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RESEARCH**

APPLICATION NUMBER:

761071Orig1s000

NON-CLINICAL REVIEW(S)

Pharmacology and Toxicology Secondary Review for BLA 761071

TO:

BLA 761071

GP2017

Proposed biosimilar to US-licensed HUMIRA (adalimumab)

FROM:

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Pharmacology-Toxicology Supervisor

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Sandoz submitted BLA 761071 under section 351(k) of the Public Health Service Act seeking approval of GP2017 as a biosimilar to US-licensed HUMIRA (adalimumab). The applicant is seeking approval for GP2017 with the proposed tradename HYRIMOZ in the following indications: rheumatoid arthritis, juvenile idiopathic arthritis in patients ≥ 4 years of age, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis. The proposed dosing regimens for each indication are identical to those listed in the US-licensed HUMIRA prescribing information. The maximum proposed daily dose of GP2017 is 160 mg via subcutaneous injection.

The primary nonclinical reviewer, Dr. Brett Jones, provided two pharmacology-toxicology memos for BLA 761071. In a memo dated May 7, 2018, Dr. Jones provided labeling recommendations and reviewed primary pharmacology, comparative pharmacokinetics (PK), and a 4-week monkey comparative toxicology studies. In a memo dated May 18, 2018, Dr. Jones reviewed the applicant's safety assessment of potential extractables and leachables from the container-closure system.

GP2017 presentations include a 40 mg (0.8 mL) pre-filled syringe and a 40 mg (0.8 mL) pre-filled pen / autoinjector. Excipients include adipic acid, citric acid monohydrate, sodium chloride, and mannitol. As discussed in Dr. Jones' review, the GP2017 formulation differs from that of US-licensed HUMIRA. No safety concerns were identified regarding excipients, extractables, or leachables.

I concur with Dr. Jones' conclusion that the pharmacology (e.g., efficacy in Tg197 and Tg5453 mouse models of arthritis), pharmacokinetics, and toxicology data generated were similar for GP2017 and EU-HUMIRA. The applicant conducted a three-way analytical and PK similarity program to allow the extrapolation of these data to support a conclusion of biosimilarity to US-licensed HUMIRA (refer to reviews from other disciplines).

The applicant's proposed labeling format complies with the Pregnancy and Lactation Labeling Rule (PLLR). I concur with Dr. Jones' recommended minor edits to the labeling to maintain consistency with other approved product labels.

Recommendation: I concur with the recommendation of the primary reviewer, Dr. Jones. There are no residual uncertainties or outstanding issues, and the application is recommended for approval from the pharmacology-toxicology perspective.

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/s/

ANDREW C GOODWIN
06/29/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY SAFETY ASSESSMENT OF EXTRACTABLES
AND LEACHABLES FOR HYRIMOZ™ (ADALIMUMAB) (GP2017)

Application number: BLA 761071
Supporting document/s: SDN # 6, SDN #14
Applicant's letter date: October 30, 2017
December 19, 2017
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December 19, 2017
Product: HYRIMOZ™, GP2017, adalimumab
(Humira®) biosimilar
Indication: Rheumatoid Arthritis, Juvenile Idiopathic
Arthritis, Psoriatic Arthritis, Ankylosing
Spondylitis, Adult Crohn's Disease, Ulcerative
Colitis, Plaque Psoriasis
Applicant: Sandoz Biopharmaceuticals
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products
Reviewer: Brett Jones, PhD
Supervisor/Team Leader: Andrew Goodwin, PhD
Division Director (Acting): Sally Seymour, MD
Project Manager: Nina Ton, PharmD

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The Sponsor submitted the present 351(k) Biologics License Application (BLA) 761,071 on October 30, 2017 to support the marketing approval of GP2017 as a biosimilar to US-licensed Humira (adalimumab). The drug product, proposed tradename HYRIMOZ™, is being developed for the subcutaneous treatment of: rheumatoid arthritis, juvenile idiopathic arthritis (i.e., in patients 4 years of age and older), psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis. This review is a nonclinical safety evaluation of potential extractables and leachables for the HYRIMOZ™ primary container closure system.

The overall nonclinical pharmacology and toxicology evaluation, as well as labeling recommendations, was provided in a separate review dated May 7, 2018.

1.2 Brief Discussion of Nonclinical Findings

At this time, there are no safety concerns based on the results from the extractable or leachable studies.

2 Drug Information

2.1 Drug

Tradename

HYRIMOZ™ (proposed)

Generic Name

Adalimumab (Humira®) biosimilar

Code Name

GP2017

Molecular Weight

~ 148 kDa

Structure or Biochemical Description

GP2017 is a human monoclonal IgG1 antibody composed of two kappa light chains and two IgG1 heavy chains, linked by disulfide bonds. Each light chain consists of 214 amino acid residues and each heavy chain consists of 451 amino acid residues. The drug substance of GP2017 originates from a cell culture bioprocess using a recombinant Chinese Hamster Ovary (CHO) cell line.

Pharmacologic ClassHuman monoclonal antibody against TNF α **2.2 Relevant INDs, NDAs, BLAs and DMFs**BLA 125057: Adalimumab (Humira[®])

IND 115732: GP2017

2.3 Drug Formulation

GP2017 40 mg solution for injection is a colorless to slightly yellowish solution comprising the drug substance, adalimumab, as the active pharmaceutical ingredient, adipic acid and citric acid monohydrate (b) (4), polysorbate 80 (b) (4), (b) (4), mannitol and sodium chloride (b) (4), and water for injection as diluent (see table below). The solution is filled in pre-filled syringes (clear glass barrel with fixed needle) with a nominal fill volume of 0.8 mL, closed with a plunger stopper and is intended for subcutaneous (s.c.) administration.

The Sponsor submitted two presentations in the BLA package:

1. Pre-filled syringe with a needle safety device and an add-on finger flange
2. Pre-filled pen (autoinjector)

GP2017 has a unit strength of 40 mg/0.8 mL.

In adults, the recommended dose of GP2017 is 40 mg given every two weeks by SC injection. For (b) (4) psoriasis, an initial (induction) dose of 80 mg is given followed one week later by 40 mg every two weeks (maintenance dose), while for ulcerative colitis the first two doses are 160 mg and 80 mg given two weeks apart followed by 40 mg every two weeks. (b) (4)

The maximum daily dose of GP2017 is 160 mg/day (i.e., 4 syringes, 3.2 mL/day).

The composition of GP2017 (HYRIMOZ[™]) is provided in the table below.

(Excerpt from Sponsor's submission)

Table 1. Composition of GP2017 solution for injection in pre-filled syringe

Component	Amount per syringe (0.8 mL)	Function	Reference to quality standards ¹
Active Ingredient			
Adalimumab ²	40 mg	Active substance	In house
Other Ingredients			
Adipic acid	2.69 mg	(b) (4)	Ph. Eur./USP
Citric acid monohydrate	0.206 mg		Ph. Eur./USP
Sodium chloride	4.93 mg		Ph. Eur./USP
Mannitol	9.6 mg		Ph. Eur./USP
Polysorbate 80	0.8 mg		Ph. Eur./USP
Sodium hydroxide	q.s.	pH adjustment	Ph. Eur./USP
Hydrochloric acid			
Water for injections	ad 0.8 mL	Solvent	Ph. Eur./USP

¹ current edition of the pharmacopoeia is used

(b) (4)

2.4 Comments on Novel Excipients

There are no safety concerns with the excipients in the proposed GP2017 subcutaneous formulation.

2.5 Comments on Extractables and Leachables Studies

This review is a nonclinical safety evaluation of potential extractables and leachables for the GP2017 drug product. Described in this section are the studies and results; the nonclinical safety evaluation is included in the **Integrated Summary and Safety Evaluation** section.

According to the Sponsor's report, the container closure system for the GP2017 drug product (i.e., 40 mg/0.8mL solution for injection) consists of a sterile, non-pyrogenic, single use, pre-filled syringe (PFS) (i.e., (b) (4) pre-fillable ISO standard glass syringe). The pre-filled syringe includes the following components:

- A glass syringe barrel with staked needle where the needle is fixed to the syringe barrel
- A rubber plunger stopper
- A rigid needle shield composed of a rubber needle shield covered by a rigid shell

The pre-filled syringe is assembled with either of the following two functional secondary packaging components:

- A plunger rod and a needle safety device with an add-on finger flange, as a safety mechanism to reduce occurrence of accidental needle sticks
- An autoinjector

The Sponsor’s report states that the plunger rod/ needle safety device are not part of the container closure system and have no contact with the sterile fluid path. GP2017 40 mg/0.8 mL solution for injection is (b) (4) filled in the glass syringe barrel and stoppered with the rubber plunger. A rubber needle shield encapsulates the needle; the rigid shell mechanically stabilizes and protects the closure. The syringe barrel, needle, and plunger stopper are (b) (4).

(Excerpt from Sponsor’s submission)

Table 2. GP2017 40 mg/ 0.8 mL solution for injection in pre-filled syringe: identity of materials of construction

Component	Description	Identity of material	Supplier	Compliance status Ph. Eur./ USP
Syringe with staked needle (sold as sterile and non-pyrogenic)				
Syringe barrel	1 mL long, colorless	(b) (4)	(b) (4)	Complies with Ph. Eur. and USP requirements for (b) (4) glass (b) (4)
Staked hypodermic needle	27 G x 1/2"	(b) (4)	(b) (4)	(b) (4)
Plunger stopper				
Plunger stopper	(b) (4) rubber stopper Rubber stopper formulation	(b) (4)	(b) (4)	Complies with Ph. Eur. and USP requirements
Rigid needle shield				
Rigid shell	Plastic shell	(b) (4)	(b) (4)	Not applicable as not in product contact
Rubber needle shield	Rubber needle shield Rubber formulation	(b) (4)	(b) (4)	Complies with Ph. Eur. and USP requirements

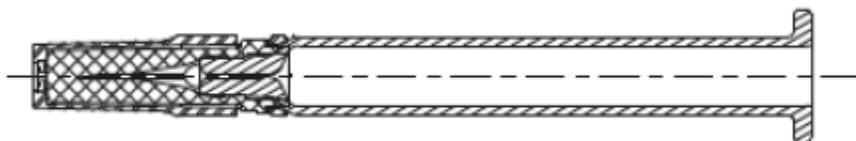
¹⁾ The rubber formulation for the plunger stopper is provided to (b) (4)

²⁾ The rubber formulation for the rubber needle shield is provided to (b) (4)

The pre-filled glass syringe barrel is made of colorless (b) (4) glass (b) (4). The syringe is assembled with a staked (b) (4) needle and a rigid needle shield (see figure below). The needle shield consists of a rubber needle shield in (b) (4) rubber formulation and a rigid shell (no direct drug product contact) made of (b) (4).

(Excerpt from Sponsor’s submission)

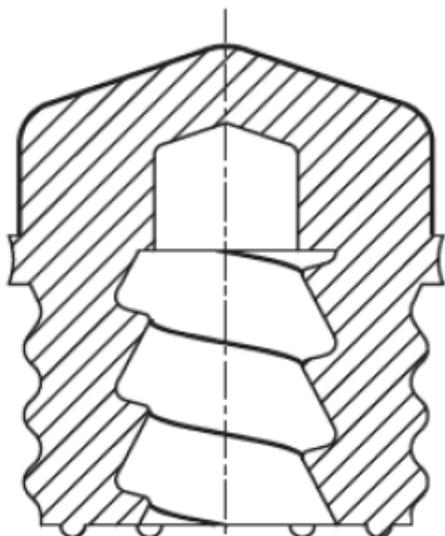
Figure 1. Technical drawing of the syringe barrel with needle shield



A rubber stopper (b) (4) is used to close the syringe. (b) (4) (see figure below).

(Excerpt from Sponsor's submission)

Figure 2. Technical drawing of the rubber stopper



Extractables Testing Strategy: The Sponsor conducted an extractables study with two pre-filled (b) (4) glass syringes. The study was performed for another Sandoz Biopharmaceutical product (using the same syringe) and were applied to GP2017. Placebo solution was provided by the Sponsor for the extractables study. An extractables screening was conducted for known and unknown compounds present in the two different rubber materials of the syringe and in the needle adhesive. The core part of the study consisted of a set of forced extraction experiments followed by subsequent analyses of the extracts by GC/MS with and without derivatization (for semi-volatiles compounds), by HPLC/UV/MS (for non-volatile and polar compounds), by headspace-GC/MS (for volatile compounds), and by ICP-MS (for elemental analysis). The study utilized guidelines of Product Quality Research Institute (PQRI) best practices for extractable and leachable studies for orally inhaled and nasal products.

According to the Sponsor's report, extraction experiments were performed directly in each syringe (containing the stopper and needle shield). Extraction experiments with water/iso-propanol mixtures were performed as follows: 1 mL of each extraction solvent was filled in syringe A or syringe B. The syringes were closed with the needle shield and the stopper and the syringes were incubated at an elevated temperature of 50°C. The solution was in contact with both rubber materials during the incubation. Extraction experiments were also performed with the placebo solution.

The following extractions were performed:

- Water/iso-propanol mixture (10 + 90, 50°C for 48 hr)
- Water (pH 3)/iso-propanol mixture (90 + 10, 50°C for 48 hr)

- Pure aqueous extract (pH 3) only for headspace-GC/MS experiments (50°C, 48 hr)
- Placebo solution (50°C, 48 hr)

The combined aqueous extract (pH 3) of both syringes as well as placebo solution were directly analyzed by headspace-GC/MS to detect volatile extractables. A screening for polar or semi-polar, non-volatile, and semi-volatile compounds as well as a target screening for typical extractables was performed by HPLC/UV/MS. Metal analysis included the quantitative determination of (b) (4) on a (b) (4) pg/μl level. The organic extracts were concentrated and reconstituted in nitric acid prior to analysis by ICP-MS.

According to the Sponsor’s report, a target Analytical Evaluation Threshold (AET) of (b) (4) ng/mL was considered for the extractables study. The limit of (b) (4) ng/mL covers the PQRI extractables threshold of (b) (4) ng per day taking into account a worst case daily uptake of three times 1.0 mL of pharmaceutical formulation and taking into account that the extracts of two syringes were pooled (see table below).

(Excerpt from Sponsor’s submission)

Table 3. Determination of the Analytical Evaluation Threshold

PQRI extractables threshold	(b) (4) ng/day
Worst-case filling volume of the syringe	1.0 ml
Maximum daily dose for a patient	3.0 ml (3 syringes)
Threshold required	(b) (4) ng / 3 ml = (b) (4) ng/ml
Analytical Evaluation Threshold in the pooled extracts	(b) (4) ng/ml

Prior to the extraction experiments, the rubber stopper, needle shield, and the needle adhesive of the syringe were investigated by TDS-GC/MS to obtain a first overview of potentially extractable compounds. The following compounds were detected in the three different materials:

Rubber stopper: intensive signals were found for (b) (4) and (b) (4). An intense signal of the (b) (4) was observed.

Needle shield: the most intense signal resulted from the (b) (4). Intense signals of (b) (4) were also detected. Different (b) (4) were also detected.

Needle adhesive: most intensive signals resulted from the (b) (4), an unknown compound, (b) (4) related compounds.

According to the Sponsor’s report, many of these compounds were found in later extracts in very low concentrations. The results of the extraction experiments showed that the presence of extractables was highly dependent on the extraction solvent used.

A summary of results of the extractables assessment is provided in the table below.

(Excerpt from Sponsor’s submission)

Table 4. Estimated daily uptake of extractables in GP2017

Compound [CAS No.]	Estimated worst-case daily uptake in µg		
	water/iso-propanol extract (10+90)	water (pH 3)/iso- propanol extract (90+10)	placebo solution
<u>Compounds determined by GC/MS</u>			
(b) (4)			
<u>Compounds determined by GC/MS after derivatization</u>			
(b) (4)			

According to the Sponsor's report, all extractables contained in GP2017 were measured at concentrations below the PQRI Safety Concern Threshold of 1.5 µg/day. A summary of extractable compounds that were detected in the GP2017 drug product components is shown in the table below.

(Excerpt from Sponsor's submission)

Table 5. Extractable results for GP2017 drug product components

Chemical name	CAS	concentration (µg/mL)	Amount per dose (µg/dose)
(b) (4)			

LEACHABLES ASSESSMENT

A general screening of leachables was conducted to determine the risk of exposure to the patient. No single compounds were identified in the extractables evaluation for further testing in the leachables studies. The SCT was converted into an AET based on the number of doses per day. All compounds over the AET were toxicologically evaluated. Only two leachables were detected in stability studies covering up to 32 months of storage at intended conditions.

In general, for leachable evaluations, compounds with expected patient exposure below the PQRI Thresholds of 5 µg/day (for sensitizer and irritants, non-genotoxic/non-carcinogen) and 1.5 µg/day (for compounds with genotoxic/carcinogenic potential) are considered qualified for safety.¹ However, the Sponsor utilized a SCT of (b) (4) µg/day for their leachables assessment, as they considered that the drug product would be administered for less than 10 years for a large majority of patients. The Sponsor's use of a (b) (4) µg/day SCT, while not preferred for a chronic indication, was considered acceptable by the reviewer based on the fact that the drug product will be administered only every 2 weeks thus providing an additional margin of safety.

According to the Sponsor's report, based on the SCT, the AET was calculated as (b) (4) µg/mL. The Sponsor stated that the method limits of quantitation are lower than the AET; therefore, the methods are sufficiently sensitive for the leachables assessment.

¹ Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. Product Quality Research Institute. August 2006.

Leachables Studies

A leachables assessment was conducted on four lots of GP2017 (40 mg/ 0.8 mL solution for injection) drug product. All samples were stored in the original containers and in a horizontal position (i.e., the drug product solution was in contact with the stopper during the entire storage time). A summary of the GP2017 leachables test method program is shown in the table below.

(Excerpt from Sponsor's submission)

Table 6. Summary of GP2017 leachables stability program

	Batch	Packaging	Storage Conditions	Testing points*
			[°C]	[unit] months
Real Time Tests	#7005939	Syringe	5 ± 3	32
Real Time Tests	#7006715	Syringe	5 ± 3	24, 30
Real Time Tests	#7007467	Syringe	5 ± 3	8, 12, 24, 30
Real Time Tests	#7007741	Syringe	5 ± 3	2**, 12, 24, 30

* Testing dates will be calculated from filling dates (see Table 3-1) as T = 0 month. The study start date will not be considered.

** measured after 4 months (see section 7.5)

(Excerpt from Sponsor's submission)

Table 7. Summary of GP2017 leachables test method program

Necessary GP2017 volume	Test	Analytical Method	SOP	Capability report	LOQ
0.3 mL	Non-volatile substances	LC-UV	[AP 95.112] *	[BP53614]	50 ng/mL
0.3 mL	Acrylates	LC-UV	[AP 95.113] *	[BP52614]	50 ng/mL
1.6 mL	Semi-volatile	GC-MS	[LV-AL29-010]	[BP76014]	100 ng/mL
0.24 mL	volatile	HS-GC-MS	[LV-AL29-009]	[BP71514]	100 ng/mL

* LV AL29-007/LV AL29-001 and LV AL29-007/LV AL29-005 were transformed into LV AL29-012 and LV AL29-014, respectively and later into SOPs [AP 95.112] and [AP 95.113], respectively the content of the procedures was not changed.

According to the Sponsor's report, samples were investigated for leachables using a complementary set of methods which cover non-volatile and semi-volatile analytes. Control samples were included in all experiments to show that the methods could detect the target analytes.

Semi-Volatile Leachables Assessment

The presence of (b) (4) was identified above the AET in one batch sample (34 months). The Sponsor stated that the sample was

derivatized by a (b) (4); with the original substance identified as (b) (4).

Volatile Leachables Assessment

No volatile leachables (e.g., (b) (4)) were identified above the AET in any samples up to 32 months.

Non-Volatile Leachables Assessment

No non-volatile leachables (e.g., (b) (4)) were identified above the AET in any samples up to 32 months.

(b) (4) **Leachables Assessment**

According to the Sponsor’s report, a method specific for (b) (4) was used as these substances are known to be leachables of (b) (4).

Only one compound, (b) (4), was detected above the AET in a single batch at 12 months storage. According to the Sponsor’s report, it was detected at a highest concentration of (b) (4) µg/mL (12 months), while after 24 and 30 months only moderate concentrations were observed.

Summary of Leachable Studies:

A total of two compounds were detected as leachables during the 32 month stability studies. (b) (4) were detected as being above the calculated AET of (b) (4) µg/mL in single batches. A summary of quantifiable leachable compounds detected in the GP2017 drug product is shown in the table below.

Table 8. Quantifiable leachable results for GP2017 drug product

Compound	Maximum Leachable Concentration (µg/mL)	Maximum Human Exposure (µg/day)
(b) (4)		

3 Studies Submitted

3.1 Studies Reviewed

STUDY	STUDY NUMBER:
Extractables study for a pre-fillable syringe (Project LA-EP2006)	10.176B
Extractables/leachables assessment	SDZ-GP2017-TOX-NVS-2015-016-V2.0
GP2017 EL 002 – Final Leachable Report	

11 Integrated Summary and Safety Evaluation

This review provides a safety assessment of extractables from the primary container system for the GP2017 drug product, based on data submitted by the Sponsor and other available information. The Sponsor did not conduct or submit any leachables studies for single compounds. A general screening for leachables (i.e., HS-GC-MS, GC-MS, LC-UV) was conducted with selected standard compounds. The drug product will be administered by the subcutaneous route.

In general, for extractable and leachable evaluations, compounds with expected patient exposure below the PQRI Thresholds of 5 µg/day (for sensitizer and irritants, non-genotoxic/non-carcinogenic) and 1.5 µg/day (for compounds with genotoxic/carcinogenic potential) were considered qualified for safety.²

Extractables Assessment

The Sponsor conducted an extractables study with two pre-filled (b) (4) glass syringes. The study was performed for another Sandoz Biopharmaceutical product (using the same syringe) and were applied to GP2017. An extractables screening was conducted for known and unknown compounds present in the two different rubber materials of the syringe and in the needle adhesive. The core part of the study consisted of a set of forced extraction experiments followed by subsequent analyses of the extracts by GC/MS with and without derivatization (for semi-volatiles compounds), by HPLC/UV/MS (for non-volatile and polar compounds), by headspace-GC/MS (for volatile compounds), and by ICP-MS (for elemental analysis). The study utilized guidelines of Product Quality Research Institute (PQRI) best practices for extractable and leachable studies for orally inhaled and nasal products.

According to the Sponsor's report, different extractables were released from the rubber components of the syringe and from the adhesive which is used for fixation of the needle. However, the extractable concentrations were very low and migration of the compounds was mainly observed into a water-isopropanol mixture with a high organic content (90%). In contrast, migration of relevant amounts of extractables into aqueous solutions (more than 90% of water) was not observed.

No extractable compound was identified at a level that exceeded the PQRI Safety Concern Threshold of 1.5 µg/day. Overall, there appear to be no safety concerns for the GP2017 drug product as described for the extractable studies for the primary container system.

Leachables Assessment

A general leachables assessment was conducted on four lots of GP2017 (40 mg/0.8 mL solution for injection) drug product. All samples were stored in the original containers

² Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Products. Product Quality Research Institute. August 2006.

and in a horizontal position (i.e., the drug product solution was in contact with the stopper during the entire storage time).

Two compounds were identified as leachables during the stability studies. The compounds, [REDACTED] (b) (4) were detected above the AET in single batches after 34 months and 12 months, respectively.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

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/s/

BRETT R JONES
05/16/2018

ANDREW C GOODWIN
05/16/2018
I concur

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 761071
Supporting document/s: SDN #6
Applicant's letter date: October 30, 2017
CDER stamp date: October 30, 2017
Product: HYRIMOZ™, GP2017, adalimumab
(Humira®) biosimilar
Indication: Rheumatoid Arthritis, Juvenile Idiopathic
Arthritis, Psoriatic Arthritis, Ankylosing
Spondylitis, Adult Crohn's Disease, Ulcerative
Colitis, Plaque Psoriasis
Applicant: Sandoz Biopharmaceuticals
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products
Reviewer: Brett Jones, PhD
Supervisor/Team Leader: Andrew Goodwin, PhD
Division Director (Acting): Sally Seymour, MD
Project Manager: Nina Ton, PharmD

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Humira (adalimumab) is a humanized monoclonal antibody directed against tumor necrosis factor alpha (TNF α). Humira is currently approved for the treatment of several immunologic-mediated diseases including: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis (in patients between 2 and 4 years of age), Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, and Uveitis.

For the current submission, the Sponsor is developing GP2017 (40 mg, SC) under the 351(k) pathway of the Public Health Service Act as a biosimilar to US-licensed Humira (adalimumab) with the proposed tradename Hyrimoz. The Sponsor is seeking licensure of GP2017 for the following indications:¹

- Rheumatoid Arthritis
- Juvenile Idiopathic Arthritis (in patients 4 years of age and older)
- Psoriatic Arthritis
- Ankylosing Spondylitis
- Adult Crohn's Disease
- Ulcerative Colitis
- Plaque Psoriasis

The application includes a 40 mg (in 0.8 mL) pre-filled syringe with a needle safety device and add-on finger flange and a 40 mg (in 0.8 mL) pre-filled pen (autoinjector).

The Sponsor submitted several nonclinical studies to support the pharmacological, toxicological, and toxicokinetic similarity between GP2017 and EU-licensed Humira.

1.2 Brief Discussion of Nonclinical Findings

GP2017 is a human monoclonal immunoglobulin (IgG1 κ subtype) against human TNF α . Several studies were conducted to compare the pharmacology, pharmacokinetics, and toxicology of GP2017 to that of EU-sourced Humira.

A GLP-compliant comparative single dose pharmacokinetic study was conducted in rabbits that compared five GP2017 formulation variants with EU-Humira. All compounds exhibited similar pharmacokinetic parameters.

A 4-week GLP-compliant repeat-dose toxicology study in cynomolgus monkeys was conducted to evaluate and compare the toxicology of GP2017 with EU-Humira. In the 4-week monkey study, cynomolgus monkeys were administered either vehicle, GP2017 (100 mg/kg, SC), or EU-Humira (100 mg/kg, SC), once weekly for 4 weeks (n=

¹ At the time of submission of this 351(k) BLA, the Humira® indications of Pediatric Crohn's Disease, Hidradenitis Suppurativa, and Uveitis are still covered by orphan drug exclusivity, and therefore will not be claimed

3/sex/group) for a total of 5 doses (Days 1, 8, 15, 22, and 29). A slight increase in incidence and severity of inflammatory lesions (i.e., dermatitis, myopathy/myositis, and fasciitis/fibrosis) at the injection sites was observed for males and females in the GP2017 and EU-Humira treatment groups relative to control animals. GP2017 and EU-Humira exhibited similar toxicokinetic profiles. No clear sex differences in exposure were observed. Similar amounts of drug accumulation (~2.5-fold) were observed over the treatment period. No anti-drug antibodies were detected; however, it is probable that drug levels were sufficiently high enough, even at prolonged sampling times, to interfere with anti-drug antibody detection. Based on this study, GP2017 and EU-Humira were toxicologically similar.

There are no safety concerns for the subcutaneous administration of GP2017. Repeat-dose pharmacokinetics and toxicology findings in cynomolgus monkeys were similar between GP2017 and EU-Humira. The applicant conducted a three-way biosimilarity program to allow the extrapolation of these conclusions to support biosimilarity to US-licensed Humira (refer to Product Quality memo for review of these data).

1.3 Recommendations

1.3.1 Approvability

BLA 761071 is recommended for approval from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

For this submission, the Sponsor provided a label for HYRIMOZ™ based upon the prescribing information previously approved for US-Humira (version 4/2017), while adapting for product-specific differences, fewer presentations and indications due to orphan exclusivity (i.e., pediatric Crohn's disease, juvenile idiopathic arthritis for patients 2 years to 4 years of age, hidradenitis suppurativa, and uveitis are excluded). The proposed label incorporates information in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

The Established Pharmacologic Class (under Indication and Usage in the Highlights of Prescribing Information), Section 8.1 (Pregnancy), Section 8.2 (Lactation), Section 12.1 (Mechanism of Action), and Section 13 (Nonclinical Toxicology) were reviewed. See the recommended label for the nonclinical section of the proposed product label below.

The Reviewer's recommended labeling is shown below. Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~ with respect to the Sponsor's proposed HYRIMOZ™ label. The recommended changes to the Sponsor's proposed label maintain consistency with other previously approved biosimilar adalimumab products.

HYRIMOZ™**Indications and Usage in the Highlights of Prescribing Information**

HYRIMOZ™ is a tumor necrosis factor (TNF) blocker indicated for treatment of:

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy****Risk Summary**

(b) (4)

Adalimumab products ~~is~~ are actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant [see *Clinical Considerations*]. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate [see *Data*]. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and (b) (4) 15–20%, respectively.

Clinical Considerations***Fetal/Neonatal adverse reactions***

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [see *Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to adalimumab products *in utero* [see *Use in Specific Populations* (8)].

Data***Human Data***

(b) (4)

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with adalimumab, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of adalimumab was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16 to 19.7 mcg/mL in cord blood, 4.28 to 17.7 mcg/mL in infant serum, and 0 to 16.1 mcg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 mcg/mL), 7 weeks (1.31 mcg/mL), 8 weeks (0.93 mcg/mL), and 11 weeks (0.53 mcg/mL), suggesting adalimumab can be detected in the serum of infants exposed in utero for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1 % to 1 % of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HYRIMOZ™ and any potential adverse effects on the breastfed child from HYRIMOZ™ or from the underlying maternal condition.

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 products also lyse^(b)₍₄₎ 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~~ HYRIMOZ™ may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic

activities and the mechanism(s) by which adalimumab products exert ^{(b) (4)} their 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 IC₅₀ of 1-2 X 10⁻¹⁰M).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of adalimumab products have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

2 Drug Information

2.1 Drug

Generic Name

Adalimumab (Humira®) biosimilar

Code Name

GP2017

Molecular Weight

~ 148 kDa

Structure or Biochemical Description

GP2017 is a human monoclonal IgG1 antibody composed of two kappa light chains and two IgG1 heavy chains, linked by disulfide bonds. Each light chain consists of 214 amino acid residues and each heavy chain consists of 451 amino acid residues. The drug substance of GP2017 originates from a cell culture bioprocess using a recombinant Chinese Hamster Ovary (CHO) cell line.

Pharmacologic Class

Human monoclonal antibody against TNF α

2.2 Relevant INDs, NDAs, BLAs and DMFs

BLA 125057: Adalimumab (Humira®)

IND 115732 (GP2017)

2.3 Drug Formulation

GP2017 40 mg solution for injection is a colorless to slightly yellowish solution comprising the drug substance, adalimumab, as the active pharmaceutical ingredient,

adipic acid and citric acid monohydrate (b) (4), polysorbate 80 (b) (4), mannitol and sodium chloride (b) (4), and water for injection as diluent (see table below). The solution is filled in pre-filled syringes (clear glass barrel with fixed needle) with a nominal fill volume of 0.8 mL, closed with a plunger stopper and is intended for subcutaneous (s.c.) administration.

The Sponsor submitted two presentations in the BLA package:

1. Pre-filled syringe with a needle safety device and an add-on finger flange
2. Pre-filled pen (autoinjector)

GP2017 has a unit strength of 40 mg/0.8 mL.

The Sponsor stated that the drug product development for GP2017 and the nonclinical studies were conducted in parallel. Consequently, the composition of the GP2017 formulation slightly changed during conduct of the nonclinical comparison studies (see Table 2 below). Briefly, (b) (4)

The exposure of both formulations was compared in a single subcutaneous dose PK bridging study in rabbits (Study No. GP17-007). A similar exposure (i.e., (b) (4)% difference) was observed for both formulations.

(Excerpt from Sponsor's submission)

Table 1. Composition of GP2017 solution for injection in pre-filled syringe

Component	Amount per syringe (0.8 mL)	Function	Reference to quality standards ¹
Active Ingredient			
Adalimumab ²	40 mg	Active substance	In house
Other Ingredients			
Adipic acid	2.69 mg	(b) (4)	Ph. Eur./USP
Citric acid monohydrate	0.206 mg		Ph. Eur./USP
Sodium chloride	4.93 mg		Ph. Eur./USP
Mannitol	9.6 mg		Ph. Eur./USP
Polysorbate 80	0.8 mg		Ph. Eur./USP
Sodium hydroxide	q.s.	pH adjustment	Ph. Eur./USP
Hydrochloric acid			
Water for injections	ad 0.8 mL	Solvent	Ph. Eur./USP

¹ current edition of the pharmacopoeia is used

(b) (4)

(Excerpt from Sponsor's submission)

Table 2. Formulation composition for GP2017 in nonclinical studies

	Early phase	Comparative nonclinical study phase	
		(b) (4)	
		Sandoz code (Study no.)	
	GP17-001 (26024) ^{#2}	GP17-002 (8240754); GP17-004 (8240794); GP17-005 (8240796); GP17-006 (BMC 250); GP17-007 (28088) ^{#3}	GP17-007 (28088) ^{#3} ; GP17-008 (30331); GP17-009 (BMC 387)
Component #1			
Adipic acid [mM]	(b) (4)		
Citric acid [mM]	(b) (4)		
Sodium chloride [mM]	(b) (4)		
Mannitol [mM]	(b) (4)		
Polysorbate 80 [mM]	(b) (4)		

^{#1} Note that for direct comparison in case of [Module 4.2.3.2 Study GP17-002 (8240754)], [Module 4.2.2.2 Study GP17-004 (8240794)], [Module 4.2.1.1 Study GP17-006 (BMC 250)], [Module 4.2.2.2 Study GP17-007 (28088)], [Module 4.2.3.6 Study GP17-008 (30331)] and [Module 4.2.1.1 Study GP17-009 (BMC 387)]

For details on the concentration of each component in mg/mL see the individual study reports.

^{#2} Study GP17-003 (BMC 247) did not assess GP2017.

^{#3} Study GP17-007 (28088) compared both formulations for bridging.

^{#4} The placebo / dilution solution used in studies GP17-002 (8240754) and GP17-006 (BMC 250) contained

(b) (4)

2.4 Comments on Novel Excipients

The composition of the proposed GP2017 drug product for subcutaneous use is provided in the table above. There are no safety concerns with the excipients in the proposed GP2017 subcutaneous formulation.

2.5 Comments on Impurities/Degradants of Concern

A separate pharmacology and toxicology review of extractables and leachables will be conducted for the pre-filled syringe and pen.

2.7 Regulatory Background

A pre-IND meeting was held with the Sponsor on January 14, 2013 (IND 115732) to discuss the proposed product quality, nonclinical, and clinical development plan for GP2017. However, no IND was opened prior to the submission of the BLA for GP2017 on August 25, 2016. The application was withdrawn by the Sponsor on October 21, 2016 as the manufacturing schedule for pre-license inspection could not be met for one of the proposed manufacturing sites for GP2017.

The Sponsor submitted a revised BLA application for GP2017 on October 30, 2017. An application orientation meeting was held with the Sponsor on December 5, 2017 to

discuss the revised product quality, nonclinical, and clinical development plan for GP2017.

3 Studies Submitted

3.1 Studies Reviewed

STUDY	STUDY NUMBER:
PRIMARY PHARMACOLOGY:	
Evaluation of the Therapeutic Efficacy of Adalimumab (Humira) in treating Arthritic Symptoms in the Tg197 Transgenic Mouse Model of Arthritis	GP17-003
Comparative Study on the Therapeutic Efficacy of GP2017 and Humira in preventing Arthritic Symptoms in the Tg197 Transgenic Mouse Model of Arthritis	GP17-006
Comparison of Efficacy of GP2017 versus Humira upon Multiple I.P Administrations in the Tg5453 Mouse Model	GP17-009
PK/ADME	
Comparative Pharmacokinetic Study on GP2017 versus Humira, following a Single Subcutaneous Administration to Rabbits	GP17-004
Assessment of the Potential Cross Reactivity of GP2017 with a Selected Panel of Human Tissues	8240796
GENERAL TOXICOLOGY	
GP2017 and Humira: Comparative Toxicity Study in the Cynomolgus Monkey with Subcutaneous Administration over 29 Days	8240754

4 Pharmacology

4.1 Primary Pharmacology

GP2017 is a humanized monoclonal antibody directed against human tumor necrosis factor alpha (TNF α). Adalimumab, the active ingredient of Humira and GP2017, binds to soluble and membrane-associated TNF α , thereby inhibiting the interaction of TNF α with the TNF α receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events, which is considered the primary mechanism of action in all indications approved for Humira.

The applicant conducted a battery of studies that compared GP2017 with EU- and US-Humira reference products with regards to physicochemical characterization and pharmacological activity. Refer to the Product Quality review for evaluation of the results of these studies conducted to support a determination that GP2017 is highly similar to US-licensed Humira.

Results of two comparative *in vivo* pharmacodynamics studies in transgenic mice are reviewed below.

Study Title: Evaluation of the Therapeutic Efficacy of Adalimumab (Humira) in treating Arthritic Symptoms in the Tg197 Transgenic Mouse Model of Arthritis (Study No. GP17-003)

The aim of this study was to evaluate the therapeutic effect afforded by commercially available EU-Humira (Adalimumab) on the development of pathology in the Tg197 transgenic murine model of Rheumatoid Arthritis using a dose range-finding approach. This study was used to determine a sensitive dose and treatment duration with which GP2017 and EU-Humira were compared in the Tg197 murine model. Mice (8/group) were allocated into 12 groups (G1-12) and received intraperitoneally 10 µl of test compounds per gram of body weight, in a therapeutic regimen initiated upon the establishment of arthritis (sixth week of age) (see table below). Groups G1 to G4 received a single bolus injection and were sacrificed 72 hr later. Groups G5 to G8 received biweekly treatment from 6 weeks to 8 weeks of age and then sacrificed. Finally, groups G9 to G12 received biweekly treatment from 6 weeks to 10 weeks of age and then sacrificed. The results showed that the therapeutic formulation of EU-Humira exhibited statistically significant dose-dependent inhibition of Tg197 arthritic pathology compared to saline treated control animals. Based on the partial correction of clinical symptoms and evidence for some correction of joint histopathology achieved with biweekly treatment from 6 week to 10 weeks of age at a dose level of 3 mg/kg, this treatment regime was selected for the planned comparative study (see figure below).

(Excerpt from Sponsor's submission)

Table 3. Study design of the Tg197 murine efficacy study with EU-Humira

Group No	Test article	Dose (mg/kg)	Dose frequency*	Dose volume (ml/kg)	Route of adm.	Animal number	Age at sacrifice
1	Vehicle control	-	single	10	IP	4m/4f	6 wks
2	HUMIRA®	3 mg/kg	single	10	IP	4m/4f	6 wks
3	HUMIRA®	10 mg/kg	single	10	IP	4m/4f	6 wks
4	HUMIRA®	30 mg/kg	single	10	IP	4m/4f	6 wks
5	Vehicle control	-	2/week	10	IP	4m/4f	8 wks
6	HUMIRA®	3 mg/kg	2/week	10	IP	4m/4f	8 wks
7	HUMIRA®	10 mg/kg	2/week	10	IP	4m/4f	8 wks
8	HUMIRA®	30 mg/kg	2/week	10	IP	4m/4f	8 wks
9	Vehicle control	-	2/week	10	IP	4m/4f	10 wks
10	HUMIRA®	3 mg/kg	2/week	10	IP	4m/4f	10 wks
11	HUMIRA®	10 mg/kg	2/week	10	IP	4m/4f	10 wks
12	HUMIRA®	30 mg/kg	2/week	10	IP	4m/4f	10 wks

*Start of administration at age of 6 weeks

Cohort 1: groups 1, 2, 3, 4

sacrifice 3 days after 1 administration

Cohort 2: groups 5, 6, 7, 8

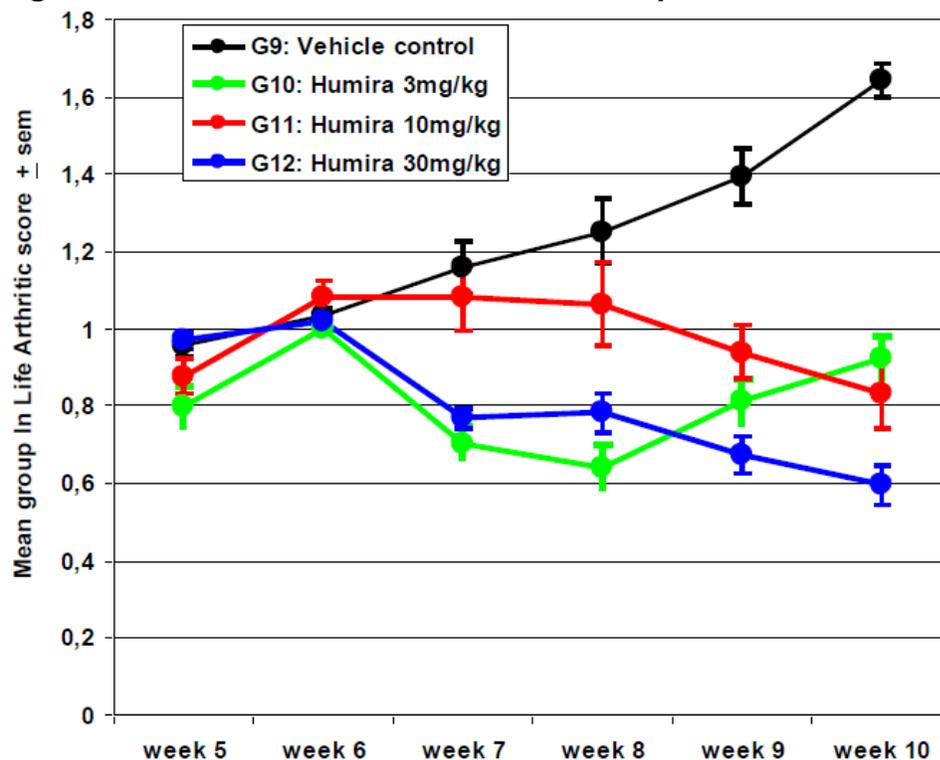
sacrifice 3 days after 5 administrations

Cohort 3: groups 9, 10, 11, 12

sacrifice 3 days after 9 administrations

(Excerpt from Sponsor's submission)

Figure 1. In-life arthritic evaluation for Groups G9-G12

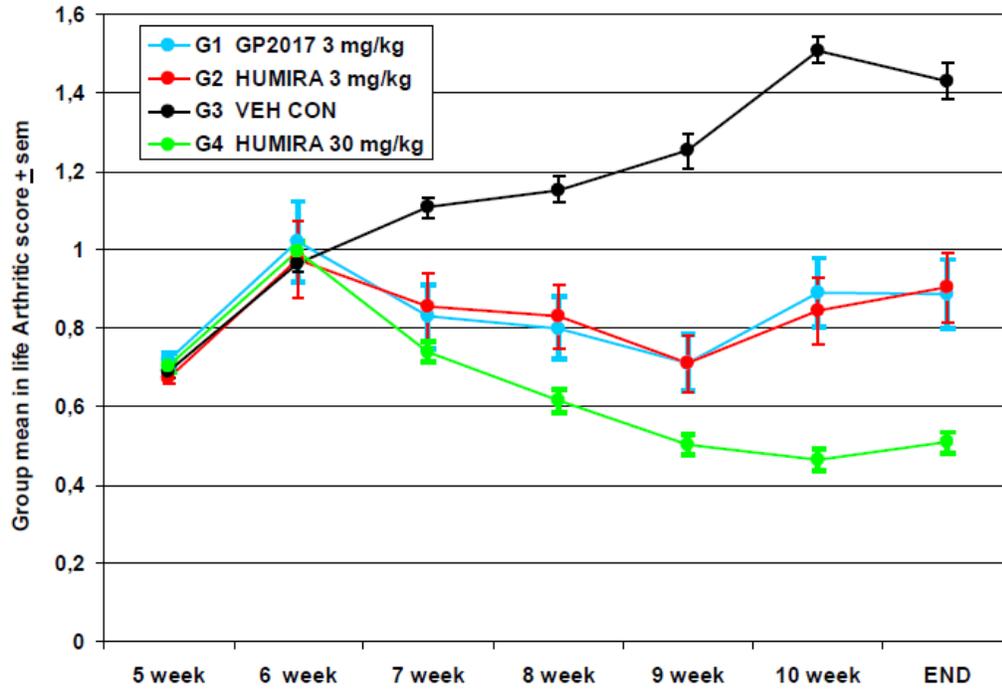


Study Title: Comparative Study on the Therapeutic Efficacy of GP2017 and Humira in preventing Arthritic Symptoms in the Tg197 Transgenic Mouse Model of Arthritis (Study No. GP17-006)

The aim of this study was to evaluate and compare the therapeutic effect of EU-Humira (adalimumab) and GP2017 on the development of pathology in the Tg197 transgenic murine model of rheumatoid arthritis. Transgenic mice were allocated in 4 groups as detailed below and received twice weekly intraperitoneal injections for 4.5 weeks following onset of arthritis at 6 weeks of age. The groups received either placebo (G3, N=20), 3 mg/kg of GP2017 (G1, N=50) or EU-Humira (G2, N=50), or 30 mg/kg of EU-Humira (G4, N=20). Following 9 injections, both the 3 mg/kg GP2017 and EU-Humira treatments exhibited a significant inhibition (~37%) of in-life arthritic scoring compared to the placebo controls (see figure below). These findings corresponded with an observed increase (~17%) in mean body weights for the 3 mg/kg GP2017 and EU-Humira treatment groups relative to control animals. A significant inhibition in mean histopathology severity scores was also observed for the 3 mg/kg GP2017 (~25.5%) and EU-Humira (22.3%) treatment groups relative to control animals at the end of the treatment period. The study showed that 3mg/kg EU-Humira and GP2017 were comparable in inhibiting the in-life Tg197 arthritic pathology as well as underlying *ex-vivo* histopathology relative to control animals.

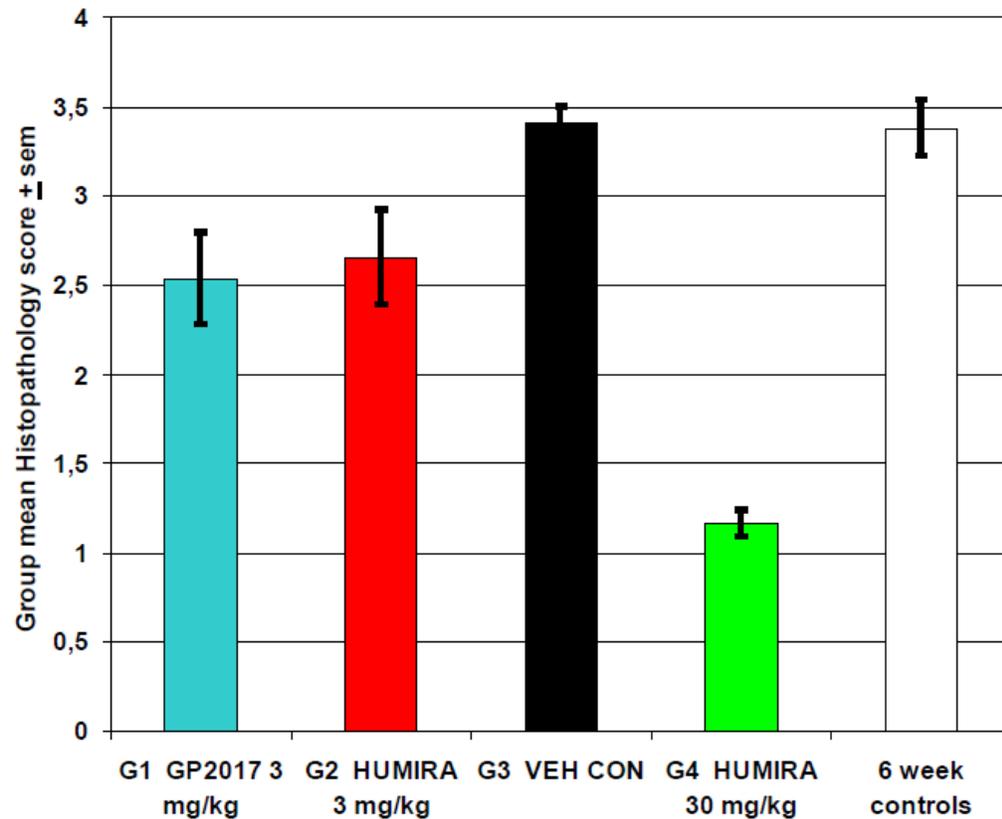
(Excerpt from Sponsor's submission)

Figure 2. In-life arthritic evaluation of GP2017 and EU-Humira in the Tg197 study



(Excerpt from Sponsor's submission)

Figure 3. Histopathological evaluation of GP2017 and EU-Humira

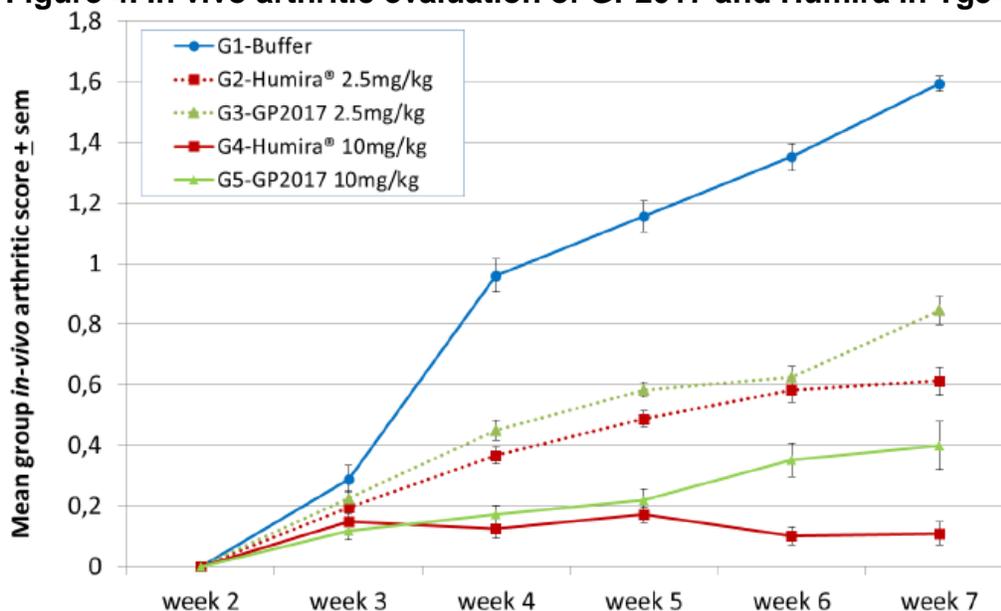


Study Title: Comparison of Efficacy of GP2017 versus Humira upon Multiple I.P Administrations in the Tg5453 Mouse Model (Study No. GP17-009)

The aim of this study was to evaluate and compare the efficacy of EU-Humira and GP2017 on alleviating the pathology in the Tg5453 transgenic mouse model of transmembrane TNF α driven disease. Transgenic mice were allocated to 5 groups (G1-G5) composed of 16 animals (G1, G4, and G5) or 30 animals (G2 and G3) each. Animals received twice weekly intraperitoneally 10 μ l per gram of body weight of either 0.25 or 1 mg/mL of test compounds prior to disease establishment. Treatment lasted for a total of 5 weeks, until the 7th week of age of the animals. Animals administered 10 mg/kg GP2017 exhibited a significant increase (~20%) in body weight gain, induced a significant inhibition (~75%) in *in vivo* arthritic evaluation, and a significant inhibition (~45%) in histopathology evaluation. At the 10 mg/kg dose level, EU-Humira and GP2017 exhibited similar effects with regards to body weight gain; however, EU-Humira was more efficacious with regards to the inhibition of arthritic pathology and histopathology evaluations at the end of the study. A dose level of 2.5 mg/kg GP2017 and EU-Humira resulted in a similar increase (~7%) in mean body weight gain, and a significant inhibition of *in vivo* arthritic evaluation profiles (~62% for EU-Humira and ~47% for GP2017). In addition, GP2017 and EU-Humira significantly inhibited mean histopathology scores by ~47% and ~62%, respectively. The comparison of both *in vivo* arthritic and histopathology scores suggested greater efficacy over time of EU-Humira compared to GP2017 across the corresponding dose responses in this prophylactic treatment model.

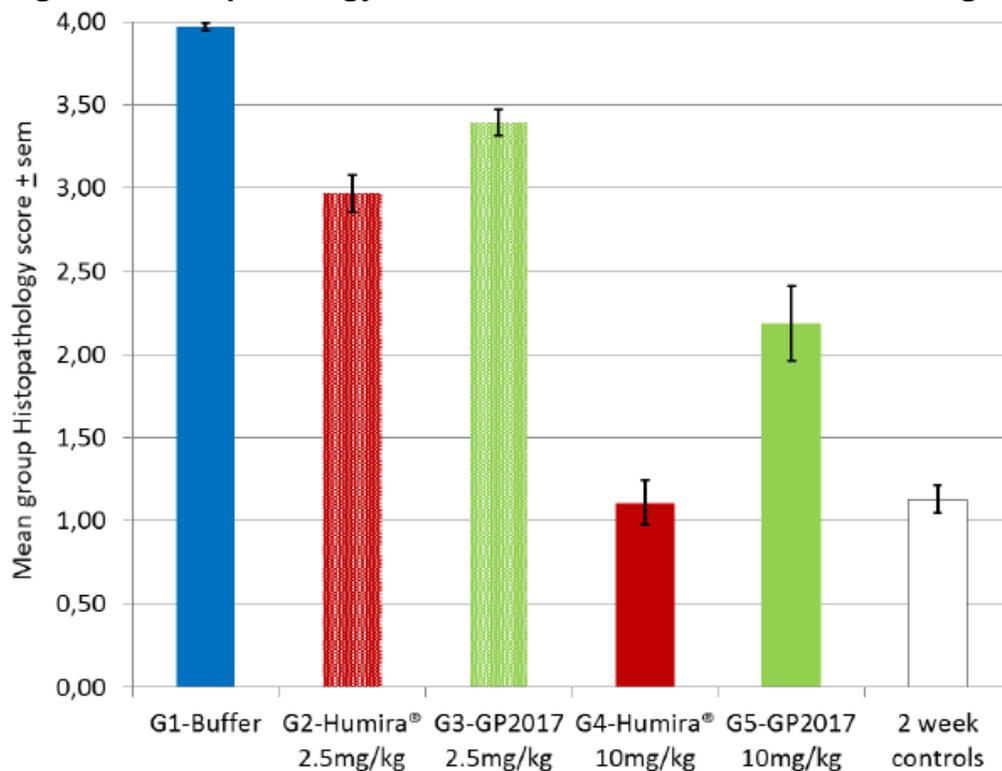
(Excerpt from Sponsor's submission)

Figure 4. In vivo arthritic evaluation of GP2017 and Humira in Tg5453 model



(Excerpt from Sponsor's submission)

Figure 5. Histopathology evaluation of GP2017 and Humira in Tg5453 model



5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study Title: Comparative Pharmacokinetic Study on GP2017 versus Humira, following a Single Subcutaneous Administration to Rabbits (Study No. GP17-004)

The aim of this study was to evaluate the pharmacokinetics of GP2017, following a single subcutaneous administration to the rabbit and compare it to EU-Humira. Male rabbits (20/group) were administered a single subcutaneous dose of either GP2017 (9.72 mg/kg) or Humira (9.28 mg/kg). Incidences of slight to moderate erythema, slight to severe edema, patchy hair growth, and bruising were observed at the injection sites of GP2017 or Humira treated animals. Anti-drug antibodies (ADA) were observed in 6 and 2 animals in the GP2017 and Humira treatment groups on Day 8, respectively. One animal in the GP2017 group exhibited a confirmed ADA response on Day 22. GP2017 and Humira exhibited mean terminal half-lives of 375 and 269 hrs, respectively. Dose normalized AUC_{0-168} values for GP2017 and Humira were 1193 and 1552 $\mu\text{g}^*\text{hr}/\text{mL}$, respectively. AUC_{0-168} , $AUC_{0-\text{tlast}}$, and C_{max} values observed for GP2017 were each approximately 25% lower than in the Humira group. The significance of results from this study is uncertain due to the fact that the rabbit is not a pharmacologically relevant species for adalimumab products.

Study Title: Comparative Single Dose Pharmacokinetic Study in Rabbits with Five GP2017 Formulation Variants versus Humira following Subcutaneous Administration – Multi-Site Study (Study No. GP17-007)

The aim of this study was to determine the AUC and C_{max} of five GP2017 formulation variants versus EU-Humira. Rabbits (20/group) were administered a single subcutaneous bolus injection of GP2017 formulations 1-5 (10 mg/kg) or EU-Humira (10 mg/kg). No signs of local intolerance reactions were observed. Based on observed AUC and C_{max} values the five GP2017 formulation variants and EU-Humira were considered as similar (all groups within 16% of Humira values). ADA formation was similar across all groups (55-70% of animals). The results of this study suggest that the addition of (b) (4) to the to-be-marketed formulation does not affect the nonclinical pharmacokinetics or local tolerability of GP2017.

Study Title: Assessment of the Potential Cross Reactivity of GP2017 with a Selected Panel of Human Tissues (Study No. 8240796)

The aim of this study was to assess the potential cross-reactivity of GP2017 with histologically prepared cryosections from a selected panel of human tissues. Preparations of peripheral blood mononuclear cells (PBMCs), coated with TNF α protein, were used as positive control material. Uncoated PBMCs were used as the negative control material and an IgG1 protein was used as a negative control antibody. Concentrations of 2.5, 5, and 10 μ g/mL biotinylated GP2017 and IgG1 protein were used for the study. No unexpected off-target staining was observed with biotinylated GP2017 in any of the human tissues studied. PBMCs coated with TNF α protein demonstrated good specific positive staining.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: GP2017 and Humira: Comparative Toxicity Study in the Cynomolgus Monkey with Subcutaneous Administration over 29 Days

Study no.:	8240754
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 4, 2011 (start of treatment)
GLP compliance:	Yes (signed)
QA statement:	Yes (signed)
Drug, lot #, and % purity:	GP2017; Lot No. 1115KC031; Purity: 99.7%

Key Study Findings

- Cynomolgus monkeys (3/sex/group) were administered either vehicle, GP2017 (100 mg/kg), or EU-Humira (100 mg/kg), SC, once weekly for 4 weeks.

- A slight increase in incidence and severity of inflammatory lesions (i.e., dermatitis, myopathy/myositis, and fasciitis/fibrosis) at the injection sites was observed for males and females in the GP2017 and EU-Humira treatment groups relative to control animals.
- GP2017 and EU-Humira exhibited similar toxicokinetic profiles. No clear sex differences in exposure were observed. Similar amounts of drug accumulation (~2.5-fold) were observed over the treatment period. No anti-drug antibodies were detected; however, it is probable that drug levels were sufficiently high enough, even at prolonged sampling times, to interfere with anti-drug antibody detection.
- Based on this study, GP2017 and EU-Humira were toxicologically similar.

Methods

Doses:	0 and 100 mg/kg/dose (GP2017 and EU-Humira)
Frequency of dosing:	Once weekly (Days 1, 8, 15, 22, and 29)
Route of administration:	Subcutaneous
Dose volume:	2 mL/kg
Formulation/Vehicle:	GP2017 formulation (b) (4) [REDACTED] [REDACTED] water for injection.
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3/sex/group
Age:	41-53 months (start of dosing)
Weight:	Males weighed 4.13-5.27 kg and females weighed 3.64-4.53 at start of treatment
Satellite groups:	None
Unique study design:	No
Deviation from study protocol:	None that affected the integrity of the study

The Sponsor's report stated that upon completion of this study and prior to the start of clinical development, the formulation of GP2017 was slightly changed. (b) (4)

[REDACTED] Exposure of both formulations was compared in a single subcutaneous dose PK bridging study (Study No. GP17-007).

(Excerpt from Sponsor's submission)

Table 4. Study design for 5-week monkey study

Group number	Description	Nominal Dose level (mg/kg/occasion)#	Number of animals/group	
			Male	Female
1	Placebo (Formulation (b) (4) matching GP2017)	0	3	3
2	GP2017	100	3	3
3	Humira® (EU-approved)	100	3	3

- Doses were administrated once weekly on Days 1, 8, 15, 22 and 29 at a dose volume of 2 mL/kg'

Observations and Results

Mortality

Animals were monitored twice daily.

There were no unscheduled deaths during the study.

Clinical Signs

All animals were observed daily for signs of ill health or overt toxicity. Each animal was given a detailed physical examination at daily intervals.

No treatment-related clinical signs were observed during the study period.

Body Weights

Individual body weights were recorded before treatment on each dosing day and on the day of necropsy.

Female animals in the GP2017 and EU-Humira treatment groups exhibited a decrease in body weight gain (Days 1-29) relative to control animals at the end of the 4-week treatment period. These findings are monitorable in a clinical setting.

Feed Consumption

Food consumption was monitored visually daily.

No treatment-related effects on food consumption were observed during the study period.

Ophthalmoscopy

Indirect investigations were performed on all animals pre-treatment and in Week 4.

No treatment-related effects on ophthalmology were observed during the study period.

ECG

ECG, blood pressure, and body temperature investigations were performed on all animals pre-treatment, on Day 2, and in Week 4.

No treatment-related effects on ECG parameters, blood pressure, or body temperature were observed during the study period.

Hematology

Blood samples were collected from all animals pre-treatment and on Day 29. A standard array of hematology parameters was evaluated.

No treatment-related effects on hematology parameters were observed during the study period.

Clinical Chemistry

Blood samples were collected from all animals pre-treatment and on Day 29. A standard array of clinical chemistry parameters was evaluated.

No treatment-related effects on clinical chemistry parameters were observed during the study period.

Urinalysis

Urine samples were collected from all animals in pre-treatment and in Week 4. A standard battery of parameters was measured.

No treatment-related effects on urinalysis parameters were observed during the study period.

Gross Pathology

All animals were subjected to necropsy.

An increase in red area at left and right anterior injection sites was observed in males in the GP2017 and EU-Humira treatment groups. These findings correlated with microscopic findings.

Several pale areas were observed in the liver and lung, and raised areas on the spleen, pancreas, and kidney of one female in the GP2017 treatment group (Animal #13F). The Sponsor's report stated that the appearance and location of the lesions were indicative of mycobacterium infection. These findings were not considered toxicologically significant.

Organ Weights

Animals were weighed before necropsy and organs in the tissue list (see below) were dissected and weighed before fixation.

No significant differences in mean organ weights were observed in the treatment groups during the 4-week treatment period. Mean weights for spleen, adrenals, and prostate were lower for males in the GP2017 and EU-Humira treatment groups relative to control animals; however, the variation was large due to the few animals studied.

The Sponsor noted that absolute liver, spleen, and adrenal weights were higher in one female (Animal #13F) in the GP2017 treatment group compared to other animals in the study.

Histopathology

Adequate Battery

At necropsy, a full macroscopic examination was performed and all lesions recorded. Samples of tissues listed below were preserved in the appropriate fixative. The following tissues were embedded in paraffin wax, sectioned at a nominal 5 µm, stained with hematoxylin and eosin and examined by the Study pathologist ([REDACTED] (b) (4)): [REDACTED]

- All protocol tissues from all animals
- Gross lesions seen in all animals at necropsy

Additional sections of lung from all animals and additional sections and impression smears of liver, spleen, pancreas, and lung from Animal #13F were stained with Ziehl-Neelsen for acid fast bacteria.

Table 5. Tissues collected and preserved from the monkey study

Tissue/organ preserved	Organ weighed	Tissue examined	Tissue/organ preserved	Organ weighed	Tissue examined
adrenal	X	X	muscle		X
animal identification			nerve, sciatic		X
aorta		X	oesophagus		X
axillary lymph nodes		X	ovary	X	X
bone marrow smear			oviduct		X
(sternum) (a) (b)			pancreas		X
brain	X	X	pituitary	X	X
caecum		X	prostate	X	X
colon		X	rectum		X
dosing sites (variable) (c)		X	salivary gland, mandibular		X
duodenum		X	salivary gland, parotid		X
eye & optic nerves (d)		X	salivary gland, sublingual		X
femur with bone marrow			seminal vesicle		X
and articular surface		X	skin/subcutis		X
gall bladder		X	spinal cord - cervical		X
gross lesions		X	spinal cord - lumbar		X
heart	X	X	spinal cord - thoracic		X
ileum (including Peyer's patch)		X	spleen	X	X
inguinal lymph nodes		X	sternum with bone marrow		X
jejunum		X	stomach		X
kidney	X	X	testis with epididymis (e)	X	X
lacrimal gland			thymus		X
larynx		X	thyroid with parathyroid	X	X
liver	X	X	tongue		X
lung with mainstem bronchi			trachea		X
and bronchioles		X	urinary bladder		X
lymph node, mandibular		X	ureter		X
lymph node, mesenteric		X	uterus with cervix	X	X
mammary		X	vagina		X

a - tissue taken into bovine serum albumin; smear prepared; air dried, then fixed in methanol

b - see clinical pathology [section 3.9.3](#)

c - all dose sites preserved

d - Davidson's fluid fixative

e - Bouin's fixative

Peer Review

No peer review was conducted.

Histological Findings

Microscopic findings are summarized in the tables below. Except for the injection sites, no treatment-related histopathology findings were observed in any tissues or organs during the 4-week treatment period.

The Sponsor's report stated that some granulomatous inflammatory areas in the femur/marrow, liver, spleen, and lung were observed for one female (Animal #13F) in the GP2017 treatment group. These foci occasionally had necrotic centers and acid fast bacteria were seen within the areas in the lung and spleen on examination with Ziehl-Neelsen staining. The Sponsor attributed this to a mycobacterium infection. These findings were not considered toxicologically significant.

A slight increase in incidence and severity of inflammatory lesions (i.e., dermatitis, myopathy/myositis, and fasciitis/fibrosis) at the injection sites was observed for males and females in the GP2017 and EU-Humira treatment groups relative to control animals (see table below). The Sponsor's report stated that the inflammatory lesions were characterized as an infiltration of predominantly mononuclear cells and fibrosis. The incidence and severity were similar for GP2017 and EU-Humira and these findings were not considered adverse.

Table 6. Histopathological findings in monkeys at the end of the 4-week treatment period

Treatment	Vehicle		GP2017		EU-Humira	
Dose (mg/kg/week)	0		100		100	
Gender	M	F	M	F	M	F
No. examined	3	3	3	3	3	3
Skin/subcutis						
-Fasciitis	0	0	2	1	1	1
-Vasculitis	0	0	0	1	0	0
Femur/Marrow						
-Granulomatous area	0	0	0	1 ^A	0	0
Liver						
-Granulomatous area	0	0	0	1 ^A	0	0
Spleen						
-Granulomatous area	0	0	0	1 ^A	0	0
Kidney						
-Focal nephropathy	0	0	1	1	0	0
-Granulomatous area	0	0	0	1	0	0
Lung						
-Granulomatous area	0	0	0	1 ^A	0	0
-Pleural fibrosis/adhesion	0	0	0	1	0	0
-Ziehl-Neelsen positivity	0	0	0	1 ^A	0	0

^AAnimal #13F

(Excerpt from Sponsor's submission)

Table 7. Histopathological findings in monkeys (injection sites)

Tissue and finding		Level (mg/kg/week)		Incidence of inflammatory lesions : injection sites – terminal necropsy					
				Males			Females		
				1M	2M	3M	1F	2F	3F
		0	GP2017 100	Humira® 100*	0	GP2017 100	Humira® 100*		
Left anterior (Injection site 1) myopathy/myositis		3	3	3	3	3	3		
	Grade -	3	1	2	2	3	0		
	1	0	1	1	1	0	3		
	2	0	1	0	0	0	0		
	fasciitis/fibrosis	Grade -	1	1	1	3	1	0	
		1	2	1	0	0	2	3	
2		0	1	1	0	0	0		
3		0	0	1	0	0	0		
Right anterior (Injection site 2) myopathy/myositis		3	3	3	3	3	3		
	Grade -	3	1	1	2	3	2		
	1	0	1	2	1	0	1		
	2	0	1	0	0	0	0		
	fasciitis/fibrosis	Grade -	1	2	2	2	1	2	
		1	2	1	0	1	2	0	
2		0	0	0	0	0	1		
3		0	0	1	0	0	0		
Left posterior (Injection site 3) dermatitis		3	3	3	3	3	3		
	Grade -	3	3	3	3	1	2		
	1	0	0	0	0	2	1		
	myopathy/myositis	Grade -	3	3	2	3	3	3	
		1	0	0	0	0	0	0	
		2	0	0	0	0	0	0	
3		0	0	1	0	0	0		
fasciitis/fibrosis	Grade -	0	2	0	2	1	0		
	1	2	1	2	1	2	3		
	2	1	0	1	0	0	0		
	Right posterior (Injection site 4) myopathy/myositis		3	3	3	3	3	3	
Grade -		2	3	2	2	3	2		
1		1	0	0	1	0	1		
2		0	0	1	0	0	0		

Key: "--" = finding not present, 1 = minimal, 2 = slight, 3 = moderate

* EU-approved Humira®

Immunogenicity

Blood samples for immunogenicity were taken from all animals pre-treatment and prior to dosing on Days 8, 15, and prior to necropsy.

The Sponsor's report stated that four samples from one female in the GP2017 treatment group (Animal #13F) were rejected for analysis as the animal was infected with tuberculosis.

Serum samples were evaluated for anti-adalimumab antibodies using a validated ECL method. Three samples exhibited a result above the cut-off in the screening assay. No specific anti-adalimumab antibodies were detected in any of the screened positive samples. All sampling timepoints in treated animals for anti-adalimumab antibody detection exhibited high plasma concentrations of GP2017 which may have led to false negative results despite acid dissociation of the anti-drug antibody/drug complexes.

Toxicokinetics

Blood samples for toxicokinetic analysis were taken from all animals at the following time points:

- Days 1 and 8: predose, 1, 2, 8, 24, 32, 40, hrs postdose and 3, 4, and 6 days postdose
- Days 15 and 22: predose only
- Day 29: predose, 1, 2, 8, 24, 32, 40 hrs postdose and 3 and 4 days postdose
- Additional samples were also taken from animals at 48 hrs after dose on Day 1

The Sponsor's report stated that due to a mycobacterial infection in Animal #13F noticed at necropsy, none of the serum samples for this animal were sent for analysis.

Following once weekly subcutaneous administration of GP2017 and EU-Humira at 100 mg/kg, serum concentrations of adalimumab increased slowly to reach maximum levels (C_{max}) at 32-144 hrs postdose in individual animals. The Sponsor's report stated that following attainment of C_{max} the disposition of adalimumab for both test articles was generally characterized by a plateau or slow decline in adalimumab serum concentrations which prevented estimation of the apparent terminal half-lives.

No significant sex differences in exposure to either GP2017 or EU-Humira were observed during the treatment period. Slight accumulation of both GP2017 and EU-Humira (i.e., ~2.5-fold) was observed between Days 1 and 29. Across males and females at Day 1 and Day 29, GP2017 C_{max} and $AUC_{0-tlast}$ values were 83-116% of the corresponding EU-Humira values.

Table 8. Summary of toxicokinetic parameters during the 4-week monkey study

	Dose (mg/kg/week)			
Treatment	GP2017		EU-Humira	
Dose (mg/kg/week)	100		100	
Gender	M	F	M	F
Day 1^A				
T_{max} (h)	72	108	93.3	90.7
C_{max} (µg/mL)	1170	1390	1430	1330
AUC_{0-tlast} (µg*hr/mL)	122000	155000	155000	142000

Day 8 ^A				
T_{max} (h)	58.7	20.0	37.3	69.3
C_{max} (µg/mL)	2260	2670	2440	2410
AUC_{0-tlast} (µg*hr/mL)	245000	287000	289000	273000
Day 29 ^B				
T_{max} (h)	48.0	84.0	58.7	35.3
C_{max} (µg/mL)	4260	4070	5250	5090
AUC_{0-tlast} (µg*hr/mL)	283000	339000	393000	337000

^AThe last AUC measurement on Days 1 and 8 were taken at 144 hrs and therefore AUC_{tlast} = AUC_{0-144 h}

^BThe last AUC measurement on Day 29 was taken at 96 hrs and therefore AUC_{tlast} = AUC_{0-96 h}

Dosing Solution Analysis

No dosing solution analysis was conducted.

10 Special Toxicology Studies

Study Title: Comparative Assessment of Local Tolerance of GP2017 and Humira[®] (latex-free, 29G, thin needle and 27G, thick needle version) upon Single S.C., I.M., I.V., I.A., and P.V. Administration to Rabbits (Study No. GP2017-008)

The aim of this study was to assess and compare the local tolerability of GP2017 ((b) (4) formulation) and EU-Humira[®] (both needle versions) upon injection via the intended as well as un-intended routes to support an assessment of similarity of the two products. Female rabbits (4/group) were administered a single intra-arterial (i.a.), intravenous (i.v.), intramuscular (i.m.), paravenous (p.v.), or subcutaneous (s.c.) injection (0.8 mL/injection site [s.c., i.a., i.v., p.v.] and 0.5 mL/injection site [i.m.]) and sacrificed on Day 1 (3 hrs postdose) or Day 3 (48 hrs postdose, s.c. only). No local tolerance reactions or microscopic findings were observed with any injection site treatments with GP2017, EU-Humira[®], or the GP2017 formulation (b) (4). No systemic toxicity was observed.

11 Integrated Summary and Safety Evaluation

GP2017 is a human monoclonal immunoglobulin (IgG1 κ subtype) against TNF α . The Sponsor conducted several pharmacology and toxicology studies comparing the effects of GP2017 to that of EU-sourced Humira.

A GLP-compliant comparative single dose pharmacokinetic study was conducted in rabbits that compared five GP2017 formulation variants, including the to-be-marketed formulation containing (b)(4), with EU-Humira. All compounds exhibited similar pharmacokinetic parameters.

A 4-week GLP-compliant repeat-dose toxicology study in cynomolgus monkeys was conducted to evaluate and compare the toxicology of GP2017 with EU-Humira. In the 4-week monkey study, cynomolgus monkeys were administered either vehicle, GP2017 (100 mg/kg, SC), or EU-Humira (100 mg/kg, SC), once weekly for 4 weeks (n=3/sex/group) for a total of 5 doses (Days 1, 8, 15, 22, and 29). A slight increase in incidence and severity of inflammatory lesions (i.e., dermatitis, myopathy/myositis, and fasciitis/fibrosis) at the injection sites was observed for males and females in the GP2017 and EU-Humira treatment groups relative to control animals. GP2017 and EU-Humira exhibited similar toxicokinetic profiles. No clear sex differences in exposure were observed. Similar amounts of drug accumulation (~2.5-fold) were observed over the treatment period. No anti-drug antibodies were detected; however, it is probable that drug levels were sufficiently high enough, even at prolonged sampling times, to interfere with anti-drug antibody detection. Based on this study, GP2017 and EU-Humira were toxicologically similar.

There are no nonclinical safety concerns for the subcutaneous administration of GP2017. The pharmacokinetics and repeat-dose toxicology data in cynomolgus monkeys provided in the BLA support a demonstration of biosimilarity (i.e., comparable systemic exposures and safety profiles) between GP2017 and EU-Humira from the nonclinical pharmacology-toxicology perspective. The applicant conducted a three-way biosimilarity program to allow the extrapolation of these conclusions to support biosimilarity to US-licensed Humira (refer to Product Quality for review of these data).

Recommendation: No residual uncertainties have been identified by this discipline and there are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective. The reviewer recommends approval of this BLA from the nonclinical perspective.

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/s/

BRETT R JONES
05/07/2018

ANDREW C GOODWIN
05/07/2018
I concur