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APPLICATION NUMBER:

761071Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type BLA 351 (k)
Application Number(s) 761071
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Review Completion Date 7-Sep-2018

Established Name adalimumab-adaz
(Proposed) Trade Name Hyrimoz, Hyrimoz Sensoready Pen,
Therapeutic Class TNF inhibitor biologic
Applicant Sandoz, Inc.

Formulation(s) 40 mg/0.8mL solution injection
Dosing Regimen

- RA, PsA, AS: 40 mg every other week (some patients with RA not receiving methotrexate may benefit from 40 mg every week)
- JIA: 40 mg every other week
- Adult CD and UC: On Day 1: 160 mg; Day 15: 80 mg; Day 29: begin maintenance dose 40 mg every other week; for UC only, only continue dosing in patients who show evidence of clinical remission by eight weeks
- PsO: 80 mg initial dose, then 40 mg every other week

Indication(s)

- Rheumatoid arthritis
- Juvenile idiopathic arthritis in patients aged 4 years or older
- Psoriatic arthritis
- Ankylosing spondylitis
- Adult Crohn's disease
- Ulcerative colitis
- Plaque psoriasis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Sandoz (also referred to as “the Applicant” in this document) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for GP2017, a proposed biosimilar to US-licensed Humira (adalimumab). Sandoz is seeking licensure of GP2017 for the following indications for which US-licensed Humira is licensed:¹

- 1) Rheumatoid Arthritis (RA):
 - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- 2) Juvenile Idiopathic Arthritis (JIA):
 - Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- 3) Psoriatic Arthritis (PsA):
 - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- 4) Ankylosing Spondylitis(AS):
 - Reducing signs and symptoms in adult patients with active AS.
- 5) Adult Crohn’s Disease (adult CD):
 - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
- 6) Ulcerative Colitis (UC):
 - Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of Hyrimoz has not been established in patients who have lost response to or were intolerant to TNF blockers.
- 7) Plaque Psoriasis (PsO):
 - The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

¹ FDA-approved Humira labeling

The Biologics Price Competition and Innovation Act (BPCI Act) is a pathway under section 351(k) of the Public Health Service Act (PHS Act) which requires that the proposed biological product is highly similar to the reference product notwithstanding minor differences between the proposed biosimilar and the reference products in terms of safety, purity, and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

This BLA had originally been submitted August 25, 2016, but was withdrawn October 21, 2016, as the Agency's expectations regarding the Pre-License Inspection scheduling could not be met for one of the proposed manufacturing sites.

The clinical data submitted in the BLA now includes the results from PK similarity studies, and a completed comparative clinical study, Study GP17-301, a multicenter, randomized, double-blind, active-controlled, comparative study in patients with moderate to severe chronic plaque psoriasis. From a clinical standpoint, the clinical pharmacology, efficacy, safety, and immunogenicity data submitted to this 351(k) BLA from the clinical development program of GP2017, support the demonstration of no clinically meaningful difference between GP2017 and US-licensed Humira in the indication studied, i.e., plaque psoriasis.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to each of the indications of use for which US-licensed Humira is currently licensed and for which GP2017 is seeking licensure.

1.2 Conclusions on the Totality of the Evidence

Sandoz submitted comparative analytical data on the GP2017 lots used in clinical studies and on lots of the proposed commercial product. Based on our review of the data provided, Sandoz's comparative analytical data for GP2017 demonstrates that GP2017 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components.

Sandoz used a non-US-licensed comparator (EU-approved Humira) in some clinical studies intended to support a demonstration of biosimilarity to US-licensed Humira. Accordingly, Sandoz provided scientific justification for the relevance of data from those studies to support a demonstration of biosimilarity of GP2017 to US-licensed Humira by establishing an adequate scientific bridge (analytical and PK) between EU-approved Humira, US-licensed Humira, and GP2017.

It is the opinion of this reviewer that the results of the comparative clinical efficacy, safety, immunogenicity, and PK studies indicate that Sandoz's data support a demonstration that there are no clinically meaningful differences between GP2017 and US-licensed Humira in

terms of safety, purity, and potency in the studied population of in moderate to severe plaque psoriasis. Safety analysis showed a similar assessment of adverse events, serious adverse events, adverse events leading to treatment discontinuations, and deaths between the reference product and the biosimilar product. Further, the single transition from US-licensed Humira or EU-approved Humira to GP2017 compared to patients who remained on US-licensed Humira or EU-approved Humira during the treatment period 2 in patients with PsO did not result in different safety or immunogenicity profiles. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to GP2017.

The Applicant has also provided an extensive data package to address the scientific considerations for the extrapolation of data to support biosimilarity in other conditions of use and licensure of GP2017 for each of the indications for which US-licensed Humira is currently licensed and for which Sandoz is seeking licensure. Also refer to BLA 761071 Division Memo, when finalized, from the collaborating review Division, Division of Gastroenterology and Inborn Errors Products (DGIEP), outlining their conclusion that demonstration of biosimilarity to indications in gastroenterology is scientifically justified.

In considering the totality of the evidence, data submitted by Sandoz support a demonstration that GP2017 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between GP2017 and US-licensed Humira in terms of the safety, purity, and potency of the product, to support licensure of GP2017 for each of the indications for which US-licensed Humira is currently licensed and for which Sandoz is seeking licensure. Thus, the DDDP and DPARP clinical teams recommend approval of this BLA.

2 Introduction and Regulatory Background

2.1 Product Information

GP2017 is a proposed biosimilar to US-licensed Humira (adalimumab). GP2017 is a recombinant human monoclonal antibody that binds specifically to TNF α to neutralize its biological function by the blocking the interaction with TNF-receptors TNFR1 and TNFR2. The analytical similarity assessment of GP2017 with US-licensed Humira, as currently assessed by the Product Quality review team, supports a demonstration that GP2017 is highly similar to US-licensed Humira except for minor differences in the clinically inactive components.

2.2 Summary of Currently Available Treatments for Proposed Indications

Available therapies may be approved for treatment of more than one condition. Currently approved non-biologic and biologic systemic therapies and the indications for which they are approved are listed in Table 1 and Table 2, respectively.

Plaque Psoriasis

The available approved systemic treatments for moderate to severe PsO in candidates for systemic therapy or phototherapy is described in Table 1 and Table 2 below. While multiple topical therapies are available, and may be used in combination with systemic treatments, topical therapies are not typically used alone for patients with psoriasis of moderate to severe severity. Phototherapy involves exposure to UVB (including narrowband) or to UVA in combination with the photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA. Phototherapy requires frequent office visits (e.g. three times per week) and carries an increased risk of squamous cell carcinoma (of the skin).

Rheumatoid Arthritis

Many effective therapies are approved for the treatment of patients with RA including nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors, corticosteroids, disease modifying anti rheumatic drugs (DMARDs) and biologics. Currently approved non-biologic and biologic systemic therapies for RA are listed in Table 1 and Table 2, respectively.

Polyarticular Juvenile Idiopathic Arthritis (JIA)

Similar to RA, effective therapies for the treatment of patients with JIA include NSAIDs, selective COX-2 inhibitors, corticosteroids, DMARDs, and biologics. Currently approved non-biologic and biologic therapies for polyarticular JIA are listed in Table 1 and Table 2 below.

Psoriatic Arthritis (PsA)

The first-line therapy for the treatment of psoriatic arthritis is typically the off-label use of small molecular immunomodulators (DMARDs, such as methotrexate (MTX), sulfasalazine, and leflunomide). NSAIDs and corticosteroids are also used. The TNF-inhibitors, infliximab, etanercept, adalimumab, certolizumab, and golimumab, as well as the IL-12/IL-23 inhibitor, ustekinumab, have been approved for treatment of active psoriatic arthritis. More recently, apremilast, a small molecule phosphodiesterase 4 inhibitor, and secukinumab, an IL-17 inhibitor, were also approved for treatment of active psoriatic arthritis. Currently approved therapies for treatment of adult patients with psoriatic arthritis are listed in Table 1 and Table 2.

Ankylosing Spondylitis (AS)

Initial treatment for AS typically includes the use of NSAIDs. Sulfasalazine may be used off-label for management of peripheral arthritis. For persistent axial symptoms, patients may be treated with TNF-inhibitors or secukinumab, an IL-17 inhibitor. Currently approved therapies for treatment of adult patients with ankylosing spondylitis are listed in Table 1 and Table 2.

Table 1: US-licensed Non-Biologic DMARDs by Indication

Product Name (Trade Name) [Applicant] {year}	Mechanism of Action	Approved Indications					
		RA	PsA	AS	pJIA	PsO	Other
Sulfasalazine (AZULFIDINE) [Pfizer]{1950}	<i>Anti-inflammatory and/or immunomodulator</i>	X			X		UC
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple] {1953}	<i>Folate anti-metabolite</i>	X			X	X	Oncology Indications
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]{1955}	<i>Unknown</i>	X					SLE, Malaria
Prednisone [Multiple sponsors]{1955}	<i>Anti-inflammatory and other unspecified mechanisms</i>	X					Multiple
Azathioprine (IMURAN) [Prometheus Labs]{1968}	<i>Anti-metabolite</i>	X					Renal transplant
Penicillamine (CUPRIMINE) [Aton]{1970}	<i>Unknown</i>	X					Wilson's Disease, cystinuria
Auranofin (RIDAURA) [Prometheus Labs]{1985}	<i>Unknown</i>	X					
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]{1990, 1995}	T-cell inhibitor	X				X	Organ rejection, KCS
Acitretin (SORIATANE) (Stiefel){1996}	<i>Retinoid</i>					X	
Leflunomide (ARAVA) [Sanofi-Aventis]{1998}	<i>Anti-metabolite</i>	X					
Tofacitinib (XELJANZ) [Pfizer] (2012)	<i>JAK kinase inhibitor</i>	X					UC
Apremilast (Otezla) [Celgene] {2014}	<i>PDE4 inhibitor</i>		X			X	
Year = Year of first approval	UC=Ulcerative Colitis, CD=Crohn's Disease, SLE=Systemic Lupus Erythematosus, KCS=Keratoconjunctivitis sicca						

Table 2: US-licensed Biologic DMARDs by Indication

Product Name (Trade Name) [Applicant] {year}	Description and <i>Mechanism of Action</i>	Approved Indications					
		RA	PsA	AS	pJIA	PsO	Other
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Fusion protein consisting of TNF-R and human IgG1 Fc <i>TNF inhibitor</i>	X	X	X	X	X	
Infliximab (REMICADE) [Centocor] {1999}	Chimeric IgG1 k mAb <i>TNF inhibitor</i>	X	X	X		X	CD, UC, Pediatric CD/UC
Anakinra (KINERET) [Amgen] {2001}	Recombinant polypeptide <i>IL-1 receptor antagonist</i>	X					
Adalimumab (HUMIRA) [Abbott] {2002}	Human IgG1 k mAb <i>TNF inhibitor</i>	X	X	X	X	X	CD, UC,
Natalizumab (TYSABRI) [Biogen] {2004}	Humanized IgG4 k mAb <i>Integrin receptor antagonist</i>						CD
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Fusion protein consisting of CTLA-4 and human IgG1 Fc <i>T cell activation inhibitor</i>	X	X		X		
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Chimeric murine/human IgG1 k mAb <i>Anti CD20, B cell depletor</i>	X					
Golimumab (SIMPONI) [Centocor] {2009}	Humanized IgG1 k mAb <i>TNF inhibitor</i>	X	X	X			UC
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Humanized Fab fragment <i>TNF inhibitor</i>	X	X	X			CD
Ustekinumab (STELARA) [Centocor Ortho Biotech] {2009}	Humanized IgG1 k mAb <i>IL-12, IL-23 antagonist</i>		X			X	CD
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Humanized IgG1 k mAb <i>IL-6 receptor inhibitor</i>	X			X		SJIA
Golimumab (SIMPONI ARIA) [Janssen Biotech] {2013}	Humanized IgG1 mAb <i>TNF inhibitor</i>	X					
Vedolizumab (ENTYVIO) [Takeda] {2014}	Humanized IgG1 mAb <i>Integrin receptor antagonist</i>						CD, UC
Secukinumab (Cosentyx) [Novartis] {2015}	Humanized IgG1 mAb <i>IL-17 inhibitor</i>		X	X		X	
Ixekizumab ((TALTZ) [Eli Lilly] {2016}	Humanized IgG4 mAb <i>IL-17 inhibitor</i>		X			X	
Brodalumab ((SILIQ) [Valeant] {2017}	Human IgG2 k mAb <i>IL-17 receptor inhibitor</i>					X	
Guselkumab ((TREMFYA) [Janssen Biotech] {2017}	Human IgG1 λ mAb <i>IL-23 antagonist</i>					x	
Year = Year of first approval	CD=Crohn's Disease, UC=Ulcerative Colitis, NOMID=Neonatal Onset Multisystem Inflammatory Disease, GPA=Granulomatosis with Polyangiitis, MPA=Microscopic Polyangiitis, NHL=Non-Hodgkin's Lymphoma, CLL=Chronic Lymphocytic Leukemia, SJIA= Systemic Juvenile Idiopathic Arthritis, HS=Hidradenitis Suppurativa						

Additionally, several biosimilars TNF inhibitors were approved for multiple indications.

Table 3: US-licensed Biosimilar Approvals

Product Name (Trade Name)
Infliximab-dyyb (Inflectra) biosimilar to Remicade
Etanercept-szsz (Erelzi) biosimilar to Enbrel
Adalimumab-atto (Amjevita) biosimilar to Humira
Infliximab-abda (Renflexis) biosimilar to Remicade
Adalimumab-abdm (Cyltezo), biosimilar for Humira
Infliximab-qbtx (Ixifi), biosimilar to Remicade

2.3 Availability of Proposed Active Ingredient in the United States

This product is not marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The US-licensed HUMIRA label (USPI) includes a boxed warning (see below) and several further conditions in the warnings and precaution section in particular serious infections, including tuberculosis and other opportunistic infections, and malignancies including non-melanoma skin cancer and lymphoproliferative disorders, which also apply to other TNF blockers.

Boxed warning:

“Serious infections

Patients treated with Humira are at increased risk for developing serious infections that may lead to hospitalization or death [...]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- *Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before Humira use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.*
- *Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.*

- *Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.*

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy [...].

Malignancy

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including Humira [...]. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including Humira. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants [...]."

The warning and precautions section (section 5 of the USPI) has additional conditions, which are also other known safety issues with Humira and other TNF blockers and include:

- Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystosis have been reported in patients receiving HUMIRA. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicemia. Hospitalization or fatal outcomes associated with infections have been reported. Tuberculosis (including pulmonary and extra-pulmonary tuberculosis), including reactivation and new onset of tuberculosis, has been reported in patients receiving HUMIRA. If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, invasive fungal infection is to be considered in the differential diagnosis.
- Malignancies including breast, colon, prostate, lung, and melanoma, non-melanoma skin cancer, lymphoma and leukemia. Additionally, lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA. Rare cases of hepatosplenic T cell lymphoma have occurred in adolescents and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.
- Hypersensitivity reactions including anaphylaxis

- Hepatitis B reactivation, some cases with fatal outcome, has occurred in patients who are chronic carriers of this virus
- Neurologic reactions (rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome)
- Hematological reactions (rare cases of pancytopenia including aplastic anemia, and adverse reactions of the hematologic system, including medically significant cytopenia, e.g. thrombocytopenia, leukopenia)
- Concurrent use of anakinra or abatacept (associated with a greater proportion of serious infections and, in case of anakinra, neutropenia). Both anakinra and abatacept were prohibited treatments during study GP17-301, and patients were only randomized after a 6-month washout period after anakinra or abatacept treatment.
- Heart failure, i.e. onset or worsening of congestive heart failure
- Autoimmunity, i.e. formation of autoantibodies and, rarely, development of a lupus-like syndrome
- Immunizations; patients on Humira may receive concurrent vaccinations, except for live vaccines

Adalimumab use has been previously described to lead to development of anti-drug antibody (ADA) formation in clinical studies, and according to the FDA-approved Humira labeling, there was a trend toward higher adalimumab apparent clearance in the presence of anti-adalimumab antibodies, but no apparent correlation between the development of anti-adalimumab antibodies and the occurrence of adverse events (AEs). In the published literature, however, anti-adalimumab antibodies are described to be associated with increased frequency of clinical adverse effects, such as thromboembolic events or hypersensitivity reactions (Korswagen et al 2011, van Schouwenburg et al 2013)^{2,3}, but other authors do not describe such an association (Vincent et al 2013).⁴

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On January 14, 2013, Sandoz met with the Agency for a Type B Pre-IND meeting to discuss the proposed development plan for GP2017. The Agency reviewed the meeting package and provided extensive comments regarding the development of GP2017 under a 351(k) pathway. In addition to providing guidance on the analytical assessment, the Agency discussed the comparative clinical study, including the need for safety and immunogenicity assessments in the setting of patients undergoing a single transition from

² Korswagen LA, Bartelds GM, Krieckaert CL, et al. Venous arterial thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies: a case series and cohort study. *Arthritis Rheum*; 63(4): 877-83.

³ Van Schouwenburg PA, van de Stadt LA, de Jong RN, et al. Adalimumab elicits restricted anti-idotypic antibody response in autoimmune patient resulting in functional neutralization. *Ann Rheum Dis*; 72(1): 104-9.

⁴ Vincent FB, Morand EF, Murphy K, et al. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralizing agents in chronic inflammatory diseases: real issue, a clinical perspective. *Ann Rheum Dis*; 72(2): 165-78.

the comparator product to GP2017 compared with patients who continue treatment with comparator product. IND 115732 was opened on November 11, 2013, with the proposed clinical study, GP17-301, “A Randomized, Double-Blind, Multicenter study to Demonstrate Equivalent Efficacy and to Compare Safety and Immunogenicity of a Biosimilar Adalimumab (GP-2017) and Humira in Patients with Moderate to Severe Chronic Plaque-Type Psoriasis”.

BLA 761071 was originally submitted on August 25, 2016, and withdrawn on October 21, 2016 because the manufacturing sites were not ready for Pre-License Inspection. The withdrawal acknowledgement was signed on November 04, 2016, with the following delineated deficiencies:

- Dataset did not include information regarding which observations were included in the Week 16 analysis of PASI 75, or how missing data were handled for per-protocol and full analysis sets
- The exclusion of subjects treated with EU-Humira at EU sites in the efficacy analysis
- Absence of extractable and leachable study reports
- Disagreement on criteria to define EAC
- Absence of analytical similarity assessment comparing the ability of GP2017 and US-Humira to elicit reverse signaling and induction of regulatory macrophages
- Pre-License facility inspection expectations not met.

The Agency confirmed agreement with the agreed iPSP on April 13, 2016. On July 31, 2017, Sandoz submitted an amendment to its agreed iPSP, in which they proposed the following two changes to the iPSP:

1. Delay the timeline for the submission of the [REDACTED] (b) (4) from 2017 in the agreed upon iPSP to 2019.
2. Include the plans for the pediatric assessment of [REDACTED] (b) (4).

Of note, the Applicant never reached agreement with the Agency on the proposed amended iPSP, and instead submitted the original agreed iPSP from April 2016 in the BLA submission.

BLA 761071 was resubmitted on October 30, 2017 and requested a review of the proposed proprietary names, submitting an amendment on November 02, 2017, clarifying that the proposed proprietary names are “Hyrimoz” for the proposed biosimilar product GP2017, and “Hyrimoz Sensoready Pen” for the autoinjector (pen) device.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic sBLA submission was well-organized and complete and there were no major amendments.

3.2 Compliance with Good Clinical Practices

All studies were conducted by Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols.

Informed consent, protocol, amendments, and administrative letter forms for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities. Written informed consent was obtained prior to the subject entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

The Office of Scientific Investigations (OSI) was consulted to conduct routine applicant/monitor inspection for GP2017, a proposed biosimilar to US-licensed Humira. A single clinical comparative study (301) was conducted to support a determination of no clinically meaningful differences, and provides the foundation for extrapolation to all indications sought for the biosimilar.

The FDA Office of Regulatory Affairs (ORA) investigator was unable to conduct an inspection at Dr. Ramon Berenguer's site (Site # 1268), since all source documents for Study GP17-301 were destroyed by a fire at the site in August of 2016, and thus the Applicant was asked (on May 23, 2018) to provide the following information: all monitoring reports for this site, all correspondences among the sponsor, the monitoring CRO, and the site related to the fire accident.

On May 31, 2018, Sandoz submitted a Clinical Amendment regarding Site #1268, detailing that the site was destroyed by a "fire accident" in August 2016, resulting in destruction of all study documentation, including all source documents for Study GP17-

301. The amendment provided “all monitoring reports for this site, all correspondences among the sponsor, the monitoring CRO, and the site related to the fire accident.”

Two types of Monitoring Visits were executed: Blinded Monitoring Visits were carried out to review activities of blinded site staff; and, Pharmacy Visits were conducted to review site staff activities related to the “Handling of Investigational Product.”

The fire occurred on August 01, 2016, and the principal investigator (PI) on September 28, 2016, provided Sandoz with a narrative of events, and confirmed that all study documentation had been destroyed by the fire or experienced extensive water damage. (b) (4) was informed that all clinical trial activities would be suspended pending relocation to a new facility. In December 2016, (b) (4) provided “Essential Documents” available in the blinded TMF to the site for replacement of destroyed documents for the Investigator Site File (ISF). The PI notified (b) (4) in February 2017 that there had been delays in opening a new research office.

On May 23, 2018, the Agency sent an electronic correspondence to the Applicant, requesting all monitoring reports for Site #1268, all correspondences among the sponsor, the monitoring CRO, and the site related to the fire accident. The Applicant submitted a Clinical Amendment on May 31, 2018, responding to this Information Request

Site 1218 (Forest Hills, NY), the second largest US site (18 subjects), was also selected for inspection.

Based on the results of these inspections, the OSI review team concluded that the study appears to have been conducted adequately, and the data generated by these sites appear acceptable to support the current BLA. Supportive statistical sensitivity analyses were conducted excluding Center 1268.

3.3 Financial Disclosures

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. The Applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified. (See attached Clinical Investigator Financial Disclosure Review form.)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

GP2017 is a proposed biosimilar product to US-licensed Humira. An analytical similarity program was designed utilizing the proposed biosimilar, GP2017, US-licensed Humira, and EU-approved Humira. The program had two goals: first, to demonstrate findings that GP2017 is “highly similar” to the US-licensed Humira notwithstanding minor differences in clinically inactive components; and second, a comparison of GP2017, US-licensed Humira, and EU-approved Humira to establish the analytical component of the scientific bridge to justify the relevance of data generated using EU-approved Humira as the comparator in some clinical and non-clinical studies. To support a demonstration that GP2017 is highly similar to the US-licensed Humira, Sandoz submitted an extensive analytical similarity package consisting of multiple orthogonal physicochemical and biological assays. Highly critical quality attributes include amino acid identity, higher order structure, in vitro TNF- α neutralization, and TNF- α binding. A comparison of the secondary and tertiary structures, and the impurity profiles, of GP2017 and US-licensed Humira support the conclusion that the two products are highly similar. Many assays were designed to specifically address and measure potential mechanisms of action of adalimumab, including TNF- α binding and neutralization, TNF- β neutralization, and Fc-mediated functions.

The results of these comparisons show that the three products met the pre-specified criteria for analytical similarity, including statistical criteria for the critical potency bioassay, TNF- α neutralization, and TNF- α binding. Thus, a pair-wise analytical comparison of GP2017 to US-licensed Humira supports the conclusion that GP2017 is highly similar to US-licensed Humira. Further, an adequate analytical bridge between EU-approved Humira, US-licensed Humira, and GP2017 was established as part of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of GP2017 to US-licensed Humira.

Refer to the CMC review for a detailed discussion of the CMC findings.

4.2 Clinical Microbiology

No issues have been identified by the Clinical Microbiology review team that would preclude approval as of the time of this review.

4.3 Preclinical Pharmacology/Toxicology

The primary nonclinical reviewer, Dr. Brett Jones, provided two pharmacology-toxicology memos for BLA 761071. In a memo dated May 7, 2018, Dr. Jones reviewed primary pharmacology, comparative pharmacokinetics (PK), and a 4-week monkey comparative toxicology study. In a memo dated May 16, 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) prefilled pen / autoinjector. Excipients include adipic acid, citric acid monohydrate, polysorbate 80, sodium chloride, water, 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.

Dr. Jones' conclusion is 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-approved 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).

There were no residual uncertainties or outstanding issues, and from the Pharmacology/Toxicology perspective the application is recommended for approval.

4.4 Clinical Pharmacology

The clinical pharmacology program of GP2017 was designed to evaluate the PK similarity between GP2017 and US-licensed Humira, and to assess the PK element of the scientific bridge between GP2017, US-licensed Humira, and EU-approved Humira.

The PK similarity study GP17-101 as well as the supportive PK study GP17-102 were conducted in healthy volunteers. A healthy volunteer population was chosen as the most sensitive setting to detect potential PK differences between GP2017, US-Humira and EU-Humira "because it is likely to produce less PK variability compared with that in patients with potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. To evaluate PK similarity, a comparison of PK profiles over a period of approximately 5 half-lives is required, and due to bi-weekly dose schema of Humira, bioequivalence assessment is not considered suitable in a patient population.

In the PK similarity study GP17-101 in healthy volunteers, for the pairwise comparison between GP2017 and US-Humira, PK similarity criteria were met for all primary PK parameters (C_{max}, AUC_{0-last} and AUC_{0-inf}) and the secondary PK parameter AUC_{0-360h}. In the comparative clinical study GP17-301 in patients with PsO, mean

adalimumab trough serum concentrations appeared to be higher in the GP2017 treatment group compared with the US-Humira treatment group, but were within the ranges given for PsO patients in the Humira USPI. Intra-group variation was high, and standard deviations across groups were largely overlapping.

The PK data from these two studies therefore address the residual uncertainty remaining from the analytical and functional assessment as well as from the supportive nonclinical evaluation, and, when combined with the aggregate clinical evidence, fulfil the statutory requirement of demonstrating that “there are no clinically meaningful differences between the biological product and the reference product in terms of safety purity, and potency”.

In the supportive PK study GP17-102, results of the primary and secondary PK endpoints were similar between GP2017 administered by AI or by PFS and therefore support approval of the Sensoready AI.

Please see the Clinical Pharmacology review for details.

5 Sources of Clinical Data

Data was submitted in the NDA under CDISC format.

5.1 Tables of Studies/Clinical Trials

Table 4: Summary of the Clinical Development Program of GP2017

Study ID	Design	Objective	Subjects	Dose	Treatments
Clinical Pharmacology Studies					
GP17-101	R, DB, SD, 3-arm, PG, using PFS	PK, immunogenicity, safety	Healthy male and female (n=219)	40 mg SC	GP2017 PFS (n=73) US-Humira (n=73) EU-Humira (n=73)
GP17-104	R, DB, SD, 3-arm, PG, using PFS	PK, immunogenicity, safety	Healthy male (n=318)	40 mg SC	GP2017 PFS (n=107) US-Humira (n=105) EU-Humira (n=106)
Comparative Clinical Study					
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)
Supportive Clinical Pharmacology Studies					
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

5.2 Review Strategy

The clinical development program for GP2017 consists of the five controlled clinical studies listed in Table 4. The following studies provide the primary evidence to support the demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira.

- GP17-101: This PK study was a single-center, randomized, double-blind, single-dose, three-arm parallel study in 219 healthy male and female subjects, which compared GP2017, US-Humira and EU-Humira.
- GP17-104: This PK study was a single-center, randomized, double-blind, single-dose, three-arm parallel study in 318 healthy male subjects comparing GP2017 with EU-Humira and EU-Humira with US-Humira.
- GP17-301: The comparative clinical study was a multicenter, randomized, double-blind study in 465 male and female patients with chronic plaque-type psoriasis with treatment duration of up to 51 weeks comparing GP2017 with Humira (patients recruited in the US received US-Humira, and patients recruited in Europe received EU-Humira).
- GP17-102 in 108 healthy male subjects, which compared GP2017 administered by autoinjector (AI; GP2017-AI) to GP2017 administered by pre-filled syringe (PFS; GP2017-PFS) and supports approval of the Sensoready AI.
- GP17-103 in 178 healthy male subjects, which compared PK, safety and immunogenicity of GP2017 drug product produced from drug substance manufactured either at (b) (4) (referred to as GP2017 (b) (4)) or at Sandoz GmbH, Biopharmaceuticals Schafftenau (BPS) in Langkampfen, Austria (referred to as GP2017-Schafftenau). For both manufacturing sites, drug substance was formulated to drug product at (b) (4)

The Applicant provided safety data for the pooled PK studies in healthy subjects for pooled GP2017 (466 subjects, who received a single dose of GP2017; all GP2017 groups pooled into one group) and pooled Humira (357 subjects; US-Humira and EU-Humira) groups and for the individual studies. For the comparative clinical study GP17-301, the safety data and immunogenicity data are reported for the following three study periods or patient groups:

- **Treatment Period 1** (Randomization to Week 17): safety and immunogenicity data are presented by treatment group (GP2017 and Humira) for the safety analysis set (SAF). The SAF included all patients who received at least one dose of IMP during Treatment Period 1. Patients were analyzed according to the treatment received.
- **Continued groups** (Randomization to Week 51): safety and immunogenicity data are presented for all patients who continued the same treatment throughout the study, including patients who were re-randomized into continued groups (GP2017 and Humira) and patients who discontinued from the study during Treatment Period 1. Data are presented for the SAF. Patients were analyzed

according to the treatment received.

- **Individual groups** (Week 17 to Week 51): safety and immunogenicity data are presented for the four individual groups after re-randomization at Week 17 (1a: continued GP2017, 1b: GP2017 to Humira, 2a: continued Humira, and 2b: Humira to GP2017). Data are presented for the safety analysis set Treatment Period 2 and Extension Period (TP2+EP SAF). The TP2+EP SAF included all patients who received at least one dose of IMP during Treatment Period 2 or the Extension Period. Patients were analyzed according to the treatment received.

For patient demographics, disease characteristics and patient disposition, further analysis sets were used:

- Patient demographics and disease characteristics of patients in Treatment Period 1 and of patients in the continued groups are summarized for the full analysis set (FAS). FAS included all randomized patients to whom study treatment was assigned. Patient demographics and disease characteristics of patients in the individual groups are summarized for the full analysis set Treatment Period 2 and Extension Period (TP2+EP FAS), which consisted of all patients who were re-randomized into Treatment Period 2.
- Patient disposition is summarized by treatment period for the FAS (Treatment Period 1), the TP2+EP FAS (Treatment Period 2), and the full analysis set Extension Period (EP FAS, consisting of all patients who entered into the Extension Period; Extension Period).

No special safety concerns arose from nonclinical safety data obtained with GP2017 that warranted consideration in the clinical evaluation of safety.

5.3 Discussion of Individual Studies/Clinical Trials

Study GP17-301

The comparative clinical study was a multicenter, randomized, double-blind study in 465 male and female patients with chronic plaque-type psoriasis with treatment duration of up to 51 weeks comparing GP2017 with Humira (patients recruited in the US received US-licensed Humira, and patients recruited in Europe received EU-approved Humira).

Study GP17-301 included male or female subjects aged 18 or above with active, clinically stable chronic plaque-type psoriasis. The main criteria for study inclusion:

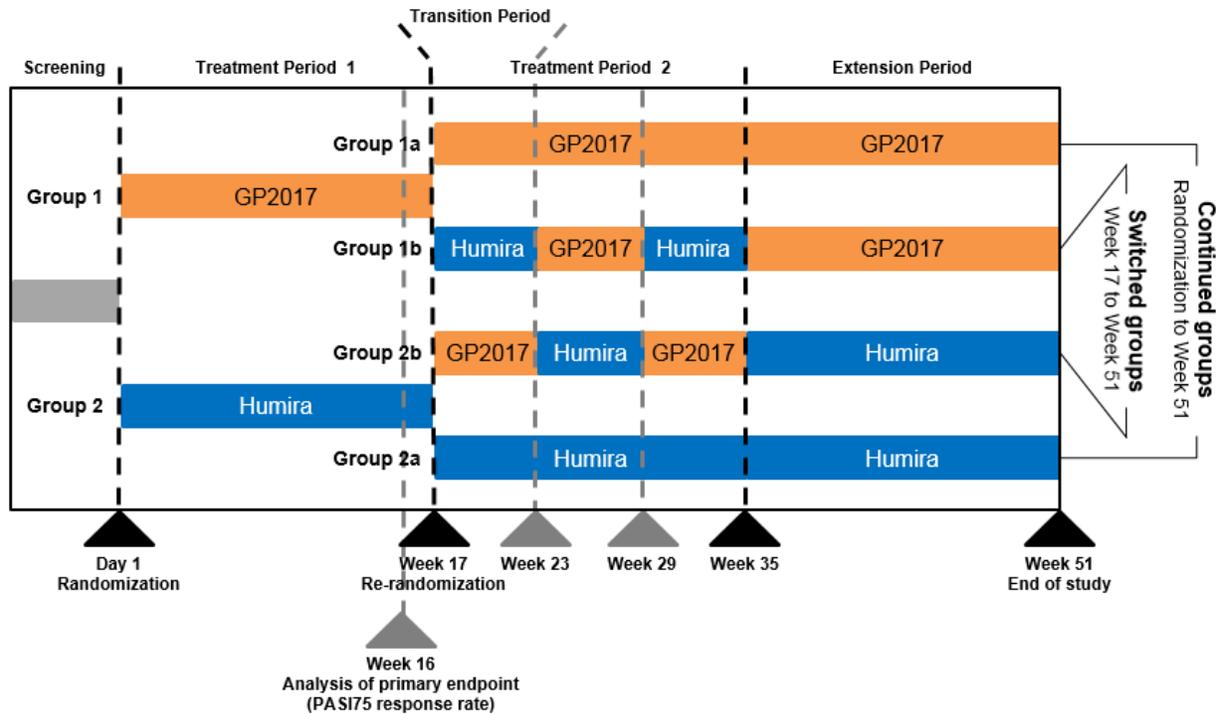
- Involvement of at least 10% of the body surface area
- Psoriasis Area and Severity Index of ≥ 12 (moderate-to-severe psoriasis) and an Investigator's Global Assessment score ≥ 3
- Previously received at least once phototherapy or systemic therapy for psoriasis or were candidates to receive such therapy in the opinion of the investigator

- Negative test results for hepatitis B and C and for the presence of latent (inactive) tuberculosis detected by imaging or by the QuantiFERON-TB Gold test at screening

Subjects were excluded from the study:

- Presented with drug-induced psoriasis (i.e. new onset or current exacerbation from e.g. betablockers, or lithium) or forms of psoriasis (e.g. pustular, erythrodermic and guttate psoriasis) that are different from chronic plaque-type psoriasis
- Had been previously exposed to adalimumab
- Presented with underlying condition which in the opinion of the investigator significantly immunocompromised the patient and/or placed the patient at unacceptable risk when receiving an immunomodulatory therapy
- Presented with pre-existing or recent-onset of central or peripheral nervous system demyelinating disorders or were considered to have an increased risk of developing a demyelinating disease
- Had a history of an ongoing, chronic, or recurrent infectious disease, history of active tuberculosis or presence of latent (inactive) tuberculosis detected by imaging or by the QuantiFERON-TB Gold test at screening
- Presented with active systemic infections during the last 2 weeks (exception: common cold) prior to randomization and any infections that reoccurred on a regular basis
- Had a history of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system (except for basal cell carcinoma or actinic keratosis that had been treated with no evidence of recurrence in the past 3 months before screening, and except for carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
- Had received live vaccination within 6 weeks prior to randomization or planned to receive one during the study

Figure 1: Diagram of Comparative Clinical Study GP-17-301



Patients were randomized at Day 1 to receive GP2017 or Humira and were administered a loading dose of 80 mg s.c., followed by 40 mg doses s.c. every other week from Week 1 up to Week 49. At Week 17, patients with a PASI50 response were re-randomized in a 2:1 ratio into continued (1a: continued GP2017 or 2a: continued Humira) or switched treatment groups (1b: GP2017 to Humira or 2b: Humira to GP2017).

PASI=Psoriasis Area and Severity Index

In this clinical trial, safety was evaluated by comparing GP2017 and US-licensed or EU-approved Humira in terms of:

- Vital signs, clinical laboratory variables, electrocardiograms (ECGs), AE monitoring, and incidence and severity of injection site reactions
- Immunogenicity as determined by measuring the rate of ADA formation against GP2017 and Humira
- Long term safety and immunogenicity of data from patients continuously treated with GP2017 (Group 1a) with those of patients continuously treated with Humira (Group 2a) and from patients who experienced repeated switches from Week 17 until Week 51 (Groups 1b and 2b) with those from patients continuously treated with GP2017 (Group 1a) or Humira (Group 2a)

6 Review of Efficacy, Study GP17-301

See full Agency Biostatistical Review by Dr. Fritsch.

The clinical review concurs with the conclusion by Dr. Fritsch in her Biostatistical review;

“Study 301 is a comparative clinical study of GP2017 versus Humira in subjects with moderate to severe psoriasis. The primary endpoint was the proportion of subjects at Week 16 with PASI 75 response. Table 21 presents the results for the overall population (all subjects), the subset of US subjects, and the subset of US subjects excluding Center 1268. In each case, the results are generally consistent and the 90% confidence intervals are contained within $\pm 18\%$, the pre-specified similarity criterion. The secondary endpoints of percent change in PASI and IGA success are consistent with the results of the primary endpoint analysis.”

Table 5: PASI 75 Response Rates at Week 16

	GP2017	Humira	Difference	90% CI
<i>PPS</i>				
Overall	N=197 66.8%	N=196 65.0%	1.8	(-6.0, 9.7)
US	N=157 68.0%	N=157 62.6%	5.3	(-3.5, 14.1)
US excluding r 1268	N=143 74.5%	N=143 68.9%	5.6	(-4.5, 15.7)
<i>FAS</i>				
Overall	N=231 58.1%	N=234 55.9%	2.2	(-5.4, 9.7)
US	N=188 57.9%	N=190 53.2%	4.7	(-3.6, 13.1)
US excluding r 1268	N=174 62.6%	N=171 59.1%	3.5	(-4.9, 12.0)

Source: DDDP Statistics Reviewer

There are no outstanding issues related to efficacy of the proposed product.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

GP17-301: The confirmatory efficacy and safety study was a multicenter, randomized, double-blind study in 465 male and female subjects with chronic plaque-type psoriasis with treatment duration of up to 51 weeks comparing GP2017 with Humira (subjects recruited in the US received US-licensed Humira, and subjects recruited in Europe received EU-approved Humira).

In this review, the focus of safety assessments will be for Treatment Period 1 (Randomization to Week 17).

7.1.2 Categorization of Adverse Events

Safety was evaluated in study GP17-301 by comparing GP2017 and Humira in terms of:

- Vital signs, clinical laboratory variable, electrocardiograms (ECGs), AE monitoring, and incidence and severity of injection site reactions
- Immunogenicity as determined by measuring the rate of ADA formation against GP2017 and Humira
- Long-term safety and immunogenicity of data from subjects continuously treated with GP2018 with those of subjects continuously treated with Humira and from subjects who experienced repeated switches from Week 17 until Week 51

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

A single confirmatory clinical study was completed in subjects with plaque psoriasis. Pharmacokinetic evaluations were done in healthy subjects.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the confirmatory efficacy and safety study GP17-301 in subjects with chronic plaque type psoriasis, GP2017 was administered S.C. by PFS. A total of 27 doses of 40 mg were planned from Randomization/Day 1 to Week 49. Subjects first received a loading

dose of 80 mg (2×40 mg/0.8 mL) on Day 1, which was followed by up to 25 doses of 40 mg/0.8 mL every other week and starting 1 week after the loading dose until Week 49. This is the labeled dosing per Humira USPI for the treatment of moderate to severe plaque psoriasis in adults who are candidates systemic or phototherapy.

In study GP17-301, at initial randomization, 231 subjects were randomized to the GP2017 group and 234 subjects to the Humira group. Duration of mean (\pm standard deviation) exposure (100.1 \pm 19.56 days vs. 98.3 \pm 22.70 days) and subject exposure in years (63.3 years vs. 63.0 years) were similar between the GP2017 and Humira groups during Treatment Period 1.

Considering the “continued groups” (from randomization to Week 51), mean (\pm SD) duration of exposure was similar between the continued GP2017 (256.2 \pm 118.57 days) and continued Humira (253.1 \pm 123.51 days) groups during Randomization to Week 51. Patient exposure in years was similar between the continued groups (continued GP2017: 117.8 years; continued Humira: 118.5 years).

Mean (\pm SD) duration of exposure was similar across the individual groups (Humira to GP2017: 195.6 \pm 53.60 days; continued Humira: 198.0 \pm 59.27 days; GP2017 to Humira: 203.2 \pm 48.69 days; continued GP2017: 197.0 \pm 59.11 days). Due to the 2:1 ratio at re-randomization at Week 17, patient exposure in years was approximately twice as high in the continued groups as in the switched groups (Humira to GP2017: 33.7 years; continued Humira: 68.8 years; GP2017 to Humira: 35.1 years; continued GP2017: 68.0 years).

A total of 466 healthy subjects received a single dose of GP2017.

7.2.2 Routine Clinical Testing

Clinical laboratory testing included all treatment groups: mean band neutrophils (% and absolute), basophils (% and absolute), eosinophils (% and absolute), lymphocytes (% and absolute), monocytes (% and absolute), mean neutrophils (% and absolute), hematocrit, hemoglobin, platelets, red blood cells, and white blood cells.

Clinical chemistry parameters were analyzed for all treatment groups: albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, bilirubin, blood urea nitrogen, calcium, creatinine, gamma glutamyl transferase, glucose, high sensitivity C_{reactive} protein, potassium, phosphate, sodium, total protein, and uric acid.

Reviewer’s comment: Shift tables were provided for the clinical laboratory testing. No clinically relevant changes were found on review. See details in laboratory section.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the initial 17 weeks of the treatment with GP2017. One subject with psoriasis in the continued GP2017 group of study GP17-301 died due to completed suicide on Day 178 (Treatment Period 2); the subject's death was not considered to be related to study treatment.

7.3.2 Nonfatal Serious Adverse Events

Three patients (1.3%) in the GP2017 group and 10 patients (4.3%) in the Humira group experienced severe AEs. For the GP2017 treatment group, two were in the infections and infestations, a subject with abdominal abscess and a subject with staphylococcal infection. The third SAE subject was angina pectoris. In the Humira group, 10 subjects had SAEs with the most common being abdominal pain (1.3%). One subject (0.4%) in the HUMIRA group experienced an SAE of toxic skin eruption during Treatment Period 1, which was reported as a suspected unexpected serious adverse reaction to the competent authorities and independent ethics committees/institutional review boards. The patient discontinued the study because of this SAE.

Most patients in any of the individual groups (Humira to GP2017, continued Humira, GP2017 to Humira, and continued GP2017) reported AEs of mild or moderate severity during Week 17 to Week 51. Overall, the proportions of patients with severe AEs were higher in the Humira to GP2017 and continued Humira groups than in the GP2017 to Humira and continued GP2017 groups. On system organ class and preferred term levels, the proportions of patients reporting severe AEs were $\leq 1.6\%$ in any treatment group.

In study GP17-104, two subjects experienced SAEs: one subject in the GP2017 group with a known history of pollinosis developed an angioedema of moderate severity, which was suspected to be related to study treatment, and one subject in the US-Humira group experienced a severe femoral neck fracture after an accident, which was not suspected to be related to study treatment. Neither SAE led to discontinuation from the study. For one subject in study GP17-102, an acute appendicitis was reported as an SAE, which was not considered to be related to study treatment and led to study discontinuation of the subject.

7.3.3 Dropouts and/or Discontinuations

A total of 465 patients were randomized and received the IMP assigned to them: 231 subjects were randomized to GP2017 and 234 subjects to Humira. Overall, 402 patients (86.5%) completed Treatment Period 1, and 63 subjects (13.5%) discontinued from the study during the study period of randomization to Week 17. The proportions of subjects

who discontinued for any reason were similar between the two treatment groups, and the main reason for discontinuation were subject/guardian decision, protocol deviation, lost to follow-up, adverse event, and lack of efficacy. No subjects died during Treatment Period 1. One subject in the HUMIRA group became pregnant and discontinued from the study.

Table 6: Subject Disposition (Randomization to Week 17) Study GP17-301

	GP 2017 N=231 n (%)	HUMIRA N=234 n (%)
Randomized	231 (100.0)	234 (100.0)
Completed Treatment Period 1	201 (87.0)	201 (85.9)
Discontinued during Treatment Period 1	30 (13.0)	33 (14.0)
Reason for discontinuation		
Subject/guardian decision	15 (6.5)	11 (4.7)
Lost to follow-up	6 (2.6)	4 (1.7)
Lack of efficacy	4 (1.7)	2 (0.9)
Adverse event ^a	3 (1.3)	5 (2.1)
Protocol deviation	2 (0.9)	8 (3.4)
Physician decision	0	2 (0.9)
Pregnancy	0	1 (0.4)
Re-randomized to Treatment Period 2	189 (81.8)	190 (81.2)

^a Recorded as per Treatment period completion

Source: Module 5.3.5.1 Applicant's submission for GP17-301

Eleven subjects (2.4%) overall experienced AEs that led to permanent discontinuation of study treatment. At preferred term level, none of the AEs leading to discontinuation were reported by more than 1 subject in any group, except for psoriasis (verbatim: worsening of psoriasis), which was reported by 2 subjects (0.9%) in the Humira group. Five of the 11 subjects experienced SAEs that led to permanent discontinuation of study treatment. In the GP2017 group, 1 subject experienced severe staphylococcal infection and hypersensitivity. Both events were considered related to study treatment. In the Humira group, 4 subjects experienced SAEs that led to discontinuation of study treatment. These were SAEs of severe cellulitis and severe toxic skin eruption, which were both considered to be related to study treatment, and severe, unrelated SAEs of ectopic pregnancy and prostate cancer. The toxic skin eruption was reported as a suspected unexpected serious adverse reaction.

Table 7: Disposition of Subjects in Treatment Period 2 (Week 17 to Week 35)

	Treatment in Period 1			
	GP2017 N=231		Humira N=234	
Completed Treatment Period 1	201		201	
	Treatment Sequence in Period 2			
	GP2017 to Switch	Continued GP2017	Humira to Switch	Continued Humira
Re-randomized	63	126	63	127
Completed Treatment Period 2	59 (94%)	112 (89%)	57 (90%)	116 (91%)
Discontinued Treatment Period 2	4 (6%)	14 (11%)	6 (10%)	11 (9%)
Subject/guardian decision	1 (2%)	7 (6%)	3 (5%)	1 (1%)
Lack of efficacy	3 (5%)	2 (2%)	2 (3%)	6 (5%)
Lost to follow-up	--	1 (1%)	1 (2%)	--
Adverse event	--	1 (1%)	--	4 (3%)
Death	--	1 (1%)	--	--
No-compliance with study treatment	--	1 (1%)	--	--
Pregnancy	--	1 (1%)	--	--

Source: DDDP Statistics Reviewer

In Treatment Period 2, subjects who achieved at least PASI 50 at Week 16 were re-randomized to continue the initial treatment or switch between treatments at six-week intervals. Approximately 9% of the 379 subjects who were re-randomized at Week 17 discontinued by Week 35. The most common reasons for discontinuation in Treatment Period 2 were subject/guardian decision and lack of efficacy. (See Table 7.)

Table 8: Disposition of Subjects in Extension Period (Week 35 to Week 51)

	Treatment in Period 1			
	GP201 7		Humira N=234	
Completed Treatment Period 1	201		201	
	Treatment Sequence in Extension			
	GP2017 to Switch	Continue d	Humira to	Continue d
Entered Extension Period	56	106	52	109
Completed Extension Period	50 (90%)	100 (94%)	47 (90%)	104 (95%)
Discontinued during Extension	6 (11%)	6 (6%)	5 (10%)	5 (5%)
Subject/guardian decision	2 (4%)	2 (2%)	2 (4%)	2 (2%)
Lack of efficacy	1 (2%)	1 (1%)	1 (2%)	3 (3%)
Lost to follow-up	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Adverse event	1 (2%)	0 (0%)	2 (4%)	0 (0%)

New therapy for study indication	1 (2%)	1 (1%)	0 (0%)	0 (0%)
No-compliance with study treatment	1 (2%)	0 (0%)	0 (0%)	0 (0%)

Source: pg 28 of Summary of Clinical Safety, submitted 10/30/2017

A total of 323 patients entered into the Extension Period, and 301 of these patients (93.2%) completed this study period. The proportions of patients who discontinued for any reason were higher in the switched groups compared with the continued groups, but overall discontinuation rates were low (Table 8). Main reasons for discontinuation were subject/guardian decision, adverse event, lack of efficacy, lost to follow-up, and new therapy for study indication. No patient died during the Extension Period.

During Week 17 to Week 51, 12 patients (3.2%) overall experienced AEs that led to permanent discontinuation of study treatment, and seven of these 12 patients (five in the continued and two in the switched groups) experienced SAEs that led to treatment discontinuation. The proportion of patients reporting AEs leading to discontinuations was similar across the four individual groups (Humira to GP2017, continued Humira, GP2017 to Humira, and continued GP2017). At preferred term level, none of the AEs leading to discontinuation were reported by more than one patient in any group. More specifically, during Week 17 to Week 35 (Treatment Period 2), in the continued GP2017 group, one patient committed suicide on Day 178. The death was not considered to be related to study treatment. In the continued Humira group, four patients experienced SAEs that led to treatment discontinuation during Week 17 to Week 35: one patient, despite negative screening tests, experienced severe SAEs of pulmonary tuberculosis, and abdominal pain; the event of pulmonary tuberculosis was considered to be treatment related; one patient experienced a severe SAE of necrotizing pneumonia, which was considered to be treatment related; and in two patients, treatment was permanently discontinued due to SAEs of severe colon adenocarcinoma and moderate chronic lymphocytic leukemia, respectively, all of which were not considered to be related to study treatment. During Week 35 to Week 51, in the Humira to GP2017 group, one patient developed severe pneumonia, which was considered to be treatment related, and in the GP2017 to Humira group, one patient was diagnosed with prostate cancer, which was reported as a moderate SAE not considered to be related to study treatment.

Four patients in the continued and one patient in the switched groups reported non-serious AEs leading to permanent discontinuation of study treatment. In the continued (GP2017) group, one patient experienced moderate lethargy during Week 17 to Week 35 and another patient moderate anemia during Week 35 to Week 51, respectively. Both events were considered to be treatment related. A third patient in the continued GP2017 group experienced a moderate cellulitis during Week 35 to Week 51, which was not considered to be related to treatment. One patient in the continued Humira group experienced a moderate nasopharyngitis, which was considered to be unrelated to treatment. The patient in the switched group (Humira to GP2017) experienced moderate arthralgia during Week 17 to Week 35, which was considered to be treatment related.

In Study GP17-102, one subject in the GP2017-PFS group discontinued prematurely due to an SAE (appendicitis) not related to IMP. There were no discontinuations due to AE in any of the other three PK studies in healthy subjects. Discontinuations in these studies were due to withdrawal of informed consent, or subjects were lost to follow-up. In study GP17-104, two subjects discontinued from the study: one subject in the GP2017 treatment group was lost to follow-up and one subject in the US-Humira treatment group withdrew informed consent. In study GP17-101, five subjects – three in the GP2017 and two in the EU-Humira treatment group – withdrew informed consent during the study. In study GP17-103, two subjects, both randomized to treatment with GP2017- (b) (4), prematurely discontinued the study: one subject withdrew consent and one subject was lost to follow-up.

7.3.4 Significant Adverse Events

AEs suspected of being related to study drug were reported for 61 patients (13.1%) total during Treatment Period 1. The most commonly affected primary system organ class was general disorders and administration site conditions (reported for 26 patients (5.6%)), including the most commonly affected preferred term injection site erythema (reported for 12 patients (2.6%)). The proportions of patients with AEs suspected of being related to study drug were generally small on system organ class and preferred term levels and similar between treatment groups.

The proportions of patients reporting AEs were similar between the continued GP2017 and Humira groups (103 patients (61.3%) vs. 111 patients (64.9%)). The most commonly affected primary system organ classes were infections and infestations (continued GP2017: 67 patients (39.9%); continued Humira: 62 patients (36.3%)) and gastrointestinal disorders (continued GP2017: 13 patients (7.7%); Humira: 31 patients (18.1%)). At preferred term level, the most commonly reported AEs were nasopharyngitis (continued GP2017: 15 patients (8.9%); continued Humira: 18 patients (10.5%)) and upper respiratory tract infection (continued GP2017: 13 patients (7.7%); continued Humira: 13 patients (7.6%)). The proportions of patients with AEs were similar between the treatment groups for most of the system organ classes and preferred terms.

The overall proportions of patients with AEs considered to be related to study drug were similar between the continued GP2017 and the Humira treatment group. The proportions of patients with SAEs (continued GP2017: 5 patients (3.0%); continued Humira: 15 patients (8.8%)) and SAEs considered to be related to study treatment (continued GP2017: two patients (1.2%); continued Humira: five patients (2.9%)) were low in each group. At the preferred term level, SAEs were reported for not more than one patient per group except for abdominal pain (continued GP2017: 0; continued Humira: two patients (1.2%)). Few patients discontinued the study drug due to AEs (eight patients (4.8%) in the continued GP2017 group and 12 patients (7.0%) in the continued Humira group). At preferred term level, there was no pattern of AEs leading to discontinuation observed in any treatment group.

The proportions of patients with ISRs were low in the two treatment groups (nine patients (5.4%) in the continued GP2017 group and 11 patients (6.4%) in the continued Humira group). All ISRs were mild, and no ISR was reported as serious.

The proportions of patients reporting AEs were similar among the individual groups during Week 17 to Week 51 (Humira to GP2017: 29 patients (46.0%); continued Humira: 71 patients (55.9%); GP2017 to Humira: 36 patients (57.1%); continued GP2017: 66 patients (52.4%)). The most commonly affected primary system organ classes were infections and infestations (Humira to GP2017: 17 patients (27.0%); continued Humira: 34 patients (26.8%); GP2017 to Humira: 21 patients (33.3%); continued GP2017: 39 patients (31.0%)) and musculoskeletal pain and connective tissue disorders (Humira to GP2017: five patients (7.9%), continued Humira: 11 patients (8.7%), GP2017 to Humira: eight patients (12.7%), continued GP2017: 12 patients (9.5%)). At preferred term level, the most commonly reported AEs were nasopharyngitis (Humira to GP2017: two patients (3.2%); continued Humira: eight patients (6.3%); GP2017 to Humira: six patients (9.5%); continued GP2017: nine patients (7.1%)) and upper respiratory tract infection (Humira to GP2017: four patients (6.3%); continued Humira: six patients (4.7%); GP2017 to Humira: 0 patients; continued GP2017: six patients (4.8%)). The proportions of patients with AEs were similar among the treatment groups for most of the system organ classes and preferred terms.

The overall proportions of patients with AEs considered to be related to study drug were similar among the individual groups. The overall proportions of patients with SAEs (Humira to GP2017: four patients (6.3%); continued Humira: eight patients (6.3%); GP2017 to Humira: two patients (3.2%); continued GP2017: three patients (2.4%)) and SAEs considered to be related to study treatment (Humira to GP2017: two patients (3.2%); continued Humira: three patients (2.4%); GP2017 to Humira: 0 patients; continued GP2017: one patient (0.8%)) were low in any of the groups during Week 17 to Week 51. At preferred term level, none of the SAEs was reported for more than one patient per group. During Week 17 to Week 51, few patients discontinued the study drug due to AEs (Humira to GP2017: two patients (3.2%); continued Humira: five patients (3.9%); GP2017 to Humira: one patient (1.6%); continued GP2017: four patients (3.2%)). At preferred term level, there was no pattern of AEs leading to discontinuation observed in any treatment group.

The proportions of patients with ISRs were low (Humira to GP2017: two patients (3.2%); continued Humira: five patients (3.9%); GP2017 to Humira: three patients (4.8%); continued GP2017: four patients (3.2%)). Most ISRs were mild or moderate; one patient (1.6%) in the GP2017 to Humira group experienced severe injection site pain during Week 35 to Week 51. No ISR was reported as serious.

The proportions of patients with at least one positive ADA response from Week 1 onwards were lower and similar in the continued GP2017 group (35.8%) and in the Humira to GP2017 group (39.3%) as compared to the other two groups, continued

Humira (45.1%) and GP2017 to Humira (46.7%). Most of the ADA positive patients also tested positive for NAb (Humira to GP2017: 100.0%; continued Humira: 85.5%; GP2017 to Humira: 75.0%; continued GP2017: 86.4%).

Finally, results from the pooled continued and pooled switched groups were in accordance with those from the individual continued groups (continued GP2017 and continued Humira) and the switched groups (Humira to GP2017 and GP2017 to Humira). Overall, safety was considered similar between the pooled continued and the pooled switched groups and no safety concerns arose during Week 17 to Week 51.

In the pooled analysis of PK studies GP17-101, GP17-104, GP17-102 and GP17-103 in healthy subjects, the nature of AEs was similar between the GP2017 groups and the Humira groups. The most commonly affected primary system organ classes were infections and infestations, nervous system disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, and respiratory, thoracic and mediastinal disorders with frequencies >10% in any group. Infections and infestations were reported for lower proportions of subjects in the GP2017 group as compared to the Humira group. The most commonly affected preferred terms were nasopharyngitis and headache with frequencies >10% in each group. Nasopharyngitis was reported for a lower proportion of subjects in the GP2017 group as compared to the Humira group. There were no anaphylactic reactions in any of the PK studies in healthy subjects.

7.3.5 Submission Specific Primary Safety Concerns

AEs of special interest were defined based on the HUMIRA USPI and the HUMIRA SmPC and included infestations, malignancies, allergic reactions, immune system disorders/autoimmune events, neurological events, hematological reactions, and congestive heart failure.

Overall, AEs of special interest were reported for 30 subjects (6.5%) during Randomization to Week 17. The proportions of subjects with AEs of special interest were similar between treatment groups (GP2017: 13 patients (5.6%); Humira: 17 subjects (7.3%)). The most commonly affected primary system organ class was infections and infestations (reported for 15 subjects (3.2%)). At preferred term level, except for basal cell carcinoma (GP2017: 3 subjects (1.3%); Humira: 2 subjects (0.9%)), AEs of special interest were reported by 2 subjects or less in any treatment group. One subject (0.4%) in the GP2017 group experienced a severe hypersensitivity, which was considered related to study treatment and led to permanent treatment discontinuation.

There was no concerning pattern of AEs of special interest beyond Week 17.

Table 9: AEs of Special Interest by SOC and PT by Treatment Group (Randomization to Week 17)

System organ class	GP2017	Humira
Preferred term	N=231	N=234
	n (%)	n (%)
Number of patients with at least one AE of special interest	13 (5.6)	17 (7.3)
Infections and infestations	6 (2.6)	9 (3.8)
Oral herpes	2 (0.9)	0 (0.0)
Vulvovaginal mycotic infection	1 (0.4)	2 (0.9)
Ophthalmic herpes zoster	1 (0.4)	0 (0.0)
Tinea cruris	1 (0.4)	0 (0.0)
Tinea versicolour	1 (0.4)	0 (0.0)
Oral candidiasis	0 (0.0)	2 (0.9)
Tinea pedis	0 (0.0)	2 (0.9)
Fungal infection	0 (0.0)	1 (0.4)
Herpes zoster	0 (0.0)	1 (0.4)
Varicella	0 (0.0)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.7)	5 (2.1)
Basal cell carcinoma	3 (1.3)	2 (0.9)
Fibrous histiocytoma	1 (0.4)	0 (0.0)
Skin papilloma	1 (0.4)	0 (0.0)
Dysplastic naevus	0 (0.0)	1 (0.4)
Prostate cancer	0 (0.0)	1 (0.4)
Seborrhoeic keratosis	0 (0.0)	1 (0.4)
Blood and lymphatic system disorders	1 (0.4)	3 (1.3)
Thrombocytopenia	1 (0.4)	2 (0.9)
Neutropenia	0 (0.0)	1 (0.4)
Immune system disorders	2 (0.9)	0 (0.0)
Drug hypersensitivity	1 (0.4)	0 (0.0)
Hypersensitivity	1 (0.4)	0 (0.0)

System organ classes and preferred terms are sorted by decreasing frequency in the GP2017 treatment group.

Percentages are based on the number of patients within the treatment group in the SAF (N). Patients experiencing multiple events within the same preferred term and/or system organ class are counted only once under those categories.

AE=adverse event; SAF=safety analysis set

Source: Table 12-21, page 276, Clinical Study Report

Table 10: AEs of Special Interest by SOC and PT by Individual Group--Week 17 to Week 51 (TP2+EP SAF)

System organ class	Humira to GP2017	Continued Humira	GP2017 to Humira	Continued GP2017
Preferred term	N=63	N=127	N=63	N=126
	n (%)	n (%)	n (%)	n (%)
Number of patients with at least one AE of special interest	3 (4.8)	12 (9.4)	6 (9.5)	7 (5.6)
Infections and infestations	1 (1.6)	6 (4.7)	2 (3.2)	4 (3.2)
Vulvovaginal mycotic infection	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes zoster	0 (0.0)	0 (0.0)	1 (1.6)	2 (1.6)
Tinea versicolour	0 (0.0)	1 (0.8)	1 (1.6)	1 (0.8)
Oral herpes	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)
Oral candidiasis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Pulmonary tuberculosis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Tinea infection	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	1 (1.6)	2 (1.6)	2 (3.2)	3 (2.4)
Neutropenia	1 (1.6)	1 (0.8)	0 (0.0)	1 (0.8)
Anaemia	0 (0.0)	0 (0.0)	1 (1.6)	2 (1.6)
Thrombocytopenia	0 (0.0)	1 (0.8)	2 (3.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.2)	3 (2.4)	2 (3.2)	0 (0.0)
Seborrheic keratosis	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Skin papilloma	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Adenocarcinoma of colon	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Chronic lymphocytic leukaemia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Haemangioma	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Melanocytic naevus	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Prostate cancer	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Immune system disorders	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Hypersensitivity	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)

System organ classes and preferred terms are sorted by decreasing frequency in the Humira to GP2017 group. The continued groups include patients who continued the same treatment throughout the study; the switched groups include patients who switched treatment between GP2017 and Humira during Treatment Period 2.

Percentages are based on the number of patients within the treatment group in the TP2+EP SAF (N). Patients experiencing multiple events within the same preferred term and/or system organ class are counted only once under those categories.

AE=adverse event; TP2+EP SAF=safety analysis set Treatment Period 2 and Extension Period

Source: Table 12-23, page 278, Clinical Study Report

Injection site reactions

The proportions of patients with injection site reactions were low and similar between the treatment groups. Overall, 23 subjects (4.9%) reported injection site reactions (GP2017: 15 subjects (6.5%); Humira: eight subjects (3.4%)) during Randomization to Week 17. Injection site erythema was more frequently reported in the GP2017 group with nine subjects (3.9%) compared to the Humira group with three subjects (1.3%).

All injection site reactions were mild or moderate, and no injection site reaction was reported as serious.

The proportions of patients with injection site reactions were low and similar between the individual groups (Humira to GP2017: two patients (3.2%); continued Humira: five patients (3.9%); GP2017 to Humira: three patients (4.8%); and continued GP2017: four patients (3.2%)) during Week 17 to Week 51. At preferred term level, as the most commonly affected AE, injection site erythema was reported by 0 patients in the Humira to GP2017 group; two patients (1.6%) in the continued Humira group; two patients (3.2%) in the GP2017 to Humira group; and four patients (3.2%) in the continued GP2017 group. Most injection site reactions were mild or moderate, and no injection site reaction was reported as serious. One patient in the GP2017 to Humira group experienced severe injection site pain on Day 274 (Extension Period) after having received GP2017.

In the healthy subject studies, two subjects overall (one in study GP17 -101 and the other in study GP17-102) reported moderate reactions, one of which was reported as a moderate AE (injection site erythema) for a subject in the EU-Humira group of study GP17-101. Overall, AEs related to injection site reactions were reported only for few subjects across the four studies and encompassed injection site hypersensitivity, pruritus, bruising, erythema, swelling, pain, and injection site discomfort.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events in Treatment Period 1 (Randomization to Week 17) revealed no clinically relevant differences between GP2017 and Humira groups with respect to the proportions of subjects reporting AEs. Overall, 239 subjects (51.4%) reported a total of 541 AEs. The most commonly affected primary system organ class was infections and infestations (23.9%).

Table 11: Adverse Events by SOC and PT (in at least 3%) in Study GP17-301 Randomization to Week 17

System organ class Preferred term	GP 2017 N=231 n (%)	HUMIRA N=234 n (%)
Number of subjects with at least one AE	116 (50.2)	123 (52.6)
Infections and Infestations	55 (23.8)	56 (23.9)
Nasopharyngitis	13 (5.6)	15 (6.4)
Upper respiratory tract infection	11 (4.8)	9 (3.8)
Sinusitis	8 (3.5)	7 (3.0)
General disorder and admin site conditions	23 (10.0)	15 (6.4)
Injections site erythema	9 (3.9)	3 (1.3)
Musculoskeletal and connective tissue disorders	22 (9.5)	15 (6.4)
Nervous system disorders	19 (8.2)	14 (6.0)
Headache	11 (4.8)	8 (3.4)
Respiratory, thoracic, and mediastinal disorders	15 (6.5)	15 (6.4)
Gastrointestinal disorders	14 (6.1)	27 (11.5)
Diarrhea	2 (0.9)	9 (3.8)
Skin and subcutaneous tissue disorders	12 (5.2)	15 (6.4)
Injury, poisoning and procedural complications	9 (3.9)	8 (3.4)
Investigations	8 (3.5)	9 (3.8)
Metabolism and nutritional disorders	5 (2.2)	7 (3.0)
Vascular disorders	2 (0.9)	7 (3.0)

System organ classes and preferred terms are sorted by decreasing frequency in the GP2017 group.

Percentages are based on the number of subjects within the treatment group in the SAF (N).

Subjects experiencing multiple events within the same preferred term and/or system organ class are counted only once under those categories.

AE=adverse event; n=number of patients in the sub-category; N=number of randomized patients per group;

SAF=safety analysis set

Source: [Module 5.3.5.1 GP17-301-Table 12-10]

According to the Humira USPI, the most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with Humira developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. In addition, the rate of serious infections was 4.3 per 100 patient-years in 7973 Humira-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients in all indications. The serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis.

The proportions of patients in the four individual groups (Humira to GP2017, continued Humira, GP2017 to Humira, and continued GP2017) who experienced AEs suspected to

be related to study drug during Week 17 to Week 51 were <6.5% at system organ class level and <3.5% at preferred term level and similar among treatment groups (Table 12).

Table 12: Adverse Events Suspected Related to Study Drug by SOC and PT (at least 2% of patients in any treatment group) by Individual Group--Study GP17-301 Week 17 to Week %1 (TP2+EP SAF)

System organ class Preferred term	Humira to GP2017 N=63 n (%)	Continued Humira N=127 n (%)	GP2017 to Humira N=63 n (%)	Continued GP2017 N=126 n (%)
Number of patients with at least one AE considered to be related to study drug	10 (15.9)	16 (12.6)	9 (14.3)	16 (12.7)
Infections and infestations	4 (6.3)	5 (3.9)	3 (4.8)	8 (6.3)
Upper respiratory tract infection	2 (3.2)	1 (0.8)	0 (0.0)	0 (0.0)
Sinusitis	1 (1.6)	0 (0.0)	0 (0.0)	3 (2.4)
General disorders and administration site conditions	3 (4.8)	6 (4.7)	3 (4.8)	4 (3.2)
Injection site erythema	0 (0.0)	2 (1.6)	2 (3.2)	4 (3.2)
Investigations	0 (0.0)	3 (2.4)	1 (1.6)	0 (0.0)

System organ classes and preferred terms are sorted by decreasing frequency in the Humira to GP2017 group. The continued groups include patients who continued the same treatment throughout the study; the switched treatment groups include patients who switched treatment between GP2017 and Humira during Treatment Period 2.

Percentages are based on the number of patients within the treatment group in the TP2+EP SAF (N). Patients experiencing multiple events within the same preferred term and/or system organ class are counted only once under those categories.

AE=adverse event; n=number of patients in the sub-category; N=number of randomized patients per group; TP2+EP SAF=safety analysis set Treatment Period 2 and Extension Period

Source: Table 2-19, page 59, Summary of Clinical Safety

Reviewer's comment: *The safety database from GP17-301 does not reveal any new adverse events that are not present in the US-licensed Humira USPI.*

Safety profiles and immunogenicity were generally similar among patients treated with GP2017 and Humira and patients undergoing multiple treatment switches. No clinically relevant differences between patients continuously treated with GP2017 and patients continuously treated with Humira and between patients continuously treated with GP2017 or Humira and patients who repeatedly switched treatments were observed in terms of long-term safety and immunogenicity.

7.4.2 Laboratory Findings

Hematology

In study GP17-301, no clinically relevant changes over time or differences between treatment groups were observed for hematology parameters (including erythrocytes, platelets, white blood cells and neutrophils). Across treatment periods, the proportions of patients with newly occurring clinically notable values of hematology parameters were low and there were no clinically relevant differences among groups.

One subject in the Humira group experienced a severe neutropenia on Day 120 (Treatment Period 1), which was not considered to be related to study treatment and led to temporary interruption of study treatment

Chemistry

No clinically relevant changes over time or differences between treatment groups were observed for clinical chemistry parameters (including liver function tests and creatinine) in study GP17-301. Across treatment periods, the proportions of patients with newly occurring clinically notable values of clinical chemistry parameters were low and there were no relevant differences among groups.

In healthy subjects, there were no clinically important trends or changes observed in hematology, clinical chemistry, coagulation and urinalysis from baseline. No clinically meaningful differences were observed among the treatment groups in the four studies.

7.4.3 Vital Signs

No clinically significant changes in the vital signs were observed in the confirmatory efficacy and safety study GP17-301.

In studies GP17-101 and GP17-103 in healthy subjects, no clinically relevant changes were observed in any of the vital signs variables. In study GP17-104, three subjects overall reported AEs related to vital signs findings. These were events of increased diastolic blood pressure and increased heart rate in the GP2017 group and an event of increased heart rate in the US-Humira group.

In study GP17-102, one subject in the GP2017-AI group showed high body temperature on Day 4 related to an AE of upper respiratory tract infection, which returned to normal on Day 6.

7.4.4 Electrocardiograms (ECGs)

In the confirmatory efficacy and safety study GP17-301, 3 subjects were reported with newly identified clinically significant abnormal ECG findings. One subject in the GP2017 group, with an ongoing medical history of peripheral venous disease, had a new clinically significant abnormal ECG at Randomization, but neither at screening nor at any later study time point. The new clinically significant abnormal ECG was reported as a non-serious, unrelated AE. The second patient, randomized to the continued GP2017

group, had new clinically significant abnormal ECG findings at Week 35 and about 2.5 months later, and a moderate, not related AE of atrial fibrillation was reported for this subject during that time. For the subject, ongoing coronary artery disease and hypertension were reported. The third subject was randomized to the continued HUMIRA group and had a new clinically significant abnormal ECG on Day 217 and reported various not related AEs including a severe, not related SAE of chest pain during that time; ongoing hypertension was reported for the subject.

In PK studies GP17-101, GP17-104, GP17-102, and GP17-103 in healthy subjects, no changes or trends of clinical significance were seen for the heart rate, PR-interval, QRS duration, QTinterval or QTcF-interval. All ECG evaluations were recorded as normal or as not clinically significant abnormal.

7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

In studies GP17-101, GP17-104, GP17-102, GP17-103, and GP17-301, immunogenicity of adalimumab was investigated in terms of ADA formation by using validated immunoassays. In the plaque psoriasis clinical study, positive ADA results were seen from Day 16 until Day 72 with the highest incidence seen on day 72.

Validated, highly sensitive and drug-tolerant immunogenicity assays for detection of binding and neutralizing anti-adalimumab antibodies were established for determination of ADA responses against GP2017 and Humira. Assays used in the clinical studies with GP2017 were different from the assays used in the Humira development, and therefore direct comparison of the results is not feasible. Overall, binding ADAs were reported for 57.9-75% in healthy subjects; up to 64.4% of healthy subjects developed neutralizing antibodies (NABs). In patients with psoriasis, 34-45% developed ADAs, and NABs were detected in up to 100% of patients with ADAs. Generally, the rates of binding ADA and/or Nab development were similar between GP2017 and Humira (Table 12 and Table 13). The Humira USPI state that there is no correlation between ADA development and AEs. In the literature, however, thromboembolic events or hypersensitivity to adalimumab were described to be associated with ADA. None of the AEs or SAEs reported in any of the five studies was indicative of an adverse effect of ADAs or NABs, e.g., no thromboembolic event or anaphylactic reactions to adalimumab was observed in ADA-positive subjects or patients in any of the studies. Furthermore, the AE profile of ADA-positive patients was similar to that of ADA-negative patients in study GP17-301.

To conclude, the overall results of the five studies showed similar safety profiles and similar immunogenicity for healthy subjects and for patients treated with GP2017 and Humira (US-Humira and EU-Humira) and also for patients undergoing repeated treatment switches.

Table 13: Anti-Drug Antibody Response in TP1 and TP2, Study GP17-301

Treatment Period	GP2017			Humira N=234		
	Positive	Negative	Missing	Positive	Negative	Missing
Baseline	3	221	7	3	222	9
Week 3	41	173	17	32	179	23
Week 7	26	181	24	20	186	28
Week 11	45	159	17	38	158	38
Week 17	48	139	44	43	139	52
TP2 + EP SAF	Continued Original Treatment			Switched Treatments		
	Cont GP2017 N=126		Cont Humira N=127	Humira to GP2017		GP2017 to Humira N=63
	Pos	Neg	Miss	Pos	Neg	Mis
Week 17	23	95	8	26	92	9
Week 51	16	80	30	19	80	29
	Pos	Neg	Miss	Pos	Neg	Miss
Week 17	12	45	6	17	42	4
Week 51	15	30	18	13	33	17

Continued GP2017: GP2017 continued from Period 1

Continued Humira: Humira continued from Period 2

Switched GP2017: Switched to treatment sequence Humira>GP2017>Humira in Period 2

Switched Humira: Switched to treatment sequence GP2017>Humira>GP2017 in Period 2

Pos=Positive, Neg = Negative, Miss=Missing

Source: FDA analysis of data from Section 4.3.2, Summary of Clinical Safety

Table 14: Immunogenicity in GP2017 Development Program

Visit		GP2017 ¹ N=466 n (%)	Humira ² N=357 n (%)
ADA	Day 1, pre-dose	7 (1.5)	9 (2.5)
	Day 16	137 (29.4)	104 (29.1)
	Day 30	107 (23.0)	69 (19.3)
	Day 44	125 (26.8)	95 (26.6)
	Day 72	284 (60.9)	233 (65.3)
Total (# of subjects with at least one positive result)		310 (66.5)	252 (70.6)
NAb	Total (# of subjects with a positive result) ³	275 (59.0)	217 (60.8)

ADA=anti-drug antibody; n=number of positive results; N=number of randomized subjects per treatment group; NAb=neutralizing antibody

¹ Includes GP2017 groups from studies GP17-104, GP17-101, GP17-102, and GP17-103.

² Includes US-Humira and EU-Humira groups from studies GP17-104 and GP17-101.

³ NAb was only analyzed for the last confirmed positive ADA sample that was collected per subject.

Source: Module 5.3.5.3 Statistical Overview—Table 14.1-4

During Treatment Period 1 (randomization to Week 17) in Study GP17-301, the numbers and proportions of patients with positive ADA responses were similar between the GP2017 and Humira groups at the individual visits, and the numbers and proportions of patients with at least one positive ADA response from Week 1 and up to Week 17 were also similar between treatment groups; NABs were detected in similar proportions between groups.

The nature of AEs reported for ADA-positive patients was similar to that reported for ADA-negative patients; therefore, ADA development is not considered to have an impact on patients' safety in this study.

At Week 17 (re-randomization), the proportions of ADA positive patients were similar in all groups, except for the GP2017 to Humira group, into which more ADA-positive patients were randomized. The proportions of patients with positive ADA responses were lowest in the continued GP2017 group. At the individual time points between Week 17 and 51, the proportions of ADA positive patients were higher in the switched groups than in the continued groups. However, patient numbers in the switched groups with evaluable data were smaller, and even minor changes in the numbers of ADA-positive patients resulted in greater changes in percentages. With respect to overall ADA response, proportions of positive ADA patients from Week 1 and up to Week 51 were lower and similar in the continued GP2017 and Humira to GP2017 groups than in the other two groups, continued Humira and GP2017 to Humira. The majority of ADAs was neutralizing. The proportion of patients with at least one sample that was positive for NABs from Week 1 was higher in the Humira to GP2017 group than in the other three groups.

In healthy subject studies GP17-101, GP17-104, GP17-102, and GP17-103, 57.9% to 75% of subjects developed binding ADAs to adalimumab, and neutralizing antibodies were detected in 51% to 64.4% of treated subjects. The numbers and proportions of ADA-positive subjects were similar between treatment groups in the pooled analysis.

None of the AEs or serious AEs reported in any of the five studies was indicative of an adverse effect of ADAs or NABs, e.g., no thromboembolic event or hypersensitivity to adalimumab was observed in any of the studies. Furthermore, the AE profile of ADA-positive patients was similar to that of ADA-negative patients.

7.5 Conclusions and Recommendations

From a clinical standpoint, the clinical pharmacology, efficacy, safety, and immunogenicity data submitted to this 351(k) BLA from the clinical development program of GP2017, support the demonstration of no clinically meaningful difference between GP2017 and US-licensed Humira in the indication studied, i.e., plaque psoriasis.

There were similar safety and immunogenicity between GP2107 and Humira based on comparisons between GP2017 with US-licensed Humira and EU-approved Humira in 823 healthy subjects and in 465 patients with moderate to severe chronic plaque-type psoriasis. Overall, there were no clinically meaningful differences in safety profiles between GP2017, US-licensed Humira, and EU-approved Humira. The rates of binding ADA and/or neutralizing antibodies (NAbs) were similar between GP2017, US-licensed Humira, and EU-approved Humira. The impact of ADA and NAb development on PK, efficacy, and safety was similar across groups. Thus, with regard to the safety profile associated with ADA development, the impact on the overall clinical benefit-risk of GP2017 is considered to be highly similar to that of Humira.

The Applicant has provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use and licensure of GP2017 for each of the indications for which US-licensed Humira is currently licensed and for which Sandoz is seeking licensure for GP2017.

8 Advisory Committee Meeting

No advisory committee was held for this biosimilar application as it was determined that there were no issues where the Agency needed input from the committee.

9 Labeling Recommendations

- Proprietary name

The proposed proprietary name for GP2017 is conditionally approved as Hyrimoz. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the name was acceptable.

- Non-proprietary/Proper name

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for GP2017 is necessary to distinguish this proposed product from US-licensed Humira (adalimumab) and other approved adalimumab products. The applicant proposed suffix, 'adaz' was found to be conditionally acceptable by the Agency.

- Physician Labeling

At the time of this review, labeling discussions are ongoing.

10 Risk Evaluation and Mitigation Strategies (REMS)

GP2017 is a proposed biosimilar to US-licensed Humira. There were no new safety signals identified in the comparative clinical study and PK studies to date. The safety profile is anticipated to be the same as US-licensed Humira. Accordingly, at this time, a Medication Guide for patients, which is included in the proposed GP2017 labeling, is appropriate, should GP2017 be approved as a biosimilar.

12 Postmarketing Requirements and Commitments

The current GP2017 presentations are not designed to allow for accurate administration of doses less than 40 mg, which impacts children with JIA who weigh less than 30 kg and children with CD who weigh less than 40 kg. For accurate weight-based dosing, an age-appropriate presentation is required under PREA. Therefore, we recommend a PREA PMR for the development of a presentation that can be used to accurately administer GP2017 to pediatric patients with JIA who weigh less than 30 kg and pediatric patients with CD who weigh less than 40 kg. Also, under PREA, Sandoz is

required to submit a pediatric assessment for patients with JIA 2 to <4 years of age, patients with CD 6 to 17 years of age, patients with UC 5 to 17 years of age.

A full waiver should be granted for pediatric studies in patients with plaque psoriasis based on the rationale that the product fails to represent a meaningful therapeutic benefit⁵ over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients, as described below:

- GP2017, a TNF-alpha inhibitor, does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients. Another TNF-alpha inhibitor is an approved product for the treatment of pediatric patients 4 years and older with moderate to severe plaque psoriasis. In addition, as a class, TNF-alpha inhibitors are generally not currently the most recommended approved therapies for the treatment of patients with moderate to severe psoriasis; more narrowly-targeted agents are recommended as first-line therapeutic options for children with psoriasis who are in need of treatment with a systemic agent. Based on the above considerations, DDDP has concluded, and DPMH agreed, that GP2017 would not provide for the meaningful therapeutic benefit over these existing therapies for pediatric patients.
- GP2017 is not likely to be used in a substantial number of pediatric patients because, based on DDDP's evaluation of use data, TNF-alpha inhibitors were used to treat psoriasis in only a very limited number of pediatric patients ((b)(4) % share of total use of all TNFs). For adalimumab, the reported number of uses was even lower (approximately (b)(4)).⁶

⁵ See section 505B(c) of the FD&C Act.

⁶ Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Jan 2009 - Jun 2015. Extracted September 2015

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/s/

MARK BORIGINI
10/29/2018

GARY T CHIANG
10/29/2018

DAVID L KETTL
10/30/2018

NIKOLAY P NIKOLOV
10/30/2018

Clinical Investigator Financial Disclosure
Review

Application Number: 761071

Submission Date(s): October 30, 2017

Applicant: Sandoz

Product: adalimumab (biosimilar to Humira)

Reviewer: Mark Borigini

Date of Review: July 03, 2018

Covered Clinical Study: GP17-101, GP17-102, GP17-103, GP17-104, and GP17-301

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/> X	No (Request list from applicant)
Total number of investigators identified: <u>383</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes	No (Request explanation from applicant)

Reviewer comments:

The applicant has adequately disclosed financial interests and/or arrangements with clinical investigators by having submitted a signed form 3454 and financial disclosure summary.

The applicant certifies that the covered studies are not funded by variable compensations and none of the investigators in the study hold any form of property interest in the product. Sandoz has examined its financial data regarding significant payments of other sorts made to all investigators who participated in the study and equity information as provided by those investigators, as defined in 21 CFR 54.2.

Certification:

Per US FDA Form 3454, certification is provided for 383 investigators involved in studies: GP17-101 (16 Is), GP17-102 (15 Is), GP17-103 (9 Is), GP17-104 (25 Is), and GP17-301 (318 Is) as listed in the study report, indicating:

- Certified investigators. A total 383 investigators involved in the aforementioned studies are certified as having no Financial Arrangements as defined in 21 CFR 54.4.
- No due diligence activities were required for this covered study.

Note that all investigators are assessed for equity, significant payments of other sorts, variable compensation, and propriety interest. Significant payments of other sorts and other financial arrangements are checked via internal Sandoz procedures.

Disclosure: n/a

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/s/

MARK BORIGINI
10/30/2018

NIKOLAY P NIKOLOV
10/30/2018

Medical Officer Review
Division of Gastroenterology and Inborn Errors Products of BLA 761071

Application Type:	351(k) BLA 761,071
Drug:	GP2017 ¹ (Hyrimoz; adalimumab-adaz, a proposed biosimilar to US licensed Humira (adalimumab))
Applicant:	Sandoz Inc.
Route of Administration:	Injection for Subcutaneous use
Pharmacologic Class:	TNF- α antagonist
Submission Date:	October 30, 2017
BSUFA Date:	October 30, 2018
DGIEP Clinical Reviewer / Team Leader:	Anil Rajpal, MD, MPH
DGIEP Associate Director:	Jessica Lee, MD, MMSc

Proposed Indications

Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.

Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.

Adult Crohn's Disease (adult CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-

¹ In this document, I generally refer to Sandoz' proposed product by the Sandoz descriptor "GP2017" which was the name used to refer to this product during development. The proposed proprietary name (Hyrimoz) and the proposed nonproprietary name (adalimumab-adaz) are only conditionally accepted for this product until the application is approved.

MP). The effectiveness of Hyrimoz has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis (PsO): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

Executive Summary

The Division of Gastroenterology and Inborn Errors Products concludes that the Applicant provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (plaque psoriasis), to support licensure of GP2017 as a biosimilar, under section 351(k) of the PHS Act, for the inflammatory bowel disease indications (ulcerative colitis and adult Crohn's disease²).

Introduction

On October 30, 2017, Sandoz Inc. submitted a biologics license application (BLA) under section 351(k) of the Public Health Service (PHS) Act for GP2017, a proposed biosimilar to US-licensed Humira (adalimumab). Humira received marketing approval in the US on December 31, 2002.

In support of the current BLA, the Applicant provided clinical study data collected from healthy subjects and patients with plaque psoriasis (PsO). The Applicant submitted two PK similarity studies (GP17-101 and GP17-104) assessing 3-way PK similarity between GP2017, EU-approved Humira, and US-licensed Humira (based on pairwise comparisons of GP2017 to US-licensed Humira, GP2017 to EU-approved Humira, and US-licensed Humira to EU-approved Humira) in healthy subjects. In addition, the Applicant submitted the results of one comparative clinical study (GP17-301) using GP2017 and US-licensed Humira in patients with moderate to severe plaque psoriasis (PsO). Supportive PK, safety, and immunogenicity data were also provided from Study GP17-102 (a single dose study comparing GP2017 administered by an auto-injector vs. a pre-filled syringe), and Study GP17-103 (a single dose study comparing GP2017 formulations from two different drug substance production sites). See Table 1 below.

The inflammatory bowel disease (IBD) indications were not directly studied in the GP2017 clinical program. For additional information on the clinical study in PsO, please refer to the collaborative review from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP) and the Cross-Discipline Team Leader (CDTL) review.

² The Applicant did not provide a scientific justification for extrapolation for pediatric Crohn's disease and is not requesting licensure for this indication; US-licensed Humira has unexpired orphan drug exclusivity for this indication.

Table 1. Overview of GP2017 Clinical Program

Study ID	Design	Objective	Subjects	Dose	Treatments
Pivotal Clinical Pharmacology Studies					
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)
Comparative Clinical Study					
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)
Supportive Clinical Pharmacology Studies					
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)

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

Extrapolation of Existing Data to Support Biosimilarity to IBD Indications

The Applicant conducted a comparative clinical study with their product in patients with PsO, and seeks licensure for the RA, JIA (in patients 4 years of age and older), PsA, AS, adult CD, and UC indications as approved for US-licensed Humira.

FDA has issued Guidance³ stating that:

If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may

³ FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015 (Biosimilars Q&A Guidance), available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf>

seek licensure for one or more additional conditions of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

The scientific justification for extrapolation should address the following issues that are described in the FDA Biosimilars Q&A Guidance:⁴

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought;
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations;
- The immunogenicity of the product in different patient populations;
- Differences in expected toxicities in each condition of use and patient population; and
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

All of these factors were adequately addressed by the Applicant, as summarized below, for the IBD indications. Therefore, the totality of the evidence provides support for licensure of GP2017 for the IBD indications (ulcerative colitis and adult Crohn's disease) under section 351(k) of the PHS Act. It should be noted that the Applicant did not provide a scientific justification for extrapolation for pediatric Crohn's disease and is not requesting licensure for this indication; US-licensed Humira has unexpired orphan drug exclusivity for this indication.

Mechanism of Action

The mechanisms of action of adalimumab that are relevant for PsO (the comparative clinical study population) are also relevant to IBD. The Applicant provided data to support that GP2017 has the same known and potential mechanisms of action as US-licensed Humira, which support extrapolation to these other indications.

The primary mechanism of action of adalimumab is direct binding of TNF- α , resulting in blockade of TNF- α receptor-mediated activities. Adalimumab blocks both TNFR1 and TNFR2 receptors by binding both soluble(s) and transmembrane(tm) TNF- α . In addition, adalimumab has mechanisms of action involving the Fc region of the antibody which are thought to be plausible mechanisms involved in the efficacy of adalimumab for the treatment of IBD. See a list of known and potential mechanisms of adalimumab related to its efficacy in the treatment of IBD (Table 2, below). Similar to the directly studied indication (PsO), TNF- α plays a central role in the pathology experienced by patients

⁴ FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf>

with IBD. TNF- α inhibition plays an important role in treating these diseases as evidenced by the efficacy of the TNF- α inhibitor class of medications in treating IBD.

Table 2. Known and Potential Mechanisms of Action of Humira

MOA of Humira	RA	AS	PsA	PsO	CD	UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via Fc γ R11a binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF						

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors^{5,6,7}

The Product Quality reviewers have concluded that the Applicant has adequately addressed each of the known mechanisms of action of US-licensed Humira, and has also addressed potential mechanisms of action. Specifically, the Applicant provided data to demonstrate that s/tm TNF- α binding, blocking of TNFR1 and TNFR2 activity, and the potential Fc region-mediated mechanisms of action are similar between GP2017 and US-licensed Humira. These data support the conclusion that GP2017 and US-licensed Humira utilize the same mechanism or mechanisms of action, to the extent such mechanism or mechanisms of action are known for US-licensed Humira.

Pharmacokinetics (PK)

Studies GP17-101 and GP17-104 were single-dose, comparative PK, and safety studies of GP2017, US-licensed Humira, and EU-approved Humira conducted in healthy subjects planned to demonstrate 3-way PK similarity of the commercial formulation of GP2017, US-licensed and EU-approved Humira. It should be noted that establishment of a scientific bridge to US-licensed Humira was necessary to justify the relevance of nonclinical and clinical data generated using EU-approved Humira in the GP2017 developmental program to a demonstration of biosimilarity to US-licensed Humira.

⁵ Oikonomopoulos A et al., Current Drug Targets, 2013, 14, 1421-1432.

⁶ Tracey D et al., Pharmacology & Therapeutics 117 (2008) 244-279.

⁷ Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

In addition, the single comparative efficacy study, Study GP17-301, collected PK information, including an immunogenicity assessment.

The clinical pharmacology reviewers concluded that the results of Studies GP17-101 and GP17-104 established 3-way PK similarity between GP2017, US-licensed Humira and EU-approved Humira in healthy subjects. The publicly available data submitted by the Applicant on US-licensed Humira do not indicate any major differences in PK based on disease state for the indications for which the Applicant is seeking licensure. Therefore, it is reasonable to conclude that a similar PK profile for GP2017 is expected between PsO patients (the studied population) and IBD patients. In addition, it should be noted that the PK of adalimumab is also influenced by immunogenicity, which is discussed further below.

Immunogenicity

Immunogenicity was found to be similar between GP2017 and US-licensed Humira in the PK similarity studies conducted in healthy subjects, GP17-101 and GP17-104, and the comparative clinical study conducted in patients with PsO, Study GP17-301. Specifically, the frequency of anti-drug antibody (ADA) positive subjects, the time course of ADA development, and median ADA titer values were found to be similar between GP2017 and US-licensed Humira. These results support a demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira in the indications for which the Applicant is seeking licensure of GP2017. Therefore, it is reasonable to conclude that immunogenicity in IBD patients receiving GP2017 would be similar to that observed in IBD patients receiving US-licensed Humira.

Toxicity

The primary assessment of adverse events was done using data from the comparative PK and safety studies of single dose GP2017 (Studies GP17-101 and GP17-104) and the comparative clinical study conducted in patients with PsO (Study GP17-301). In controlled clinical studies of US-licensed Humira submitted to support its approval and described in the approved labeling, the types of adverse events and their rates were similar across indications. Given the similar product quality attributes, PK, and immunogenicity, there is no reason to expect that the safety profile in the IBD population would be different from that demonstrated in the PsO population.

Conclusion

Consistent with the principles of the FDA Guidance outlined above, the applicant provided sufficient scientific justification (based on the mechanism of action, PK, immunogenicity and toxicity profile), and sufficient information, including clinical data from the studied population, to support licensure of GP2017 for the inflammatory bowel disease indications (ulcerative colitis and adult Crohn's disease).

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/s/

ANIL K RAJPAL
10/29/2018

JESSICA J LEE
10/29/2018



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

DATE: 06/29/2018

TO: File for BLA 761071

THROUGH: Nikolay Nikolov, MD

FROM: Mark Borigini, MD

SUBJECT: **Primary Clinical Review**

APPLICATION/DRUG: **BLA 761071 HYRIMOZ (adalimumab)**

Sandoz submitted a 351(k) Biological Licensing Application (BLA) on October 30, 2017, seeking approval of the product GP-2017 (proposed trade name: HYRIMOZ), a proposed biosimilar to US-licensed HUMRIA (adalimumab, a TNF α -inhibitor). HUMIRA is approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis (≥ 2 years of age), psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, pediatric Crohn's disease, hidradenitis suppurativa, and uveitis. The indications for GP2017 sought by Sandoz include all of the approved Humira indications, with the exception of polyarticular juvenile idiopathic arthritis between ages 2 and 4 years, pediatric Crohn's disease, hidradenitis suppurativa, and uveitis, all of which are covered by orphan exclusivity at the time of this review.

This BLA had originally been submitted August 25, 2016, but was withdrawn October 21, 2016, as the Agency's expectations regarding the Pre-License Inspection scheduling could not be met for one of the proposed manufacturing sites.

The submitted BLA includes the results from one completed clinical study to support similarity in clinical efficacy: Study GP17-301, a multicenter, randomized, double-blind, active-controlled, comparative study in patients with moderate to severe chronic plaque psoriasis. From a clinical standpoint, the clinical pharmacology, efficacy, safety, and immunogenicity data submitted to this 351(k) BLA from the clinical development program of GP2017, support the demonstration of no clinically meaningful difference between GP2017 and US-licensed Humira in the indication studied, i.e., plaque psoriasis.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use and potential licensure of GP2017 for each of the indications for which US-licensed Humira is

currently licensed and for which GP2017 is eligible for licensure.

The clinical review has been completed. A collaborative review (DARP and DDDP) has been used for this supplement, and the clinical review will be archived as such.

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MARK BORIGINI
06/29/2018