

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761071Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

# Office of Clinical Pharmacology

## 351(k) Biosimilar Review

---

<b>351(k) BLA Number</b>	761071
<b>Applicant</b>	Sandoz Inc.
<b>Submission Date</b>	October 30, 2017
<b>Submission Type</b>	Standard review
<b>Link to EDR</b>	<a href="\\CDSESUB1\evsprod\BLA761071\0005">\\CDSESUB1\evsprod\BLA761071\0005</a>
<b>Brand (Generic) Name</b>	Proposed name – Hyrimoz™ (adalimumab- <sup>(b) (4)</sup> )
<b>Dosage Form and Strength</b>	Single-use pre-filled syringe: 40 mg/0.8 mL Autoinjector injector (Sensoready®): 40 mg/0.8 mL
<b>Route of Administration</b>	Subcutaneous
<b>Proposed Indication(s)</b>	<ul style="list-style-type: none"> <li>• Rheumatoid Arthritis (RA)</li> <li>• Juvenile Idiopathic Arthritis (JIA)</li> <li>• Psoriatic Arthritis (PsA)</li> <li>• Ankylosing Spondylitis (AS)</li> <li>• Adult Crohn’s Disease (CD)</li> <li>• Ulcerative Colitis (UC)</li> <li>• Plaque Psoriasis (Ps)</li> </ul>
<b>Associated IND</b>	IND 115732
<b>Reference Product Information (U.S.-licensed)</b>	
<b>Brand (Generic) Name</b>	Humira® (adalimumab)
<b>Dosage Form and Strength</b>	Pre-filled syringe: 80 mg/0.8 mL, 40 mg/0.8 mL, 40 mg/0.4 mL, 20 mg/0.4 mL, 20 mg/0.2 mL, 10 mg/0.2 mL, 10 mg/0.1mL Pen injector: 80 mg/0.8 mL, 40 mg/0.8 mL, 40 mg/0.4 mL Single use institutional use vial: 40 mg/0.8 mL
<b>OCP Review Team Signers</b>	
<b>OCP Review Team</b>	Mohammad (Abir) Absar, PhD (Primary Reviewer) Anshu Marathe, PhD (Team Lead)

## Table of Contents

1. EXECUTIVE SUMMARY.....	5
1.1 Recommendations.....	6
1.2 Post-Marketing Requirements and Commitments .....	6
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT .....	6
2.1 Clinical Pharmacology and Pharmacokinetics.....	6
2.2 Outstanding Issues .....	8
3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW .....	8
3.1 Regulatory Background .....	8
3.1.1. Describe relevant regulatory history for the review of this 351(k) BLA .....	8
3.2 Clinical Pharmacology Review Questions.....	9
3.2.1 What are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity? .....	9
3.2.2 What are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity? .....	10
3.2.3 Are the pharmacologically active moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters? .....	10
3.2.4 Is PK similarity met? .....	10
3.2.5 Is the immunogenicity assay capable of detecting the antidrug antibodies (ADA) in the presence of concentration of product in the study samples?.....	18
3.2.6 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?.....	19
3.2.7 What is the incidence of anti-drug antibodies (ADA)?.....	19
3.2.8 Do the anti-drug antibodies (ADA) have neutralizing activity? .....	20
3.2.9 What is the impact of anti-drug antibodies (ADA) on the PK, activity, and safety of the therapeutic protein?.....	20
4. APPENDICES .....	22
4.1 Summary of Bioanalytical Method Validation and Performance .....	22
4.1.1 Pharmacokinetics .....	22
4.1.1.1 How are the concentrations of the pharmacologically active moieties measured in the plasma and other matrices in the clinical pharmacology studies?.....	22
4.1.1.2 For all moieties measured, is free, bound, or total measured? .....	24

4.1.1.3 What is the concentration range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used? .....	24
4.1.1.4 What are the lower and upper limits of quantification (LLOQ/ULOQ)? .....	24
4.1.1.5 What are the accuracy, precision, and selectivity at these limits? .....	24
4.1.1.6 What is the sample stability under the conditions used in the study? .....	25
4.1.1.7 What is the plan for the QC samples and for reanalysis of the incurred samples? .....	25
4.1.1.8 What are the findings from OSIS inspection? .....	25
4.1.2 Immunogenicity .....	25
4.1.2.1 What bioanalytical methods are used to assess the immunogenicity? .....	25
5. LABELING RECOMMENDATIONS .....	26

### **List of Tables**

Table 1: Summary results of the comparison of the pharmacokinetic parameters between test and reference products (Study GP17-104) .....	7
Table 2: Listing of clinical studies.....	9
Table 3: Summary results of the comparison of the pharmacokinetic parameters between test and reference products (Study GP17-101) .....	11
Table 4: Descriptive statistics for the adalimumab PK parameters (Study GP17-101).....	12
Table 5: Summary results of the comparison of the pharmacokinetic parameters between test and reference products (Study GP17-104) .....	13
Table 6: Descriptive statistics for the adalimumab PK parameters (Study GP17-104).....	14
Table 7: Summary results of the comparison of the pharmacokinetic parameters between GP2017 from AI and PFS (Study GP17-102).....	16
Table 8: Summary results of the comparison of the pharmacokinetic parameters between GP2017- <sup>(b) (4)</sup> and GP2017-Schaftenau products (Study GP17-103) .....	18
Table 9: Summary of binding and neutralizing ADAs in healthy subjects and psoriasis patients	19
Table 10: Summary of patients with confirmed positive ADA response by individual group (Study GP17-301; Week 17 to 51).....	20
Table 11: Logistic regression analysis on PASI response at Week 16 by ADA status .....	22
Table 12: Summary of ELISA validation results (human serum of healthy donors, Method 13010-R) .....	23
Table 13: Summary of the ELISA validation results (human serum of patients with psoriasis, Method BA14007-R) .....	24

### **List of Figures**

Figure 1: Arithmetic mean adalimumab serum concentration-time profiles (Study GP17-101); Source: BLA 761071, Module 5.3.3.1 CSR GP17-101 .....	11
Figure 2: Arithmetic mean adalimumab serum concentration-time profiles (Study GP17-101); Source: FDA analysis of data from BLA 761071, Module 5.3.3.1, CSR GP17-104 .....	13
Figure 3: Study design (GP17-301) .....	14

Figure 4: Arithmetic mean (SD) adalimumab serum concentration-time profile for (A) treatment period 1 (up to Week 17), and (B) entire study duration (continued group up to Week 51) (excluding patients with pre-dose PK concentrations at baseline).....	15
Figure 5: Comparison of GP2017 PK profile from AI and PFS by body weight. ....	17
Figure 6: Comparison of adalimumab exposure by ADA status (Study GP17-104).....	21
Figure 7: PK comparison (C <sub>trough</sub> ) in plaque psoriasis patients by ADA status (Study GP17-301) .....	22

## **1. EXECUTIVE SUMMARY**

Sandoz submitted a Biologic License Application (BLA) for GP2017, a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody that binds to human tumor necrosis factor alpha (TNF $\alpha$ ), under Section 351(k) of the Public Health Services Act (42 U.S.C. 262(k)). The applicant is seeking approval for GP2017 as a biosimilar to US-licensed Humira<sup>®</sup> (BLA 125057 by AbbVie, approved on 12/31/2002), and licensure for the following approved indications for US-Humira<sup>®</sup>:

- Rheumatoid Arthritis (RA)
- Juvenile Idiopathic Arthritis (JIA)
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Adult Crohn's Disease (CD)
- Ulcerative Colitis (UC)
- Plaque Psoriasis (Ps)

GP2017 drug product is supplied as a sterile, preservative-free, clear, colorless to slightly yellowish solution for subcutaneous (SC) administration. The drug product is supplied either as a single-dose, pre-filled pen (Sensoready<sup>®</sup> Pen) or as a single-dose, 1 mL pre-filled glass syringe containing 40 mg/0.8 mL of adalimumab.

The clinical development for GP2017 included five clinical studies (GP17-101, GP17-104, GP17-102, GP17-103 and GP17-301). Pharmacokinetic (PK) similarity of GP2017 to US-licensed Humira<sup>®</sup> was evaluated in two pivotal double-blind, three-arm, parallel study to determine the pharmacokinetics and safety of GP2017, EU-approved Humira<sup>®</sup> and US-licensed Humira<sup>®</sup> following a single 40 mg SC injection in healthy subjects (Studies GP17-101 and GP17-104). PK and immunogenicity were also assessed for GP2017, US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup> in patients with psoriasis (Ps) (Study GP17-301). In addition, the applicant conducted two supportive clinical studies: an open-label, parallel study was conducted to determine the PK and safety of GP2017 following a single 40 mg SC injection by an autoinjector (AI) or by a pre-filled syringe (PFS) in healthy male subjects (Study GP17-102). A double-blind, two-arm parallel study was conducted in healthy male subjects following a single SC injection to determine the PK, safety and immunogenicity of GP2017 from two drug substance production facilities – Schaftenuau, Austria and (b) (4) (Study GP17-103).

PK similarity was demonstrated between GP2017 and US-licensed Humira<sup>®</sup> in Study GP17-104. In this study, the 90% confidence intervals (CI) for the geometric mean ratios (GMR) of GP2017 to US-licensed Humira<sup>®</sup>, GP2017 to EU-approved Humira<sup>®</sup>, and US-licensed Humira<sup>®</sup> to EU-approved Humira<sup>®</sup> for C<sub>max</sub>, AUC<sub>0-last</sub> and AUC<sub>0-inf</sub> were all within the PK similarity acceptance interval of 0.8 to 1.25. The study also established the PK portion of the scientific bridge between GP2017, US-licensed Humira<sup>®</sup>, and EU-approved Humira<sup>®</sup>, which supports the use of EU-approved Humira<sup>®</sup> in the comparative clinical study (Study GP17-301). The clinical pharmacology results add to the totality of evidence to support a demonstration of biosimilarity of GP2017 and US-licensed Humira<sup>®</sup>. In addition, PK was demonstrated to be comparable between GP2017 administered from an autoinjector and that from the pre-filled syringe (Study GP17-102) (see CDRH review by Dr. Kathleen Fitzgerald for the proposed auto-injector device evaluation). Analytical comparability was demonstrated for GP2017 from two drug substance production facilities (see OBP review by Dr. Yanming An). In addition, PK was, in general, comparable

between drug products formulated from drug substance manufactured at these two different manufacturing sites (Study GP17-103).

Immunogenicity of GP2017, US-licensed Humira® and EU-approved Humira® was assessed in healthy subjects in Studies GP17-101, GP17-102, GP17-103 and GP17-104, and in patients with psoriasis in Study GP17-301. Similar incidences of anti-drug antibody (ADA) were observed between GP2017 and US-licensed Humira®.

### 1.1 Recommendations

The Office of Clinical Pharmacology has determined that PK similarity has been established between GP2017 and US-licensed Humira®, and the PK results support a demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira®.

Review Issue	Recommendations and Comments
<b>Pivotal evidence of PK similarity</b>	PK similarity was demonstrated between GP2017 and US-licensed Humira®. In addition, the PK portion of the scientific bridge between GP2017, US-licensed Humira® and EU-approved Humira® has also been demonstrated. The 90% CI of the geometric mean ratio for each pairwise comparison for C <sub>max</sub> , AUC <sub>0-last</sub> and AUC <sub>0-inf</sub> fell within the pre-specified margin of 0.8 to 1.25.
<b>Evidence of immunogenicity comparability</b>	The immunogenicity results from the studies submitted indicate similar incidence of ADA among GP2017, US-licensed Humira® and EU-approved Humira®.

### 1.2 Post-Marketing Requirements and Commitments

None.

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

### 2.1 Clinical Pharmacology and Pharmacokinetics

The clinical development for GP2017 included five clinical studies: two pivotal double-blind, three-arm, parallel PK similarity study of GP2017, EU-approved Humira® and US-licensed Humira® in healthy subjects (Studies GP17-101, n=219 and GP17-104, n=318) and a pivotal comparative efficacy and safety study of GP2017 and EU-approved Humira®/US-licensed Humira® (pooled) in 465 patients with psoriasis (Study GP17-301). The applicant also conducted two supportive clinical studies: an open-label, parallel study to determine the PK and safety of GP2017 following a single SC injection by an autoinjector or by a pre-filled syringe in healthy male subjects (n=108) (GP17-102), and a double-blind, two-arm parallel study to determine the PK, safety and immunogenicity of GP2017 from two drug substance production facilities – Schafteuau, Austria and (b)(4) – following a single SC injection in healthy male subjects (n=176) (GP17-103).

In Study GP17-101, the 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of GP2017 to US-licensed Humira® for the PK parameters (i.e., C<sub>max</sub>, AUC<sub>0-last</sub> and AUC<sub>0-inf</sub>) were all within the pre-specified acceptance interval of 0.80–1.25. However, the 90% CI for the GMR of GP2017 to EU-approved Humira® and US-licensed Humira® to EU-approved Humira® were

outside the pre-specified upper limit of 1.25 for the PK parameters  $AUC_{0-last}$  and  $AUC_{0-inf}$ , while GMR for  $C_{max}$  were within the pre-specified acceptance interval for both comparisons. The applicant conducted a root cause analysis with the aim to identify reasons for the failure to demonstrate PK similarity, but no single root cause related to the product or study conduct was identified. The observed variability for  $AUC_{0-last}$  of >40% was higher than the anticipated variability of 31% used for powering the study. Therefore, the applicant conducted Study GP17-104 with increased sample size.

In Study GP17-104, an inter-subject CV% of 42% for  $AUC_{0-inf}$  was used for the sample size calculation. In addition, the study included only healthy male subjects to reduce variability. The 90% CIs for the GMR of GP2017 to EU-approved Humira<sup>®</sup>, GP2017 to US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup> to US-licensed Humira<sup>®</sup> for the PK parameters (i.e.,  $C_{max}$ ,  $AUC_{0-last}$  and  $AUC_{0-inf}$ ) were all within the pre-specified interval of 0.80–1.25, as presented in Table 1. These pairwise comparisons met the pre-specified criteria for PK similarity between GP2017, US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup>. A scientific PK bridge was, therefore, established to support the relevance of the data generated using EU-approved Humira<sup>®</sup> in the comparative clinical study (Study GP17-301). For details, refer to section 3.2.4.

**Table 1: Summary results of the comparison of the pharmacokinetic parameters between test and reference products (Study GP17-104)**

Comparison	PK Parameter	GMR (90% CI)
GP2017 vs US-licensed Humira <sup>®</sup>	$C_{max}$	1.00 (0.94, 1.06)
	$AUC_{0-last}$	1.05 (0.96, 1.14)
	$AUC_{0-inf}$	1.08 (1.00, 1.18)
GP2017 vs EU-approved Humira <sup>®</sup>	$C_{max}$	1.05 (0.99, 1.11)
	$AUC_{0-last}$	1.06 (0.97, 1.15)
	$AUC_{0-inf}$	1.04 (0.96, 1.13)
EU-approved Humira <sup>®</sup> vs US-licensed Humira <sup>®</sup>	$C_{max}$	0.95 (0.90, 1.01)
	$AUC_{0-last}$	0.99 (0.91, 1.08)
	$AUC_{0-inf}$	1.04 (0.96, 1.13)

Source: BLA 761071, Module 2.7.2 – Summary of Clinical Pharmacology Studies, Tables 2-15 and 2-17, Results based on ANCOVA model with treatment as a fixed effect and body weight as a covariate.

In Study GP17-301, serum trough concentrations assessed both at treatment period 1 (up to Week 17) in all patients (i.e., n=225 for GP2017; n=229 for pooled US-licensed and EU-approved Humira<sup>®</sup>) and at the extended period (up to Week 51) in a subset of patients (i.e., n=165 patients who continued GP2017 throughout the treatment; n=168 patients who continued pooled US-licensed and EU-approved Humira<sup>®</sup> throughout the treatment) were generally comparable between GP2017 and Humira<sup>®</sup> treatment groups. The incidence of immunogenicity at Week 52 for GP2017, pooled US-licensed and EU-approved Humira<sup>®</sup> were 39% (62/160) and 45% (72/159),

respectively, and, therefore, were in general comparable between GP2017 and the Humira<sup>®</sup> treated patients. For details refer to section 3.2.4.

Overall, the submitted clinical pharmacology data support a demonstration of PK similarity among GP2017 and US-licensed Humira<sup>®</sup>, EU-approved Humira<sup>®</sup>.

### Supporting studies

Study GP17-102 was conducted to determine the PK and safety of GP2017 following a single SC injection by an AI or by a PFS in healthy male subjects. The applicant conducted this dedicated PK study (GP17-102) in healthy male subject with one site of administration, i.e., abdomen. The PK parameters (i.e.,  $C_{max}$ ,  $AUC_{0-last}$  and  $AUC_{0-inf}$ ) were comparable between the PFS and AI across a wide range of body weight. The 90% CI for the GMR of GP2017 from autoinjector (AI) to GP2017 from pre-filled syringe (PFS) for the PK parameters (i.e.,  $C_{max}$ ,  $AUC_{0-last}$  and  $AUC_{0-inf}$ ) were within the pre-specified interval of 0.80–1.25. For details refer to section 3.2.4. Per the applicant, the proposed AI device uses the same AI platform that is being used in Erelzi<sup>®</sup> (BLA 761042; etanercept) and Cosentyx<sup>®</sup> (BLA 125504; secukinumab) for which the drug product is administered in multiple injection sites in similar patient population.<sup>1</sup> The proposed auto-injector has three different components (rear end cover, plunger rod, plunger spring) compared to the currently marketed AI device. Pending evaluation of the auto-injector device by CDRH, the PK comparability demonstrated in Study GP17-102 is deemed acceptable from a clinical pharmacology perspective.

The applicant proposes [REDACTED]<sup>(b) (4)</sup>, as one of the drug substance production site for the commercial formulations. Analytical comparability was demonstrated for GP2017 formulations from the two drug substance production sites – Schaftenau (current) and [REDACTED]<sup>(b) (4)</sup> (new) (refer to OBP review by Dr. Yanming An). In addition, the applicant conducted Study GP17-103 to determine the PK, safety and immunogenicity of GP2017 from two drug substance production facilities. The 90% CI for the GMR of GP2017 formulations from two drug substance production facilities (i.e., [REDACTED]<sup>(b) (4)</sup> and Schaftenau) were 1.03 (0.97, 1.10) for  $C_{max}$ , 1.17 (1.06, 1.31) for  $AUC_{0-last}$  and 1.13 (1.01, 1.26) for  $AUC_{0-inf}$ . The PK parameters (i.e.,  $C_{max}$ ,  $AUC_{0-last}$  and  $AUC_{0-inf}$ ) were, in general, comparable between the two sites supporting the determination of analytical comparability. For details, refer to Section 3.2.4.

## **2.2 Outstanding Issues**

None.

## **3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW**

### **3.1 Regulatory Background**

#### **3.1.1. Describe relevant regulatory history for the review of this 351(k) BLA**

GP2017 is being developed as a proposed similar biological product to Humira<sup>®</sup> (adalimumab). During the clinical development of GP2017, the applicant had a Type-B pre-IND meeting held on January 11, 2013, and discussed the study design for the pivotal PK similarity study in healthy subjects, PK assessment in the comparative clinical study, and PK comparability study between

---

<sup>1</sup> Erelzi<sup>®</sup> is indicated for RA, AS and JIA; Cosentyx<sup>®</sup> is indicated for Ps, PsA and AS.

proposed AI and PFS product. BLA 761071 was originally submitted on August 25, 2016, but was withdrawn by the applicant.

### **3.2 Clinical Pharmacology Review Questions**

#### **3.2.1 What are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity?**

The clinical development of GP2017 included five completed clinical studies, as listed in Table 2 below.

**Table 2: Listing of clinical studies**

<b>Study ID</b>	<b>Design</b>	<b>Objective</b>	<b>Subjects</b>	<b>Dose</b>	<b>Treatments</b>
<b>Pivotal Clinical Pharmacology Studies</b>					
GP17-101	R, DB, SD, 3-arm, PG	PK, immunogenicity, safety	Healthy male and female (n=219)	40 mg SC	GP2017 PFS (n=73) US-Humira® PFS (n=73) EU-Humira® PFS (n=73)
GP17-104	R, DB, SD, 3-arm, PG	PK, immunogenicity, safety	Healthy male (n=318)	40 mg SC	GP2017 PFS (n=107) US-Humira® (n=105) EU-Humira® (n=106)
<b>Comparative Clinical Study</b>					
GP17-301	R, DB, MC, PG TP1: 0-17W TP2: 17-35 W Ext: 35-51 W	Efficacy, safety, immunogenicity, PK	Patients with plaque psoriasis (n=465)	80 mg SC loading dose followed by 40 mg every other week SC	GP2017 PFS (n=231) US- /EU-Humira® (pooled) (n=234)
<b>Supportive Clinical Pharmacology Studies</b>					
GP17-102	R, OL, SD, PG	PK, immunogenicity, safety	Healthy male (n=108)	40 mg SC	GP2017 PFS (n=54) GP2017 AI (n=54)
GP17-103	R, DB, SD, PG	PK, immunogenicity, safety	Healthy male (n=176)	40 mg SC	GP2017 PFS- (b) (4) (n=86) GP2017 PFS-Schaftenau (n=90)

Abbreviations: R – randomized; DB – double blind; OL – open label; PG – parallel group; TP – treatment period; SD – single dose; MC – multicenter; SC – subcutaneous; PFS – pre-filled syringe; AI – autoinjector

Source: BLA 761071, Module 5.2

Study GP17-101 and GP17-104 were pivotal double-blind, three-arm, parallel PK similarity studies comparing GP2017, EU-approved Humira® and US-licensed Humira® in healthy subjects. In addition, PK of GP2017 and EU-approved / US-licensed (pooled) Humira® was also assessed in patients with moderate-to-severe Ps in Study GP17-301.

Study GP-102 was a supporting randomized, open-label, single dose parallel group PK comparability study comparing GP2017 from PFS and AI in healthy male subjects who were stratified by six body-weight categories, 50–64.9 kg, 65–79.9 kg, 80–94.9 kg 95–109.9 kg, 110–124.9 kg, 125–140 kg. In Study GP17-103, which was a randomized, double-blind, single dose parallel group study in healthy males, PK of GP2017 was compared between formulations with

two different drug substance production sites – [REDACTED]<sup>(b)(4)</sup> and Schaftenu, Austria. The applicant used the proposed to-be-marketed formulation in the clinical studies.

### **3.2.2 What are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity?**

PK ( $C_{\max}$ ,  $AUC_{0-\text{last}}$  and  $AUC_{0-\text{inf}}$ ) was assessed as primary endpoint in the Study GP17-101 to evaluate and compare the PK profiles of GP2017, EU-approved Humira<sup>®</sup> and US-licensed Humira<sup>®</sup> in healthy male and female subjects. Safety, tolerability and immunogenicity were the secondary endpoints. In Study GP17-104, PK ( $C_{\max}$  and  $AUC_{0-\text{inf}}$ ) were assessed as primary endpoint to compare PK profiles of GP2017, EU-approved Humira<sup>®</sup> and US-licensed Humira<sup>®</sup> in healthy male subjects.  $AUC_{0-\text{last}}$ , in addition to immunogenicity, safety and tolerability were assessed as secondary endpoint. PK similarity was assessed based on 90% CI of GMR of GP2017 to US-licensed Humira<sup>®</sup>, GP2017 to EU-approved Humira<sup>®</sup>, and US-licensed Humira<sup>®</sup> to EU-approved Humira<sup>®</sup> for  $C_{\max}$ ,  $AUC_{0-\text{last}}$  and  $AUC_{0-\text{inf}}$  being within the pre-specified interval of 0.80 to 1.25.

In supporting Study GP17-102,  $C_{\max}$  and  $AUC_{0-360\text{h}}$  were assessed as the primary endpoint to compare PK of GP2017 from PFS and AI device.  $AUC_{0-\text{last}}$ ,  $AUC_{0-\text{inf}}$ , in addition to safety, tolerability and immunogenicity, were assessed as secondary endpoint. For Study GP17-103,  $C_{\max}$ ,  $AUC_{0-\text{last}}$  and  $AUC_{0-\text{inf}}$  were assessed as the primary endpoint to compare PK of GP2017 between formulations with two different drug substance manufacturing sites. Safety, tolerability and immunogenicity were assessed as secondary endpoint. Irrespective of the endpoints being primary or secondary, the 90% CI of the GMR for  $C_{\max}$ ,  $AUC_{0-\text{last}}$  and  $AUC_{0-\text{inf}}$  were calculated and reported for all clinical pharmacology studies.

Study GP17-301 was a comparative efficacy trial in patients with moderate-to-severe plaque psoriasis. Therefore, the primary efficacy endpoint was PASI75 response rate, defined as the proportion of patients achieving a reduction of at least 75% of the PASI score at Week 16 as compared to baseline. Safety, immunogenicity and PK at steady-state ( $C_{\text{trough}}$ ) were also evaluated in this study.

### **3.2.3 Are the pharmacologically active moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters?**

Concentration of free adalimumab in plasma was measured using a validated ELISA technique. Refer to Section 4.1.1 for additional detail.

### **3.2.4 Is PK similarity met?**

#### PK similarity studies:

#### Study GP17-101

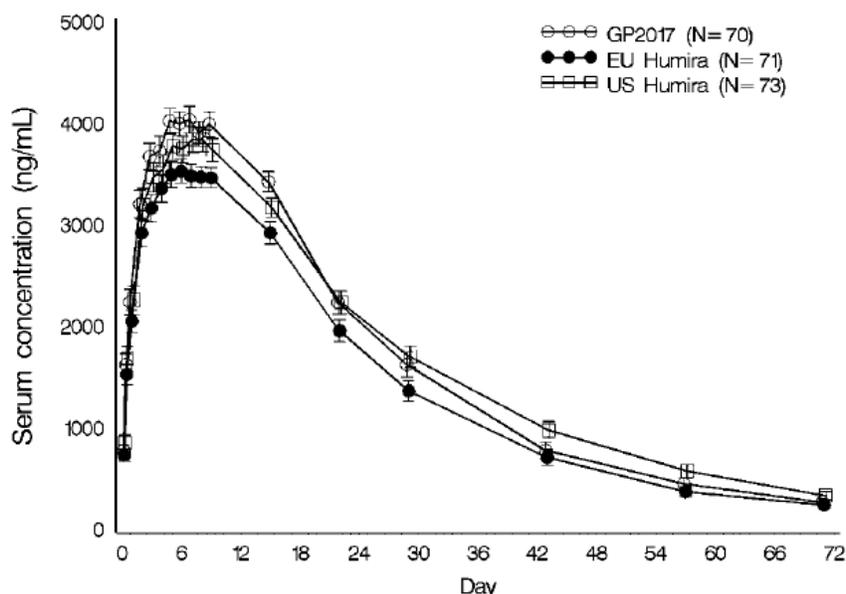
The first PK similarity Study GP17-101 was a randomized, double-blind, 3-arm, parallel group single-dose study. A total of 219 healthy male and female subjects were enrolled and randomized to 3 parallel arms with 73 subjects in each arm. All subjects received a single-dose of 40 mg of either GP2017, US-licensed Humira<sup>®</sup> or EU-approved Humira<sup>®</sup> through subcutaneous injection in the abdomen by pre-filled syringe. The PK, safety, tolerability and immunogenicity of GP2017, EU-approved Humira<sup>®</sup>, and US-licensed Humira<sup>®</sup> were assessed. For PK similarity comparison between GP2017 and US-licensed Humira<sup>®</sup>, the 90% CIs for the GMR of  $C_{\max}$ ,  $AUC_{0-\text{last}}$  and  $AUC_{0-\text{inf}}$  were all contained within the pre-specified similarity range of 0.80–1.25 (Table 3).

However, for the comparison between GP20107 vs EU-approved Humira<sup>®</sup>, and US-licensed Humira<sup>®</sup> vs EU-approved Humira<sup>®</sup> the of 90% CIs for the GMR of AUC<sub>0-last</sub> and AUC<sub>0-inf</sub> were outside upper limit of the pre-specified range of 1.25, while that for C<sub>max</sub> were within the similarity range (Table 3). The mean serum concentration-time profiles are presented in Figure 1; descriptive statistics for the PK parameters are presented in Table 4.

**Table 3: Summary results of the comparison of the pharmacokinetic parameters between test and reference products (Study GP17-101)**

Comparison	PK Parameter	GMR (90% CI)
GP2017 vs US-licensed Humira <sup>®</sup>	C <sub>max</sub>	1.05 (0.97, 1.14)
	AUC <sub>0-last</sub>	0.99 (0.88, 1.12)
	AUC <sub>0-inf</sub>	0.94 (0.83, 1.07)
GP2017 vs EU-approved Humira <sup>®</sup>	C <sub>max</sub>	1.15 (1.06, 1.24)
	AUC <sub>0-last</sub>	1.23 (1.08, 1.38)
	AUC <sub>0-inf</sub>	1.16 (1.02, 1.31)
US-licensed Humira <sup>®</sup> vs EU-approved Humira <sup>®</sup>	C <sub>max</sub>	1.09 (1.01, 1.18)
	AUC <sub>0-last</sub>	1.24 (1.10, 1.40)
	AUC <sub>0-inf</sub>	1.23 (1.08, 1.40)

Source: BLA 761071, Module 2.7.2 – Summary of Clinical Pharmacology Studies, Table 2-7, Results based on ANOVA model with treatment and body weight as a fixed effects



**Figure 1: Arithmetic mean adalimumab serum concentration-time profiles (Study GP17-101); Source: BLA 761071, Module 5.3.3.1 CSR GP17-101**

**Table 4: Descriptive statistics for the adalimumab PK parameters (Study GP17-101)**

Parameter	GP2017 (N=70) GM (%CV)	EU-Humira® (N=73) GM (%CV)	US-Humira® (N=71) GM (%CV)
C <sub>max</sub> (µg/mL)	4.44 (23.7)	3.80 (27.7)	4.23 (28.3)
AUC <sub>0-last</sub> (µg.h/mL)	2438 (40.9)	2087 (40.2)	2505 (40.6)
AUC <sub>0-inf</sub> (µg.h/mL)	2692 (42.4)*	2416 (40.9)*	2900 (42.0)*

\*For AUC<sub>0-inf</sub>, n=70, 69 and 72 for GP2017, EU-approved Humira® and US-licensed Humira®, respectively. Source: BLA 761071, Module 2.7.2 – Summary of Clinical Pharmacology Studies, Table 2-6.

Applicant’s root-cause analysis did not identify a single root cause related to the product or study conduct to explain why PK similarity could not be demonstrated for the pairwise comparisons of GP20107 vs EU-approved Humira® and US-licensed Humira® vs EU-approved Humira®. The observed variability for AUC<sub>0-last</sub> of >40% was higher than the applicant’s anticipated variability of 31% when powering the study. The applicant reasoned that since the observed PK variability in the study was higher than that assumed for sample size calculation, the study was not adequately sized to statistically prove PK similarity. The reviewer notes that the PK similarity between GP2017 and US-licensed Humira® was established in this study. The reason for the lower exposure from the EU-approved Humira® remains unclear. Consequently, the applicant conducted another PK similarity study with increased sample size.

#### Study GP17-104

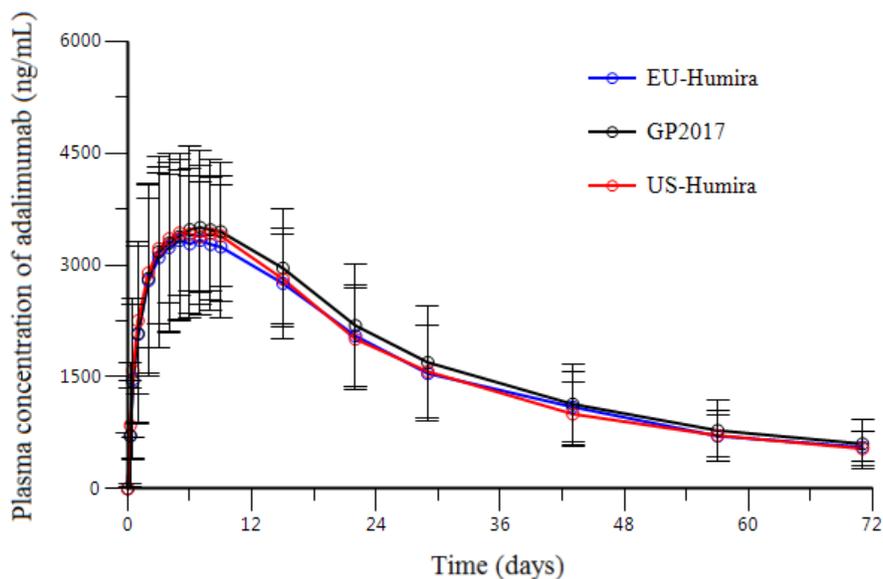
Study GP17-104 was designed by taking into account the observed variability from GP17-101 with additional restrictions (e.g., BMI, male subjects only) with respect to baseline characteristics of the subject to enroll a more homogenous population. This was a randomized, double-blind, 3-arm, parallel group single-dose study. A total of 318 healthy male subjects were enrolled and randomized to 3 parallel arms with 105 to 107 subjects in each arm. All subjects received a single-dose of 40 mg of either GP2017 (n=107), US-licensed Humira® (n=105) or EU-approved Humira® (n=106) through subcutaneous injection in the abdomen by pre-filled syringe. The PK, safety, tolerability and immunogenicity of GP2017, EU-approved Humira®, and US-licensed Humira® were assessed.

The pairwise comparisons of GP2017 vs EU-approved Humira®, GP2017 vs US-licensed Humira®, and EU-approved Humira® vs US-licensed Humira® met the pre-specified acceptance criteria for PK similarity (i.e., 90% CIs for the ratios of geometric mean of C<sub>max</sub>, AUC<sub>0-last</sub> and AUC<sub>0-inf</sub> were within the interval of 0.80 to 1.25) as summarized in Table 5. The mean serum concentration-time profiles of GP2017, EU-approved Humira® and US-licensed Humira® are presented in Figure 2; the descriptive statistics are outlined in Table 6. Among the 318 healthy male subjects randomized in this study, 12 subjects were excluded from the PK analysis set. Of these 12 subjects, 10 subjects were excluded as they were not ADA negative prior to drug administration, and remaining 2 subjects did not complete PK profiling due to early discontinuation.

**Table 5: Summary results of the comparison of the pharmacokinetic parameters between test and reference products (Study GP17-104)**

Comparison	PK Parameter	GMR (90% CI)
GP2017 vs US-licensed Humira®	C <sub>max</sub>	1.00 (0.94, 1.06)
	AUC <sub>0-last</sub>	1.05 (0.96, 1.14)
	AUC <sub>0-inf</sub>	1.08 (1.00, 1.18)
GP2017 vs EU-approved Humira®	C <sub>max</sub>	1.05 (0.99, 1.11)
	AUC <sub>0-last</sub>	1.06 (0.94, 1.15)
	AUC <sub>0-inf</sub>	1.04 (0.96, 1.13)
EU-approved Humira® vs US-licensed Humira®	C <sub>max</sub>	0.95 (0.90, 1.01)
	AUC <sub>0-last</sub>	0.99 (0.91, 1.08)
	AUC <sub>0-inf</sub>	1.04 (0.96, 1.13)

Source: BLA 761071, Module 2.7.2 – Summary of Clinical Pharmacology Studies; Tables 2-15 and 2-17, Results based on ANCOVA model with treatment as a fixed effect and body weight as a covariate.



**Figure 2: Arithmetic mean adalimumab serum concentration-time profiles (Study GP17-101); Source: FDA analysis of data from BLA 761071, Module 5.3.3.1, CSR GP17-104**

**Table 6: Descriptive statistics for the adalimumab PK parameters (Study GP17-104)**

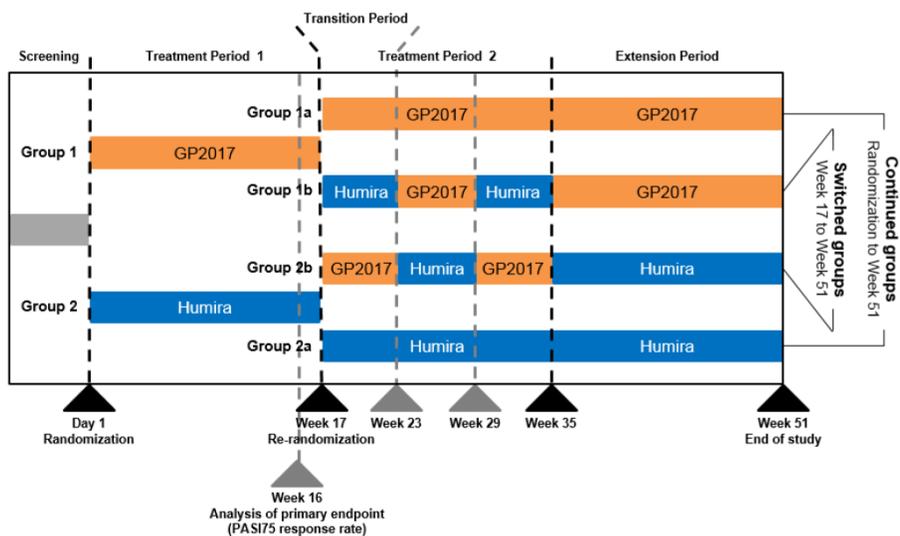
Parameter	GP2017 (N=104)	EU-Humira® (N=103)	US-Humira® (N=99)
	GM (%CV)	GM (%CV)	GM (%CV)
C <sub>max</sub> (µg/mL)	3.67 (29.0)	3.54 (29.9)	3.75 (22.9)
AUC <sub>0-last</sub> (µg.h/mL)	2261 (42.0)	2162 (37.5)	2201 (32.8)
AUC <sub>0-inf</sub> (µg.h/mL)	2849 (34.0)*	2766 (35.9)*	2604 (29.2)*

\*For AUC<sub>0-inf</sub>, n=81, 85 and 82 for GP2017, EU-approved Humira® and US-licensed Humira®, respectively. Source: BLA 761071, Module 2.7.2 Summary of Clinical Pharmacology Studies, Table 2-14

Independent analyses on the PK analysis set were conducted by the reviewer and the 90% CI of the GMR of C<sub>max</sub>, AUC<sub>0-last</sub> and AUC<sub>0-inf</sub> were all within the pre-specified range of 0.80–1.25 for the pairwise comparisons among GP2017, EU-approved Humira® and US-licensed Humira®. In addition, analysis conducted including all subjects also met the pre-specified acceptance criteria.

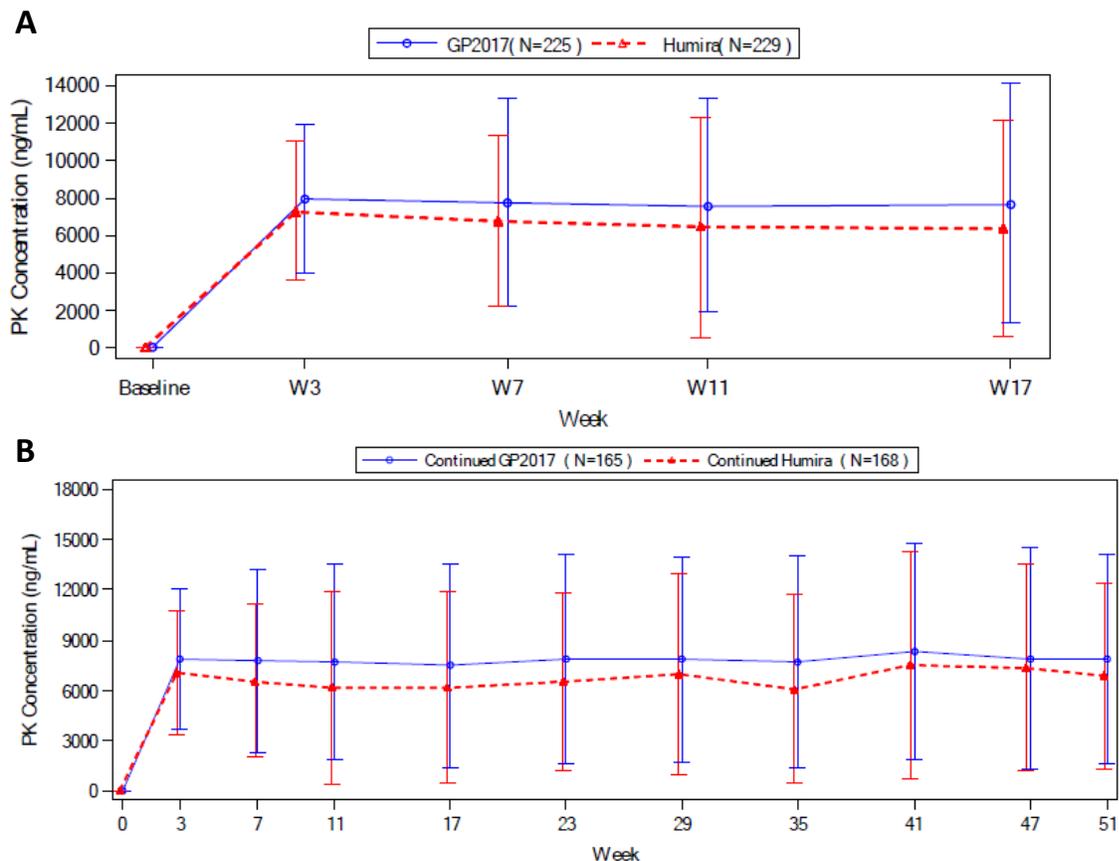
Comparative clinical study:

The PK of GP2017, and EU-approved/US-licensed (pooled) Humira® was also assessed in the comparative efficacy Study GP17-301. This randomized, double-blind, multicenter study was conducted to demonstrate efficacy and to compare safety and immunogenicity of GP2017 and Humira® in patients with moderate to severe chronic plaque psoriasis. A total of 465 patients were randomized to receive either GP2017 (n=231) or EU-approved/US-licensed (pooled) Humira® (n=234). The study consisted of 4 periods (screening period, 2 treatment periods and an extension period). Treatment period 1 started at the time of randomization and ended prior to drug administration at Week 17. Patients received either GP2017 PFS or Humira® SC as a loading dose of 80 mg at the randomization visit and subsequently a dose of 40 mg every other week. Period 2 started at Week 17 and ended at Week 35. At Week 17, the qualifying patients from both treatment groups were re-randomized in a 2:1 ratio to either remain on their initial study treatment or to receive GP2017 or Humira® during 3 alternating periods of 6 weeks each, up to Week 35. The extension period started at Week 35 and ended at Week 51; during this period, patients received the same study treatment as in treatment period 1 (Figure 3).



**Figure 3: Study design (GP17-301)**

The primary endpoint of the study was PASI75 at Week 16. PK analyses was performed in all patients and serum drug concentrations were reported at baseline and prior to dosing at Week 3, 7, 11, 17, 23, 29, 35, 39. As shown in Figure 4, the trough concentrations are comparable at each time point between GP2017 and the pooled Humira® group during treatment period 1 as well as the entire study duration.



**Figure 4: Arithmetic mean (SD) adalimumab serum concentration-time profile for (A) treatment period 1 (up to Week 17), and (B) entire study duration (continued group up to Week 51) (excluding patients with pre-dose PK concentrations at baseline**

Source: BLA 761071, Module 5.3.5.1, CSR GP17-301

Supportive clinical pharmacology studies:  
Study GP17-102

The supportive PK comparability study GP17-102 was a randomized, open-label, single-dose, parallel-group study in 108 healthy male subjects to determine the PK and safety of GP2017 following single SC injection by an AI or a by a PFS. In this study, healthy male subjects received one single dose of 40 mg GP2017 administered SC in the abdomen by an AI (n=54) or by a PFS (n=54). Subjects were stratified by 6 body weight categories (50.0–64.9 kg, 65.0–79.9 kg, 80.0–94.9 kg, 95.0–109.9 kg, 110–124.9 kg, and 125.0–140.0 kg). The PK, safety, and immunogenicity of GP2017 were assessed.

The 90% confidence interval CIs for the ratios of geometric mean of  $C_{max}$ ,  $AUC_{0-last}$  and  $AUC_{0-inf}$  were within the pre-specified interval of 0.80 to 1.25 for the entire study population (50.0–140.0

kg), as summarized in Table 7. Further analysis based on body weight range of <70 kg, 70–100 kg and >100 kg demonstrated comparable PK parameters between the two devices in each of the weight category (Figure 5).

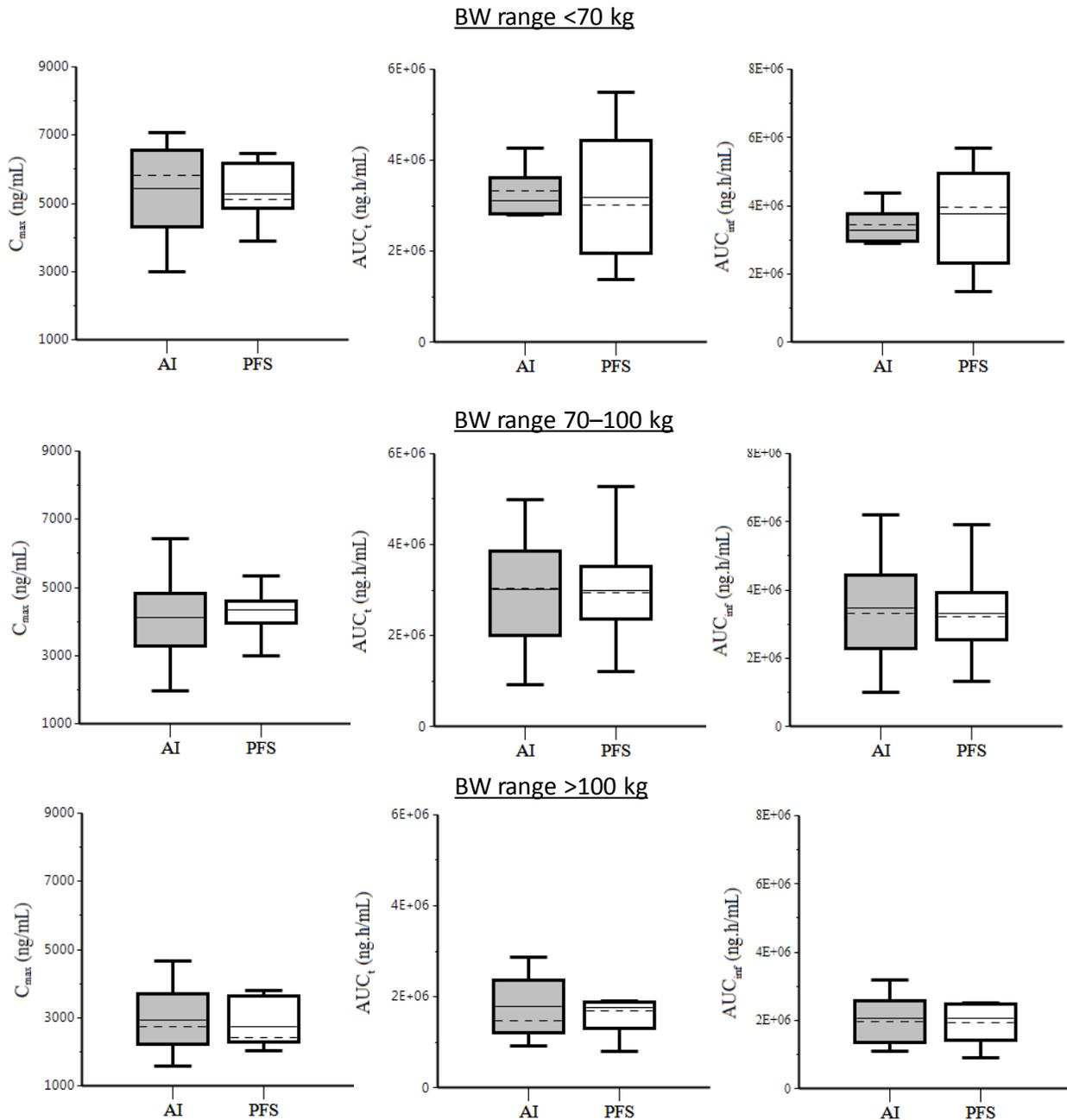
**Table 7: Summary results of the comparison of the pharmacokinetic parameters between GP2017 from AI and PFS (Study GP17-102)**

Comparison	PK Parameter	<u>GMR (90% CI)</u>
		BW range 50.0–140.0 kg
GP2017 AI vs PFS	C <sub>max</sub>	0.95 (0.88, 1.02)
	AUC <sub>0-last</sub>	0.99 (0.88, 1.13)
	AUC <sub>0-inf</sub>	1.01 (0.89, 1.15)

Source: BLA 761071, Module 2.7.2 – Summary of Clinical Pharmacology Studies, Tables 2-24, 2-25 and 2-26, Results based on ANCOVA model with treatment as a fixed effect and body weight as a covariate.

Independent PK analyses were conducted by the reviewer that confirmed that systemic exposure is comparable between the two devices across a range of body weight. Per the applicant, the proposed AI device uses the same AI platform that is being used in Erelzi<sup>®</sup> (BLA 761042; etanercept) and Cosentyx<sup>®</sup> (BLA 125504; secukinumab) for which the drug product is administered in multiple injection sites in similar patient population.<sup>2</sup> The proposed auto-injector has three different components (rear end cover, plunger rod, plunger spring) compared to the currently marketed AI device. Pending evaluation of the auto-injector device by CDRH, the PK comparability demonstrated in Study GP17-102 is deemed acceptable from a clinical pharmacology perspective.

<sup>2</sup> Erelzi<sup>®</sup> is indicated for RA, AS and JIA; Cosentyx<sup>®</sup> is indicated for Ps, PsA and AS.



**Figure 5: Comparison of GP2017 PK profile from AI and PFS by body weight.**

Source: FDA analysis of Data from BLA 761071, Module 5.3.3.1, CSR GP17-102

#### Study GP17-103

Study GP17-103 was a randomized, double-blind, parallel group study in 178 healthy male subjects to evaluate the PK, safety and immunogenicity of the GP2017 drug product made from drug substance manufactured either at (b) (4) (referred to as GP2017-(b) (4)) or at Sandoz GmbH, Biopharmaceuticals Schaftenau in Austria (referred to as GP2017-Schaftenau). For both sites, drug substance was formulated to drug product at (b) (4). While clinical development program for GP2017 was carried out with GP2017-Schaftenau drug

substance, the applicant intends to establish both sites as alternative drug substance manufacturing sites.

Analytical comparability was demonstrated between the drug products made from drug substance manufactured in these two sites (refer to OBP review by Dr. Yanming An). In addition, a PK study was conducted to complement the analytical data. In this study, subjects were randomized to receive a single-dose of 40 mg of either GP2017- (b) (4) (n=88) or GP2017-Schaftenau (n=90) through SC injection in the abdomen by pre-filled syringe.

The 90% CI for the GMR of GP2017 formulations from two drug substance production facilities (i.e., (b) (4) and Schaftenau) were 1.03 (0.97, 1.10) for  $C_{max}$ , 1.17 (1.06, 1.31) for  $AUC_{0-last}$  and 1.13 (1.01, 1.26) for  $AUC_{0-inf}$  (Table 8). The PK parameters (i.e.,  $C_{max}$ ,  $AUC_{0-last}$  and  $AUC_{0-inf}$ ) were, in general, comparable between the two sites supporting the determination of analytical comparability. Independent analyses were conducted by the reviewer and the PK comparison was in agreement with those reported by the applicant. Considering the demonstrated analytical comparability of the drug formulations from these two drug substance production sites, the result was deemed acceptable from a clinical pharmacology perspective.

**Table 8: Summary results of the comparison of the pharmacokinetic parameters between GP2017- (b) (4) and GP2017-Schaftenau products (Study GP17-103)**

Comparison	PK Parameter	GMR (90% CI)
GP2017- (b) (4) vs GP2017-Schaftenau	$C_{max}$	1.03 (0.97, 1.10)
	$AUC_{0-last}$	1.17 (1.06, 1.31)
	$AUC_{0-inf}$	1.13 (1.01, 1.26)

Source: BLA 761071, Module 2.7.2 – Summary of Clinical Pharmacology Studies, Table 2-32, Results based on ANCOVA model with treatment as a fixed effect and body weight as a covariate.

## **Immunogenicity**

### **3.2.5 Is the immunogenicity assay capable of detecting the antidrug antibodies (ADA) in the presence of concentration of product in the study samples?**

The immune response after adalimumab administration was evaluated by a multi-tiered approach comprising a validated ECL bridging immunogenicity assay for the (i) screening, (ii) confirmation and (iii) titration of binding ADA, and a validated competitive ligand binding assay (neutralizing antibody (Nab) assay) for the (iv) assessment of the neutralizing capacity of the antibodies. A single assay was used for the detection of ADAs against GP2017 and originator, and the capability of the assay to detect antibodies against all products equally was demonstrated during assay validation. The validated drug tolerance limit for the assays was 40 µg/mL. Refer to the OBP review by Dr. Yanming An for detailed information regarding assay validation and analysis of clinical study samples.

### 3.2.6 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?

Yes, the sampling schedule for ADA in Study GP17-301 was adequate to capture baseline, early onset, and dynamic profile of ADA formation. In Study GP17-301, blood samples for ADA assessment were collected at baseline and at Weeks 3, 7, 11, 17, 23, 29, 35, 41, 47 and 51. During PK similarity studies (Study GP17-101 and GP17-104) as well as supportive PK studies (GP17-102 and GP17-13), blood samples for ADA were collected at baseline and on Days 16, 30, 44 and 72.

### 3.5.7 What is the incidence of anti-drug antibodies (ADA)?

In Studies GP17-101 and GP17-104, the incidence of ADAs following a single dose of 40 mg SC of study drug to healthy subjects was, in general, comparable among all three treatment arms. In Study GP17-301 in psoriasis patients, following repeat dosing the rates of immunogenicity were, in general, comparable between continued GP2017, EU-approved/US-licensed pooled Humira® groups up to Week 51. Table 9, summarizes the ADA incidence from GP2017 in comparison to Humira®. Table 10 summarizes the immunogenicity data from transition of products between GP2017 and Humira® (Week 17 to Week 51). Refer to the clinical review by Dr. Mark Borigini for further detail.

**Table 9: Summary of binding and neutralizing ADAs in healthy subjects and psoriasis patients**

	Healthy subjects (Study GP17-101)			Healthy subjects (Study GP17-104)			Plaque psoriasis (Study GP17-301)	
	GP2017 (n=73)	EU-Humira® (n=73)	US-Humira® (n=73)	GP2017 (n=107)	EU-Humira® (n=106)	US-Humira® (n=105)	GP2017 (n=160)	Pooled Humira® (n=159)
<b>ADA+ n (%)</b>	49 (67%)	55 (75%)	50 (68%)	62 (58%)	74 (69%)	73 (69%)	62 (39%)	72 (45%)
<b>NAb+ n (%)</b>	44 (60%)	46 (63%)	37 (51%)	58 (54%)	68 (64%)	66 (63%)	55 (34%)	61 (39%)

Source: BLA 761071, Module 5.3.3.1 CSR GP17-101, GP17-104, Module 5.3.5.1, CSR GP17-301. For GP17-301, ADA incidence represents patients who continued with GP2017 or Humira® treatment at Week 51.

**Table 10: Summary of patients with confirmed positive ADA response by individual group (Study GP17-301; Week 17 to 51)**

ADA response	Humira to GP2017 N=63 n/N' (%)	Continued Humira N=127 n/N' (%)	GP2017 to Humira N=63 n/N' (%)	Continued GP2017 N=126 n/N' (%)
<b>Anti-drug antibodies<sup>a</sup></b>				
Week 17	12/57 (21.1)	26/118 (22.0)	17/59 (28.8)	23/118 (19.5)
Week 23	14/56 (25.0)	24/112 (21.4)	18/57 (31.6)	15/106 (14.2)
Week 29	15/56 (26.8)	22/104 (21.2)	17/56 (30.4)	20/104 (19.2)
Week 35	17/53 (32.1)	22/104 (21.2)	14/54 (25.9)	15/101 (14.9)
Week 41	14/45 (31.1)	23/97 (23.7)	16/49 (32.7)	14/98 (14.3)
Week 47	16/45 (35.6)	21/99 (21.2)	12/46 (26.1)	15/95 (15.8)
Week 51	15/45 (33.3)	19/98 (19.4)	13/46 (28.3)	16/96 (16.7)
<b>Neutralizing antibodies<sup>a,b</sup></b>				
Week 17	12/12 (100.0)	25/26 (96.2)	16/17 (94.1)	23/23 (100.0)
Week 23	14/14 (100.0)	24/24 (100.0)	18/18 (100.0)	15/15 (100.0)
Week 29	15/15 (100.0)	22/22 (100.0)	17/17 (100.0)	20/20 (100.0)
Week 35	17/17 (100.0)	21/22 (95.5)	14/14 (100.0)	15/15 (100.0)
Week 41	14/14 (100.0)	23/23 (100.0)	16/16 (100.0)	14/14 (100.0)
Week 47	16/16 (100.0)	18/21 (85.7)	12/12 (100.0)	15/15 (100.0)
Week 51	15/15 (100.0)	18/19 (94.7)	13/13 (100.0)	16/16 (100.0)
<b>Overall from Week 1<sup>c</sup></b>				
Negative	37/61 (60.7)	67/122 (54.9)	32/60 (53.3)	79/123 (64.2)
Positive	24/61 (39.3)	55/122 (45.1)	28/60 (46.7)	44/123 (35.8)
Neutralizing	24/24 (100.0)	47/55 (85.5)	21/28 (75.0)	38/44 (86.4)
Transient <sup>d</sup>	4/24 (16.7)	25/55 (45.5)	11/28 (39.3)	19/44 (43.2)

Source: BLA 761071, Module 2.7.4, Summary of Clinical Safety. Table 4-8

### 3.2.8 Do the anti-drug antibodies (ADA) have neutralizing activity?

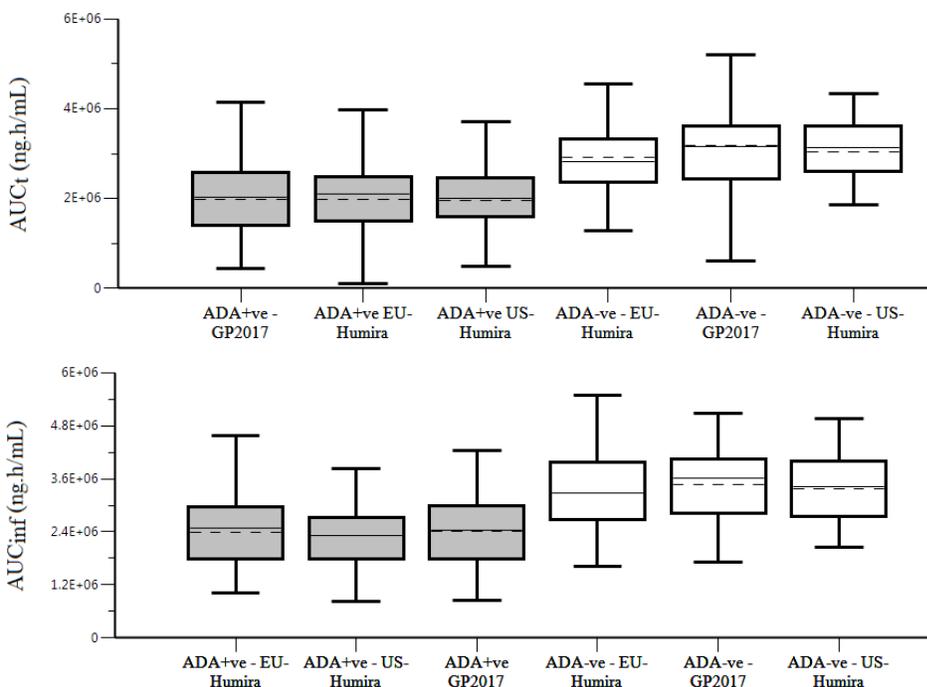
Yes, in Study GP17-301, the incidence of neutralizing antibody was 34 to 39% for GP2017 and pooled US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup> in psoriasis patients (Table 9). Among the ADA+ subjects in Study GP17-301, almost all subjects developed neutralizing antibody (89% and 85% for continued GP2017 and continued Humira<sup>®</sup> group, respectively). Overall, the rate of neutralizing ADA was comparable among all three treatment arms.

### 3.2.9 What is the impact of anti-drug antibodies (ADA) on the PK, activity, and safety of the therapeutic protein?

#### Impact on PK

While the development of ADAs appears to increase clearance of the products, the impact of ADAs on PK was similar on GP2017, US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup>.

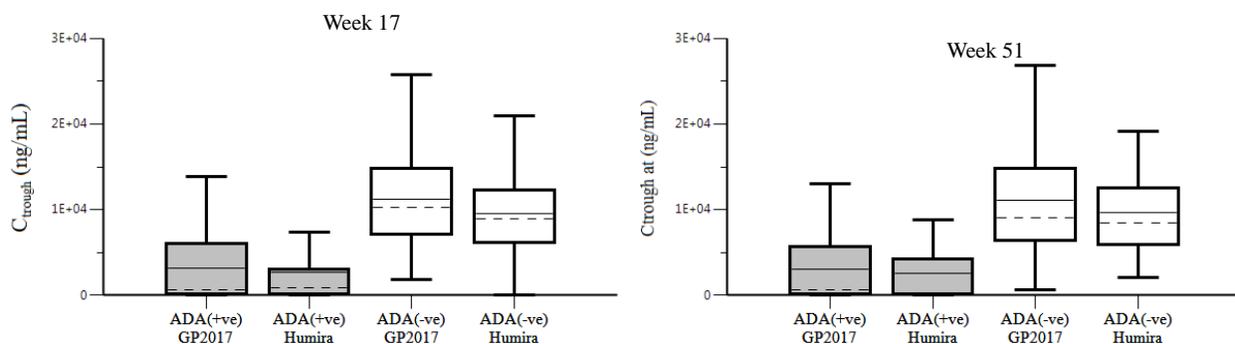
In this submission, the systemic exposure (AUC) of GP2017 or US-licensed Humira® or EU-approved Humira® in healthy subjects who were ADA-positive were about 35–45% lower in Study GP17-101 and 30–40% lower in Study GP17-104 for all three treatments compared to ADA-negative subjects, as presented in Figure 6. While the development of ADAs appears to increase clearance of the products, the impact of ADAs did not influence PK similarity following treatment with GP2017, US-licensed Humira® and EU-approved Humira® since comparable ADA incidence was observed following all three treatments. Therefore, the ADA formation did not affect the PK similarity between GP2017 and US-licensed Humira®.



**Figure 6: Comparison of adalimumab exposure by ADA status (Study GP17-104)**

Source: FDA analysis of Data from BLA 761071, Module 5.3.3.1, CSR GP17-104

To investigate the potential impact of ADA on PK in plaque psoriasis patients, the relationship between ADA and trough concentrations in Study GP17-301 was examined. The overall steady-state trough concentrations by ADA status were evaluated at the end of treatment period 1 (Week 17) and at the end of study (Week 51) (Figure 7). While the development of ADA seems to increase apparent clearance of adalimumab and decrease the serum concentrations of adalimumab, the trough concentrations for ADA-negative and ADA-positive subgroups were consistent between GP2017 and pooled Humira® group.



**Figure 7: PK comparison (C<sub>trough</sub>) in plaque psoriasis patients by ADA status (Study GP17-301)**

Source: FDA analysis of Data from BLA 761071, Module 5.3.5.1, CSR GP17-301

#### Impact on efficacy and safety

In the ADA positive subpopulation, the clinical responses were numerically lower than the ADA negative group, but were similar by ADA status between GP2017 and pooled Humira® group. ADA does not appear to affect the efficacy similarity between GP2017 and pooled Humira® group (Table 11). The overall incidence of adverse events in Study GP17-301 were similar between ADA-positive and ADA-negative subjects. See Clinical/ Statistical review by Dr. Mark Borigini and Dr. Robert Abugov for further detail.

**Table 11: Logistic regression analysis on PASI response at Week 16 by ADA status**

	Treatment	n/N	Adjusted response rate (SE) [%]
<b>Total</b>	GP2017	132/197	66.8 (3.33)
	Humira®	127/196	65.0 (3.38)
<b>ADA negative</b>	GP2017	111/149	74.3 (3.58)
	Humira®	105/146	72.1 (3.70)
<b>ADA positive</b>	GP2017	17/40	42.8 (7.72)
	Humira®	15/38	39.2 (7.80)

N=number of patients per treatment group/subgroup; n=number of patients per treatment group/subgroup achieving PASI75 response; PPS=per-protocol set

Source: BLA 761071, Module 5.3.5.1, CSR GP17-301

## **4. APPENDICES**

### **4.1 Summary of Bioanalytical Method Validation and Performance**

#### **4.1.1 Pharmacokinetics**

##### **4.1.1.1 How are the concentrations of the pharmacologically active moieties measured in the plasma and other matrices in the clinical pharmacology studies?**

Adalimumab PK assay for Studies GP17-101, GP17-102, GP17-103 and GP17-104:

The serum concentrations of free adalimumab were quantified using a validated Enzyme Linked ImmunoSorbent Assay (ELISA) (method validation report BA13010-R). In brief, a microtiter plate was coated with TNF $\alpha$ . Once specific binding sites had been blocked, the serum samples containing adalimumab were added. The detection of adalimumab captured on the TNF $\alpha$ -coated

microtiter plate was done with an enzyme labeled anti-human IgG (Fc-specific) secondary antibody and the subsequent color reaction. For this, a chromogen was added to the wells and was oxidized by HRP (horseradish-peroxidase) 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.

Adalimumab concentrations from GP2017, US-licensed Humira® and EU-approved Humira® were determined on a standard curve ranged from 0.25 µg/mL to 8 µg/mL using a five-parameter curve-fitting program. The minimal required dilution was 1:200. The tolerance of the assay to anti-adalimumab positive control antibody interference was tested during the validation of the method. At a drug concentration of 6000 ng/mL, no interference with anti-adalimumab antibody was observed up to a concentration of 20 µg/mL for US-licensed Humira® and EU-approved Humira®, and up to 40 µg/mL for GP2017. At a drug concentration of 750 ng/mL, no impact of ADAs up to a concentration of 5 µg/mL was observed for US-licensed Humira® and EU-approved Humira®, and 10 µg/mL for GP2017. The tolerance of the assay to target (TNFα) interference was also tested; a TNFα concentration up to 200 ng/mL had no impact on the detection of adalimumab from GP2017, US-licensed Humira® and EU-approved Humira®. The validation results are shown in Table 12.

**Table 12: Summary of ELISA validation results (human serum of healthy donors, Method 13010-R)**

Validation parameter	Validation Results		
	GP2017	US-licensed Humira®	EU-approved Humira®
Intra-assay precision	2–5% LLOQ/ULOQ 4–5%	2–4% LLOQ/ULOQ 3–5%	4% LLOQ/ULOQ 2–4%
Inter-assay precision	9–16% LLOQ/ULOQ 8–11%	7–14% LLOQ/ULOQ 8–10%	7–11% LLOQ/ULOQ 7–11%
Intra-assay accuracy	91–97% LLOQ/ULOQ 85–99%	91–93% LLOQ/ULOQ 89–95%	91–95% LLOQ/ULOQ 87–99%
Inter-assay accuracy	98–103% LLOQ/ULOQ 94–104%	96–104% LLOQ/ULOQ 90–105%	98–103% LLOQ/ULOQ 94–104%
Freeze/thaw stability	Demonstrated for 5 freeze-thaw cycles		
Short-term stability	Demonstrated up to 3 days at 2–8° C, and up to 20 h at RT		
Long-term stability	Demonstrated up to 5 months at -20° C, and up to 8 months at -70° C		
Dilution testing	Accuracy: 111–119% Precision: 16–19%	Accuracy: 90–103% Precision: 2–5%	Accuracy: 97–104% Precision: 2–4%

Source: Adapted from BLA 761071, Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods; VS – Validation sample.

#### Adalimumab PK assay for Study 301:

For the determination of free adalimumab concentrations in human serum samples of patients with psoriasis in Study GP17-301, the ELISA method used for healthy volunteer study sample analysis was re-validated for patient matrix (Method BA14007-R). In brief, a microtiter plate was coated with TNFα. Once unspecific binding sites were blocked, the serum samples containing adalimumab (e.g. standards, QCs and study samples) were added. The detection of bound

adalimumab was done with an enzyme labeled antihuman IgG (Fc-specific) secondary antibody and the subsequent color reaction. For this 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 minimum required dilution was 1:200, and the assay range was 0.25 µg/mL to 8 µg/mL. The validation results are shown in Table 13.

**Table 13: Summary of the ELISA validation results (human serum of patients with psoriasis, Method BA14007-R)**

Validation parameter	Validation Results		
	GP2017	US-licensed Humira®	EU-approved Humira®
Intra-assay precision	2–3% LLOQ/ULOQ 3–7%	3–4% LLOQ/ULOQ 4%	1–3% LLOQ/ULOQ 5–6%
Inter-assay precision	4–7% LLOQ/ULOQ 4–6%	4–13% LLOQ/ULOQ 5–15%	5–7% LLOQ/ULOQ 4–7%
Intra-assay accuracy	95–99% LLOQ/ULOQ 94–97%	95–96% LLOQ/ULOQ 87–95%	91–94% LLOQ/ULOQ 85–90%
Inter-assay accuracy	95–98% LLOQ/ULOQ 88–98%	98–99% LLOQ/ULOQ 96–100%	93–97% LLOQ/ULOQ 87–95%
Freeze/thaw stability	Demonstrated for 5 freeze-thaw cycles		
Short-term stability	Demonstrated up to 3 days at 2–8°C, and up to 20 h at RT		
Long-term stability	Demonstrated up to 15 months at -20°C and -70°C		
Dilution testing	Accuracy: 100–104% Precision: 1–4%	Accuracy: 100–103% Precision: 2–3%	Accuracy: 95–99% Precision: 1–5%

Source: Adapted from BLA 761071, Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods

#### 4.1.1.2 For all moieties measured, is free, bound, or total measured?

Free adalimumab concentration in serum was measured in the clinical studies.

#### 4.1.1.3 What is the concentration range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

Adalimumab concentrations from GP2017, US-licensed Humira® and EU-approved Humira® were determined on a standard curve ranged from 0.25 µg/mL to 8 µg/mL using a five-parameter curve-fitting program. The standard curve consisted of six non-zero calibrator concentrations covering the entire range. Standard curves were prepared in appropriate matrix as the study samples.

#### 4.1.1.4 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower and upper limit of quantification for adalimumab was 0.25 µg/mL and 8 µg/mL, respectively.

#### 4.1.1.5 What are the accuracy, precision, and selectivity at these limits?

In serum of healthy subjects, the intra-assay and inter-assay accuracy of LLOQ and ULOQ samples ranged from 85% to 99%, and from 90% to 105%, respectively. The intra-assay and inter-assay precision of LLOQ and ULOQ samples ranged from 2% to 8%, and from 7% to 11%, respectively.

In serum of psoriasis patients, the intra-assay accuracy of LLOQ and ULOQ samples ranged from 85% to 97%; the inter-assay accuracy ranged from 87% to 100%. The intra-assay precision of LLOQ and ULOQ samples ranged from 3% to 7%; the inter-assay precision ranged from 4% to 15% (Tables 11 and 12).

#### **4.1.1.6 What is the sample stability under the conditions used in the study?**

Pharmacokinetic samples were stored and analyzed within the validated storage stability period and conditions for GP2017, US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup>.

##### Short-term stability at room temperature

Based on the validation report submitted by the applicant, GP2017, US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup> were stable in human serum for 20 hours at room temperature.

##### Freeze-thaw stability

Based on the validation report submitted by the applicant, the freeze-thaw stability for GP2017, US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup> was established up to five freeze-thaw cycles.

##### Long-term storage stability

Based on the validation report, frozen GP2017, US-licensed Humira<sup>®</sup> and EU-approved Humira<sup>®</sup> samples were stable in human serum from healthy donor up to 5 months and 8 months at <-20°C and <-70°C, respectively, and in human serum of psoriasis patients up to 15 month at <-20°C and <-70°C.

#### **4.1.1.7 What is the plan for the QC samples and for reanalysis of the incurred samples?**

Three quality control (QC) samples were used during the assay of PK samples; the accuracy and precision for QC samples in all studies were within acceptance limit.

For assay methods BA13010-R and BA14007-R, PK samples from Study 101 and 301 were re-analyzed as part of the incurred sample reproducibility assessment. The results of the incurred sample reanalysis met the acceptance criteria demonstrating satisfactory reproducibility of the PK assay throughout the sample analysis period.

#### **4.1.1.8 What are the findings from OSIS inspection?**

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and bioanalytical sites of the pivotal clinical pharmacology Study GP17-104. OSIS recommended accepting the clinical site data without an on-site inspection of the clinical site ( (b) (4) ). Refer to the OSIS Memorandum (DARRTS dated 02/26/2018) for further details.

For the bioanalytical site (Hexal AG, Oberhaching, Germany), an inspection was conducted, and OSIS recommended that data from Study GP17-104 and other studies using similar methods be accepted for further Agency review. Refer to OSIS Memorandum (DARRTS dated 04/27/2018) for further details.

### **4.1.2 Immunogenicity**

#### **4.1.2.1 What bioanalytical methods are used to assess the immunogenicity?**

Refer to Section 3.2.5 and the OBP review for information about the analytical method validation for assessment of immunogenicity.

## 5. LABELING RECOMMENDATIONS

Labeling statements to be removed are shown in ~~red strikethrough~~ font and suggested labeling to be included is shown in underline blue font.

### 7 DRUG INTERACTIONS

#### 7.1 Methotrexate

Adalimumab products have been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent clearance of adalimumab products, the data do not suggest the need for dose adjustment of either HYRIMOZ™ or MTX [see *Clinical Pharmacology* (12.3)].

#### 7.2 Biological Products

In clinical studies in patients with RA with adalimumab, an increased risk of serious infections has been seen with the combination of TNF-blockers with anakinra or abatacept, with no added benefit; therefore, use of HYRIMOZ™ with abatacept or anakinra is not recommended in patients with RA [see *Warnings and Precautions* (5.7 and 5.11)]. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF-blocker. There is insufficient information regarding the concomitant use of adalimumab and other biologic products for the treatment of RA, PsA, AS, CD, UC, and Ps (b) (4). Concomitant administration of HYRIMOZ™ with other biologic DMARDs (e.g., anakinra and abatacept) or other TNF-blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

#### 7.3 Live Vaccines

Avoid the use of live vaccines with HYRIMOZ™ [see *Warnings and Precautions* (5.10)].

#### 7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF $\alpha$ , IL-6) during chronic inflammation. It is possible for products that antagonize cytokine activity, such as adalimumab products, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HYRIMOZ™ in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Adalimumab products bind specifically to TNF-alpha and block its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Adalimumab products do not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In Ps, treatment with adalimumab may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab products exerts its clinical effects is unknown.

Adalimumab products also modulate biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC<sub>50</sub> of 1-2 X 10<sup>-10</sup>M).

### 12.2 Pharmacodynamics

After treatment with adalimumab, a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease, and ulcerative colitis (b) (4). Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after adalimumab administration.

### 12.3 Pharmacokinetics

The maximum serum concentration (C<sub>max</sub>) and the time to reach the maximum concentration (T<sub>max</sub>) (b) (4) were 4.7 ± 1.6 mcg/mL and 131 ± 56 hours respectively, following a single 40 mg subcutaneous administration of adalimumab to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64 %. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

The single dose pharmacokinetics of adalimumab in RA patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume ( $V_{ss}$ ) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96 % of those in serum.

In RA patients receiving 40 mg adalimumab every other week, adalimumab mean steady-state trough concentrations of approximately 5 mcg/mL and 8 to 9 mcg/mL, were observed without and with methotrexate (MTX), respectively. MTX reduced adalimumab apparent clearance after single and multiple dosing by 29 % and 44 % respectively, in patients with RA. Mean serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40, and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Adalimumab mean steady-state trough concentrations were slightly higher in psoriatic arthritis patients treated with 40 mg adalimumab every other week (6 to 10 mcg/mL and 8.5 to 12 mcg/mL, without and with MTX, respectively) compared to the concentrations in RA patients treated with the same dose. The pharmacokinetics of adalimumab in patients with AS were similar to those in patients with RA.

In patients with CD, the loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves mean serum adalimumab trough levels of approximately 12 mcg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 mcg/mL were observed at Week 24 and Week 56 in CD patients after receiving a maintenance dose of 40 mg adalimumab every other week.

In patients with UC, the loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves mean serum adalimumab trough levels of approximately 12 mcg/mL at Week 2 and Week 4. Mean steady-state trough level of approximately 8 mcg/mL was observed at Week 52 in UC patients after receiving a dose of 40 mg adalimumab every other week, and approximately 15 mcg/mL at Week 52 in UC patients who increased to a dose of 40 mg adalimumab every week.

In patients with Ps, the mean steady-state trough concentration was approximately 5 to 6 mcg/mL during adalimumab 40 mg every other week monotherapy treatment.

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to >75 years.

Minor increases in apparent clearance were also predicted in RA patients receiving doses lower than the recommended dose and in RA patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

In Study JIA-I for patients with polyarticular JIA (b) (4) the mean steady-state trough serum adalimumab concentrations for patients weighing (b) (4)

(b) (4)  $\geq 30$  kg receiving 40 mg adalimumab subcutaneously every other week as monotherapy or with concomitant MTX were 6.6 mcg/mL and 8.1 mcg/mL, respectively.

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

MOHAMMAD S ABSAR  
07/02/2018

ANSHU MARATHE  
07/02/2018