 109-subject safety set to compare the PK parameters between EU-Enbrel and US-Enbrel. The results are similar to the results obtained from per-protocol set analysis: 90% CI of the ratios (EU-Enbrel/US-Enbrel) of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} are all within the goal post 80% - 125% (Table 4.32).

Table 4.32 Comparison of PK Parameters of EU-Enbrel/US-Enbrel in Report 105 (Per-Protocol Set, N=109)

Parameter	EU-Enbrel	US-Enbrel	Ratio (EU-Enbrel/US-Enbrel)[3]
$AUC_{0\text{-}t}$ (µg·h/mL)[1]	395.388 (N=52)	412.543 (N=55)	0.9584 (0.8550, 1.0743)
$AUC_{0\text{-}inf}$ (µg·h/mL)[1]	419.320 (N=52)	436.971 (N=56)	0.9596 (0.8600, 1.0708)
C_{max} (µg/mL)[1]	1.990 (N=53)	2.128 (N=56)	0.9348 (0.8177, 1.0686)
T_{max} (hour)[2]	72 (24 – 120)	78 (24 – 120)	-

[1] Least-squares geometric means (N)
[2] Median (range)

[3] Ratio (90% CI)
Source: Reviewer's analysis, the ANOVA model included treatment and period as fixed effects.

The geometric mean PK profiles of GP2015 and EU-Enbrel following 50 mg single dose subcutaneous injection are presented in Figure 4.11.

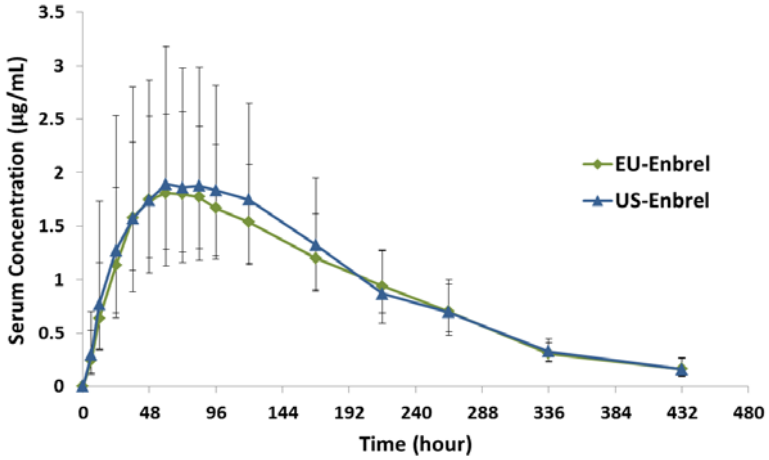

Figure 4.11 EU-Enbrel (green, N=50) and US-Enbrel (blue, N=54) geometric serum concentration-time profile from Report 105 (per-protocol set). The error bars represent SD. During the Period II, the pre-dose carryover concentrations from Period I were set at 0.

4.1.6 Study 302

Study Type: multiple dose, efficacy and safety study in patients with plaque type psoriasis
Study Dates: 06/24/2014 – 06/24/2014 (data cut-off date for Week 12 analysis)
Study Center: 74 Study centers screened patients and 71 Study centers randomized patients (in Bulgaria, Czech Republic, Estonia, Germany, Hungary, Poland, Romania, Russia, Slovakia, South Africa, United Kingdom and Ukraine).
Drug Products Batch: GP2015 (batch no. S0011, S0012, and S0014) and EU-Enbrel (batch no. G75422, H18066, and H76640)

Title:
A randomized, double-blind, multicenter study to demonstrate equivalent efficacy and to compare safety and immunogenicity of a biosimilar etanercept (GP2015) and Enbrel in patients with moderate to severe chronic plaque-type psoriasis

Objective:

- The primary objective was to demonstrate equivalent efficacy of GP2015 and EU-Enbrel in patients with moderate to severe chronic plaque-type psoriasis with respect to Psoriasis Area and Severity Index (PASI) 75 response rate at Week 12.

- The clinical pharmacology-related secondary objectives in Treatment Period 1 (TP1; Week 12) were:
  - To compare the PK of GP2015 and EU-Enbrel in terms of trough serum concentrations in a subset of 100 patients
  - To compare immunogenicity as determined by measuring the rate of anti-drug antibody formation against GP2015 and EU-Enbrel.

- The clinical pharmacology-related secondary objectives in Treatment Period 2 (TP2; Week 12 to Week 30) were:
  - To compare immunogenicity of pooled data from patients who underwent repeated switches (Groups 1b and 2b) with those from patients who were constantly treated with GP2015 (Group 1a) and Enbrel (Group 2a).
  - To compare immunogenicity data from patients who were constantly treated with GP2015 (Group 1a) versus those from patients who were constantly treated with Enbrel (Group 2a).

- The objectives in the Extension Period (EP; Week 30 to Week 52) were:
  - To compare immunogenicity of pooled data from patients who underwent repeated switches and continued with the last treatment after Week 30 for further 22 weeks (Groups 1b and 2b) with those from patients who were constantly treated with GP2015 (Group 1a) and Enbrel (Group 2a) for 52 weeks
  - To compare immunogenicity data from patients who were constantly treated with GP2015 (Group 1a) versus those of patients who were constantly treated with Enbrel (Group 2a) after Week 30 up to Week 52.

Study Design and Method:
This study was a multi-center, randomized, double-blind, confirmatory efficacy and safety study intended to enroll 546 patients with moderate to severe chronic plaque-type psoriasis. The study consisted of 4 periods: screening period (of at least 2 weeks and up to 4 weeks), TP1 (12 weeks), TP2 (18 weeks), and an

EP (22 weeks) (Figure 4.12).

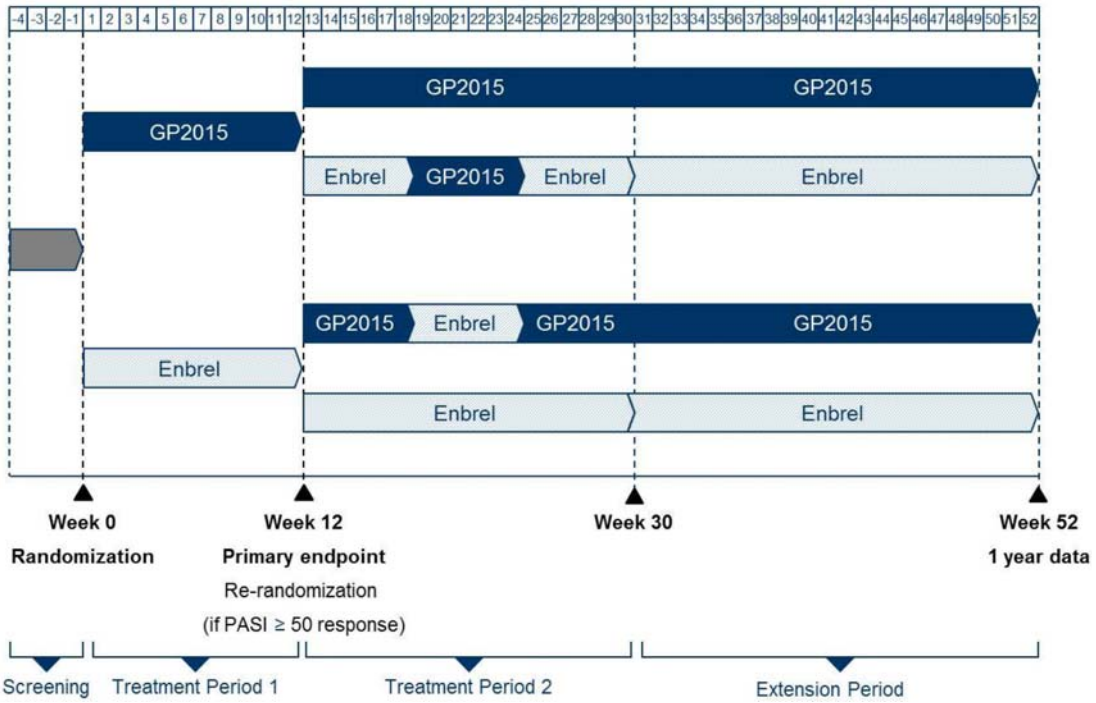

Figure 4.12 Study design of Study 302 (Source: CSR 302, page 35, Figure 9-1)

- Treatment Period 1

GP2015 (Group 1) and EU-Enbrel (Group 2): 50 mg subcutaneous (s.c.) injection of study drug until Week 12. Patients were to self-administer doses of GP2015 and Enbrel twice per week.

- Treatment Period 2

Only patients who had achieved at least a PASI 50 response at Week 12 were to proceed to TP2.

  - Continued GP2015 (Group 1a), continued Enbrel (Group 2a): 50 mg s.c. injection of study drug from Week 13 until Week 30. Patients were to self-administer doses of GP2015 and EU-Enbrel once per week.
  - Switch to EU-Enbrel (Group 1b) or to GP2015 (Group 2b): 50 mg s.c. injection of study drug once per week from Week 13 until Week 30. During TP2 patients in Groups 1b and 2b were to self-administer alternating treatment with GP2015 or EU-Enbrel for periods of 6 consecutive weeks, i.e., switching after Week 12 and switching back to the original treatment after Week 18 followed by a third switch of treatment regimen after Week 24.

- Extension Period

After the end of TP2, patients were to continue to be treated for an additional 22 weeks during the EP. They were to receive the treatment they had last received during TP2. If patients have not responded adequately to study drug until Week 30, in the opinion of the investigator, and/or if they require treatment with a medication prohibited according to the exclusion, they were to be discontinued from study drug and a follow-up (FU) visit was to be scheduled.

Noteworthy inclusion criteria included:

- Men or women at least 18 years of age at time of screening
- Chronic plaque-type psoriasis diagnosed at least 6 months before baseline:

- Moderate to severe psoriasis as defined at baseline by:
  - PASI score of 10 or greater and,
  - IGA score of 3 or greater (based on a scale of 0 - 4) and,
  - BSA affected by plaque-type psoriasis of 10% or greater
- Chronic plaque-type psoriasis patients who had previously received phototherapy or systemic psoriasis therapy at least once or who were candidates for such therapies in the opinion of the investigator.

Noteworthy exclusion criteria included:

- Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic, and guttate psoriasis)
- Drug-induced psoriasis (i.e., new onset or current exacerbation from e.g., beta-blockers, or lithium)
- Ongoing use of prohibited psoriasis treatments (e.g., topical corticosteroids, UV-therapy)
- Previous exposure to etanercept
- Active ongoing inflammatory diseases other than psoriasis that could confound the evaluation of the benefit of treatment with etanercept
- History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase could not exceed 2.5 x upper limit of normal at screening
- Patients with a serum creatinine level exceeding 176.8 μmol/L (2.0 mg/dL)
- Significant cardiovascular problems, including but not limited to the following:
  - uncontrolled hypertension (≥160 systolic / 95 diastolic mmHg)
  - congestive heart failure with known decreased left ventricular ejection fraction

PK assessments
At baseline (Day 1) and at Weeks 2, 4, 8 and 12, trough serum concentrations of the investigated drugs were to be analyzed in a subset of approximately 100 patients (approximately 50 patients treated with GP2015 and 50 patients treated with EU-Enbrel). Two serum samples per scheduled time point for PK assessment were to be generated.

In total 632 serum samples of 147 patients were analyzed by ELISA to determine the concentration of GP2015/EU-Enbrel in serum from patients with psoriasis. The samples were stored until analysis at -70 °C. The analysis of the serum samples was done in duplicate. The minimum required dilution in blocking buffer of all the study samples collected at baseline was 1:100. An additional 1:4 dilution in 1:100 diluted healthy human serum pool were used for all the samples collected at Weeks 2, 4, 8 and 12. All samples were measured against a calibration curve of the reference item prepared in 1:100 diluted human serum pool (diluent: blocking buffer). The LLOQ of GP2015/EU-Enbrel in bioanalytical assay for Study 302 was 33.3 ng/mL. For details of ELISA bioanalytical method, refer to section 2.5.

PD assessments
Blood samples for the assessment of high sensitivity C-reactive protein (hsCRP) were obtained at baseline and at Weeks 4 and 12.

Immunogenicity assessment
Blood samples for assessing anti-drug-antibody (ADA) were collected at baseline and at Weeks 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, and 52. Two serum samples per scheduled timepoint for ADA assessment were to be generated.

All samples were first analyzed in a screening assay. Study samples with a result below the validated screening cut-point were reported negative for ADAs. In the event of a positive result (result above or equal to the screening cut-point blank+12.8 counts), the sample was to be additionally analyzed in a secondary confirmatory assay (specificity assay). In case the assay signal could be reduced after addition of excess of etanercept beyond the validated confirmatory assay cut-point (more than 23% reduction), a sample was to be reported as confirmed binding positive. In contrast, samples were to be reported as negative. In addition, confirmed positive ADA samples were to be analyzed for their neutralization potential in a neutralizing competitive ligand binding antibody assay.

Results:

- **Data sets analyzed**

Among 774 screened patients, 531 were randomized with 264 patients assigned to group 1 (receiving GP2015 during TP1) and 267 patients assigned to group 2 (receiving EU-Enbrel during TP1) (Table 4.33). Immunogenicity assay was conducted in all 531 patients. PK evaluation was only conducted in 147 patients (72 from group 1 and 75 from group 2).

Table 4.33 Analysis Data Sets for Treatment Period 1

Disposition/Reason	GP2015 N=264 n (%)	Enbrel N=267 n (%)	Total N=531 n (%)
Screened			**774**
Randomized	264 (100.0)	267 (100.0)	531 (100.0)
FAS[1]	264 (100.0)	267 (100.0)	531 (100.0)
PPS[2]	239 (90.5)	241 (90.3)	480 (90.4)
Safety[3]	264 (100.0)	267 (100.0)	531 (100.0)
Immunogenicity set	264 (100.0)	267 (100.0)	531 (100.0)
PK set	72 (27.3)	75 (28.1)	147 (27.7)

FAS: full analysis set
PPS: per-protocol analysis set
Source: CSR302, page 84, Table 11-1

The demographic characteristics of full analysis set and PK set are summarized in Table 4.34

Table 4.34 Patient Demographics of Full Analysis Set and PK Set for Treatment Period 1

Demographic Variable		Full Analysis Set			PK Set		
		GP2015 N=264	EU-Enbrel N=267	Total N=531	GP2015 N=72	EU-Enbrel N=75	Total N=147
Age (years)	Mean (SD)	42.1 (12.3)	42.7 (12.9)	42.4 (12.6)	41.7 (12.4)	40.7 (12.9)	41.2 (12.7)
	Range	18 - 78	19 - 75	18 - 78	18 - 72	19 - 67	18 - 72
Body Weight (Kg)	Mean (SD)	86.3 (21.1)	85.9 (18.7)	86.1 (19.9)	86.7 (22.3)	85.3 (20.9)	86.0 (21.5)
	Range	47 – 148.5	46.5 - 158	46.5 - 158	49.9 – 148.5	46.5 - 158	46.5 - 158
Sex n (%)	Male	157 (59%)	172 (64%)	329 (62%)	47 (65%)	48 (64%)	95 (65%)
	Female	107 (41%)	95 (36%)	202 (38%)	25 (35%)	27 (36%)	52 (35%)
Race n (%)	White	263 (100%)	264 (99%)	527 (99%)	72 (100%)	74 (99%)	146 (99%)

	Black	1	0	1 (<1%)	0	0	0
	Asian	0	1 (<1%)	1 (<1%)	0	0	0
	Other	0	1 (<1%)	1 (<1%)	0	1 (1%)	1 (1%)
	Unknown	0	1 (<1%)	1 (<1%)	0	0	0

Source: CSR302, page 85, Table 11-2

- **PK**

In the PK set, there were 136 PK samples collected at baseline. Subject 3603007 showed quantifiable EU-Enbrel concentration of 2151.2 ng/mL at baseline, which is about half the value of population mean trough concentration at steady state. The same subject also had the only BLQ post-dose sample (at Week 12) among 480 samples collected during post-dose.

The time course of trough concentrations indicates an achievement of steady-state at least from Week 2 in both treatment arms (Figure 4.13), which is consistent with the drug's half-life of 4-5 days. The steady-state appeared maintained throughout the 12 week observational period in both treatment groups.

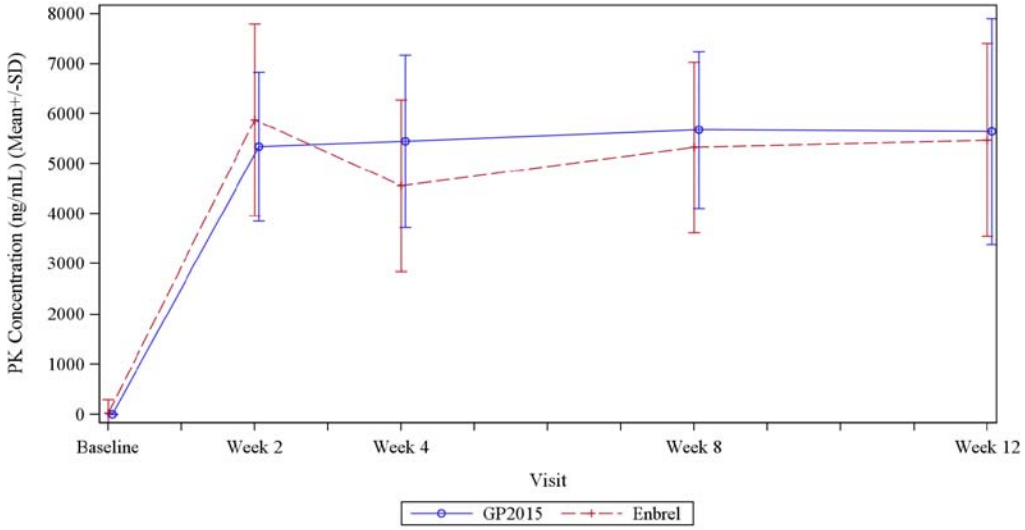

Figure 4.13 EU-Enbrel (red, N=75) and GP2015 (blue, N=72) arithmetic serum concentration-time profile from Study 302. The error bars represent SD. Source: CSR302, page 104, Figure 11-8.

Mean pre-dose concentrations at Weeks 2, 4, 8 and 12 are comparable between GP2015 and EU-Enbrel (Table 4.35). The differences of point estimate are less than 20%.

Table 4.35 Arithmetic mean (SD) Trough Serum Concentration of GP2015/EU-Enbrel during Treatment Period 1 (PK set)

	GP2015 50 mg			Enbrel 50 mg		
Week	n	Mean (SD) (ng/mL)	CV (%)	n	Mean (SD) (ng/mL)	CV (%)
Week 2	60	5338.03 (1493.646)	27.981	59	5879.39 (1921.866)	32.688
Week 4	60	5448.04 (1725.352)	31.669	56	4561.57 (1709.804)	37.483
Week 8	60	5677.59 (1568.213)	27.621	63	5323.35 (1702.528)	31.982
Week 12	60	5640.81 (2263.144)	40.121	62	5474.32 (1931.050)	35.275

Source: CSR302, page 104, Table 11-11

- **PD**

The geometric mean of plasma hsCRP concentration at baseline was 2.00 mg/L (N=265, CV=156%) and 2.31 mg/L (N=262, CV=165%) for patients in EU-Enbrel treatment group and GP2015group, respectively (Figure 4.14). Consistently, proportions of patients with high plasma hsCRP levels (> 3 mg/L) were also greater in GP2015 group than EU-Enbrel (43% vs. 32%). However, the geometric mean of plasma hsCRP levels reduced to approximately 1.0 mg/L for both groups after 12-week treatment.

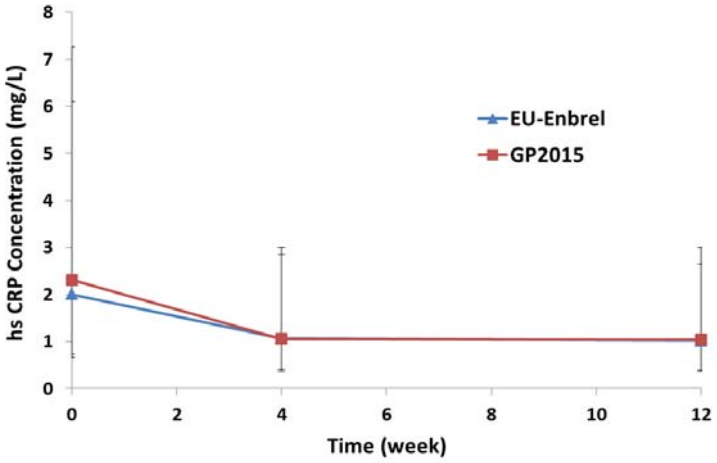

Figure 4.14 hsCRP geometric mean plasma concentration-time profile from EU-Enbrel group (blue, N=266) and GP2015 group (red, N=262) during PT1 in Study 302. The error bars represent SD. Source: asapted from CSR302, page 105, Figure 11-9.

- **Immunogenicity**

Among 531 subjects in the safety set, only Subject 4901005 (in EU-Enbrel group during TP1) does not have ADA results for any blood samples. The immunogenicity results by timeline are summarized in Table 4.36. A total of 5 patients, all in the Enbrel group in TP1, showed a confirmed positive binding ADA response during the study up to week 12. The ADA response was mostly transient as 4 of those 5 patients had positive ADA result in only one sample. The available ADA samples of those 5 patients collected during TP2 and EP were all negative. All ADA-positive samples were tested negative for neutralizing antibodies. Additionally 466 patients (234 from Group 1 and 232 from group 2) were tested for ADA from Week 18 to Week 42 and all had negative results.

Table 4.36 Summary of ADA Positive Incidence by Treatment Group during TP1

Time Points	EU-Enbrel (N=266)	GP2015 (N=264)	Total (N=530)
Baseline*	0/259 (0)	0/260 (0)	0/519 (0)
Week 2*	1/254 (0.4%)	0/250 (0)	1/504 (0.2%)
Week 4*	5/255 (2.0%)	0/258 (0)	5/513 (1.0%)
Week 8*	0/248 (0)	0/251 (0)	0/499 (0)
Week 12*	0/250 (0)	0/251 (0)	0/501 (0)
Total*	5/266 (1.9%)	0/264 (0)	5/530 (0.9%)

*confirmed ADA-positive subject number/total subject number whose samples were analyzed (%)
Source: adapted from CSR302, page 2942, Table 14.3.5-1.1

The demographic information and ADA titers of ADA-positive subjects are listed in Table 37.

Table 4.37 Summary of Patients with Confirmed Positive ADA Response to EU-Enbrel during TP1

Subjects ID	Age	Sex	Race	Positive Sample	Concentration (ng/mL)*	Titer[1]	Reduction Binding by etanercept[2]	Follow-up Samples
3601002	55	Female	White	Week 4	312.6	1:6	35.4%	Negative from Week 8 to Week 42[4]
3701003	71	Female	White	Week 4	173.3	< 1:3	28.5%	Negative from Week 8 to Week 18[4]
3701004	60	Female	Unknown	Week 2	158.5	1:3	27.3%	Negative from Week 8 to Week 30[4]
				Week 4	<150[3]	< 1:3	23.5%	
3704018	50	Male	White	Week 4	215.2	1:3	41.1%	Negative from Week 8 to Week 30[4]
4218001	32	Male	White	Week 4	225.5	N/A	35.5%	Negative from Week 8 to Week 42[4]

[1] As measured in screening assay
[2] As measured in confirmatory assay (specificity assay)
[3] LLOQ
[4] Last time point when ADA sample collected
Source: adapted from CSR302, page 149, Table 12-24

- **ECG**

The majority of patients had normal ECG results at Screening in both treatment groups; 72.3% in the GP2015 group and 71.5% in the Enbrel group. At Week 12, these proportions remained much the same with normal results in 73.1% and 76.0% of patients in the GP2015 and Enbrel groups, respectively.

The proportion of patients with abnormal but non-clinically significant results at Screening was similar between the two groups; 26.9% in the GP2015 group and 27.7% in the Enbrel group. At Week 12, these proportions had decreased slightly with abnormal but non-clinically significant results in 22.7% and 19.1% in the GP2015 and Enbrel groups, respectively. This reduction in proportions is chiefly accounted for by missing data at Week 12.

At Screening, 2 patients (0.8%) in the GP2015 group (Patient 4406003 and Patient 4803020) and 2 patients (0.7%) in the Enbrel group (Patient 3704/028 and Patient 4901002) had abnormal ECG results that were considered clinically significant. Of the patients in the GP2015 group, 1 patient (Patient 4406/003) still had clinically significant abnormal results at Week 12 while the other patient (Patient 4803/020) had non-clinically significant abnormal results at Week 12. Of the patients in the Enbrel group, 1 patient (Patient 3704/028) had normal results at Week 12 while the other patient (Patient 4901/002) had non-clinically significant abnormal results at Week 12.

Conclusions:

- The PK sub-study in 147 male and female patients with chronic plaque-type psoriasis showed similar trough serum concentration levels after multiple s.c. dosing of GP2015 50 mg or EU-Enbrel 50 mg at Weeks 2, 4, 8 and 12 within and across both treatment groups.

- Although the mean plasma concentration of hsCRP was slightly higher in GP2015 treatment group, the mean hsCRP concentrations were reduced to the similar level following 4-week treatment of either GP2015 or EU-Enbrel. The concentrations were kept at low level at Week 12.

- Regarding immunogenicity, all subjects had negative ADA results for GP2015. Additionally, immunogenicity was low with a total of 5 patients (0.9%) having a confirmed positive ADA result in the EU-Enbrel treatment group. All of these cases occurred within the first 4 weeks of treatment and tested negative for neutralizing anti-etanercept antibodies.

Reviewer's Analysis:

The geometric mean trough concentration-time profiles of GP2015 and EU-Enbrel following 50 mg subcutaneous injection twice a week are presented in Figure 4.15.

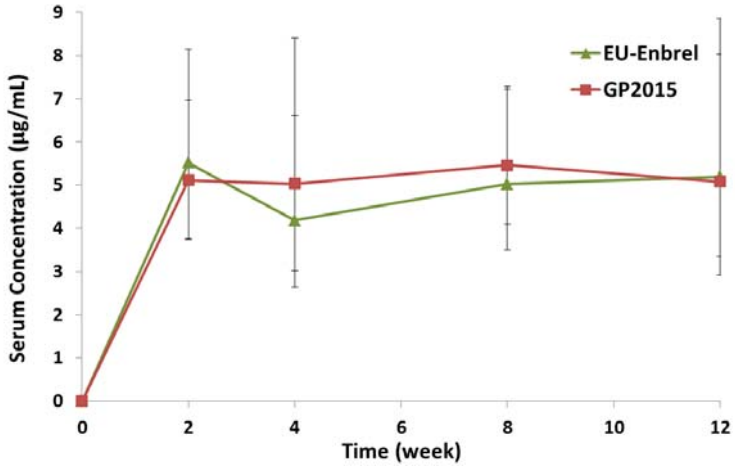

Figure 4.15 EU-Enbrel (green, N=75) and GP2015 (red, N=72) geometric trough concentration-time profile following 50 mg subcutaneous injection twice a week. The error bars represent SD. The pre-first dose concentration from Subject 3603007 was set as 0 and the Week 12 BLQ sample from the same subject was treated as missing.

4.2 Appendix – Biologics License Application Filing Memo

Application Information			
BLA Number	761042	**SDN**	1
Applicant	Sandoz	**Submission Date**	**7/30/2015**
Proper Name	GP2015	**Brand Name**	(b) (4)
Drug Class	TNFR-IgG1 fusion protein		
Indication	• Rheumatoid Arthritis (RA) • Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Plaque Psoriasis (PsO)		
Dosage Regimen	• Adult RA and PsA: 50 mg once weekly with or without methotrexate • AS: 50 mg once weekly • Adult PsO: 50 mg twice weekly for 3 months, followed by 50 mg once weekly • JIA: 0.8 mg/kg weekly, with a maximum of 50 mg per week		
Dosage Form	• 50 mg (1.0 mL) Single-use Prefilled Syringe with BD UltraSafe Passive™ Needle Guard • 50 mg (1.0 mL) Single-use Prefilled Sensoready Pen • 25 mg (0.5 mL) Single-use Prefilled Syringe with BD UltraSafe Passive™ Needle Guard	**Route of Administration**	subcutaneous injection
OCP Division	II	**OND Division**	DPARP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Yunzhao Ren MD, Ph. D	Ping Ji, Ph.D.	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	09/02/2015	**74-Day Letter Date**	10/12/2015
Review Due Date	04/03/2016	**BsUFA Goal Date**	05/27/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

Is there a need for clinical trial(s) inspection?

☑ Yes
☐ No

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence		4	Studies 101, 102, 103, and 104
☐ Food Effect			
☑ Bioanalytical methods		5	Bioanalytical Reports BA12017-R, BA12008-R, BA12023-R, BA14011-R, BA13005-R, BA14020-R
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	4	Studies 101, 102, 103, and 104
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	1	Study 302
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			

☐ Effects of Primary Drug					
Pharmacodynamics					
☐ Healthy Subjects					
☐ Patients					
Pharmacokinetics/Pharmacodynamics					
☐ Healthy Subjects					
☐ Patients					
☐ QT					
Pharmacometrics					
☐ Population Pharmacokinetics					
☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies/Reports		**In Vitro**		**In Vivo**	5
Total Number of Studies/Reports to be Reviewed					5

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/s/

YUNZHAO REN
07/25/2016

PING JI
07/25/2016