Cross-Discipline Team Leader/Division Summary Review

Date	*see electronic stamp date*
From	Stefanie Freeman, MD, Raj Nair MD, Nikolay Nikolov, MD, Lei He, PhD, Ping Ji, PhD
Subject	Cross-Discipline Team Leader Review Division Summary Review
NDA/BLA #	BLA 761042 Supplement-018
Applicant	Sandoz Inc.
Date of Submission	May 28, 2021
BSUFA Goal Date	June 28, 2022
Proprietary Name/ Proper name/Code name	Erelzi (etanercept-szzs) (GP2015)
Pharmacologic Class	TNF inhibitor
Formulation(s)/Presentation(s)	Formulation: 25 mg lyophilized powder in multiple dose vial for reconstitution
Proposed Dosing regimen	For pediatric patients less than 63 kg (138 pounds), 0.8 mg/kg weekly
Recommended Action	*Approval*

1 Introduction

The Applicant, Sandoz Inc. (Sandoz), submitted this supplemental Biologics License Application (BLA) under section 351(k) of the Public Health Service Act (PHS Act). The submission is a prior approval supplement (PAS) to fulfill PREA postmarketing requirement (PMR) 3110-1 to develop a presentation that can be used to accurately administer etanercept-szzs to pediatric patients who weigh less than 63 kg. On May 28, 2021, Sandoz submitted the PAS for a 25 mg lyophilized powder in multiple dose vial for reconstitution (GP2015 LYVI or Erelzi LYVI) and a dilutant pre-filled syringe for the GP2015 LYVI Kit.

Erelzi (etanercept-szzs) was initially approved as a biosimilar to US-licensed Enbrel on August 30, 2016. It is currently approved for the treatment of adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis in patients 4 years or older, and for treatment of polyarticular juvenile idiopathic arthritis in patients 2 years and older. The PAS does not propose any new indications or seek any changes to the currently approved indications but provides a new presentation for use in patients who weigh less than 63 kg. The dosing for pediatric PsO or JIA is 0.8 mg/kg weekly with a maximum of 50 mg per week.

To support approval of the Erelzi (etanercept-szzs) 25 mg lyophilized powder in multiple dose vial for reconstitution, also referred to as a GP2015 LYVI and Erelzi LYVI, Sandoz submitted analytical, clinical pharmacokinetics, and device data. The Applicant also submitted a Risk

Assessment of the primary packaging material used in the PK study and GP2015 pediatric kit as the finished kit was not available at the time of the clinical study CGP2015_2106.

This memorandum provides an overview of the supplement with a focus on the data relevant to whether the supplement meets the approval standards for licensure under section 351(k) of the PHS Act. During development, etanercept-szzs was also referred to by the Applicant's developmental name, GP2015 and this reference is also used in the text, and tables below.

In summary based on the review of the information in the BLA, including the current supplemental application, Erelzi (etanercept-szzs) LYVI is highly similar to US-licensed Enbrel LYVI, notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between Erelzi LYVI and US-licensed Enbrel LYVI in terms of safety, purity, potency.

2 Background and Regulatory History

Erelzi (etanercept-szzs) is a dimeric fusion protein consisting of the extracellular ligand binding domain of the p75 tumor necrosis factor receptor (TNFR) linked to the Fc portion of a type-1 immunoglobulin (IgG1). Etanercept-szzs competitively inhibits TNF-α binding to cell surface TNFR, preventing TNF-mediated cellular responses. Erelzi was licensed as a biosimilar to US-licensed Enbrel (etanercept) on August 30, 2016 (BLA 761042).

In the pediatric indications of US-licensed Enbrel (etanercept), children weighing ≥ 63 kg (138 pounds) are treated with a fixed weekly dose of 50 mg. In addition to the 25 mg and the 50 mg pre-filled syringe (PFS), a 25 mg dose-adjustable lyophilizate dosage form (25 mg in 1.00 mL after reconstitution) is currently marketed for the US-licensed Enbrel (Enbrel LYVI) to allow the accurate weight-dependent dosing of pediatric patients with < 63 kg (138 pounds) of body weight[1].

Erelzi (etanercept-szzs) is currently approved for the treatment of adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis in patients 4 years or older, and for treatment of polyarticular juvenile idiopathic arthritis in patients 2 years and older. A dose-adjustable dosage form of Erelzi allowing weight-dependent dosing of pediatric patients (as required by the Pediatric Research Equity Act) was not included in the original 351(k) biosimilar application. At that time only the 25 mg and 50 mg pre-filled syringe and auto-injector (PFS/AI) formulations were included, and development of the pediatric presentation for patients weighing <63 kg was deferred. At the time of the approval a postmarketing requirement (PMR) for a pediatric formulation was issued, PMR 3110-1. The initial date for completion was December 2019. Due to changes in CMC the submission date for the PMR completion date was deferred to

[1] A 25mg/0.5 mL single-dose vial has also been approved for US-licensed Enbrel. This presentation for US-licensed Enbrel was approved after the original approval of Erelzi and the issuance of PMR 3110-1.

May 2021. Sandoz has submitted this supplemental application to comply with the submission date.

The development of the pediatric presentation was discussed prior to the submission. Two BPD Type 2 meetings were held on May 18, 2016, and August 28, 2017. Written responses were provided for the study protocol (CGP2015_2106) under the IND 114187 on February 27, 2018, and March 13, 2018. An additional BPD Type 4 meeting was held on March 19, 2021. The main points of discussion around the pediatric presentation included a discussion that the protein concentration (in mg/mL) of reconstituted GP2015 should fall within the range of US-licensed Enbrel, (BPD Type 2 meeting August 28, 2017, and BPD Type 4 meeting March 2021). At the Type 4 meeting it was noted that the mean protein concentration of the reconstituted GP2015 LYVI (in mg/mL) was (b) (4) mg/mL higher than the mean protein concentration for reconstituted US-licensed Enbrel LYVI. The Applicant was asked to provide justification why this difference in protein concentration would not preclude a demonstration that GP2015 LYVI is highly similar to US-licensed Enbrel LYVI.

In the BPD Type 2 meeting in 2016 it was also discussed that that GP2015 should include a dose-adjustable form for multiple-use similar to the multiple-use lyophilized US-licensed Enbrel vial and any differences in the design and use of the proposed product should include appropriate justification that the differences do not negatively impact the ability of the end-users, including patient and caregivers to use the proposed products. Of note, the 25 mg/0.5mL single dose vial for US-licensed Enbrel was not available at the time of the BPD Type 2 meeting. The 25 mg/0.5 mL single dose vial for US-licensed Enbrel was approved 3/5/2020.

Additional points in the FDA written responses for GCP2015_2106 included that if the to-be-marketed kits were not available at the time of the study the Sponsor should perform a risk assessment to identify potential differences in the syringe to be used in the PK study and the syringe in the to-be-marketed kit that could impact product quality. Any residual uncertainty that could arise from the differences would need to be addressed.

During the course of this supplemental review additional information was received related to Chemistry and Manufacturing which was considered a major amendment for the application. Additionally, the review of this submission involved novel considerations that required additional time to address, which resulted in a delay of this action.

3 Product Quality

Product Review Team: Deborah Schmiel, Ph.D. /Rachel Novak, Ph.D.
Microbiology/Facility Team: Charles Yuan-Chia Kuo, Ph.D., Maxwell Van Tassell, Ph.D., Zhong Li, Ph.D.

1) Chemistry, Manufacturing and Controls, General Product Quality and Device Considerations

Erelzi (etanercept-szzs) is currently approved in two strengths: a 25 mg/0.5 mL single dose PFS and a 50 mg/mL solution in a single-dose PFS and autoinjector. The Applicant is seeking approval of GP2015 LYVI (25 mg of lyophilized powder in a multiple-dose vial).

The GP2015 LYVI is a sterile, preservative-free white powder in a glass vial to be reconstituted with 1 ml of 0.98% benzyl alcohol in sterile water for injection; the diluent is provided in a glass prefilled syringe (PFS) as part of the kit.

To support a demonstration that lyophilized GP2015 25 mg for Injection (GP2015 LYVI) is highly similar to lyophilized US-Enbrel 25 mg for Injection, Sandoz describes a comparability study of GP2015 LYVI to GP2015 injection and an abbreviated comparative analytical assessment of GP2015 LYVI to US-Enbrel LYVI for a subset of product quality attributes (QA) and diluent QAs.

Review of chemistry, manufacturing, and controls by the Office of Product Quality (OPQ) has determined the quality of the drug product LYVI (25 mg lyophilized powder) presentation is comparable to the approved Erelzi liquid for intravenous infusion and is highly similar to US-licensed Enbrel. The Applicant has provided sufficient supportive data in terms of product quality, manufacturing, safety, and potency to approve the GP2015 lyophilized presentation and dilutant PFS that comprises the kit. Review by OPQ has determined that the efficacy supplement fulfills PMR 3110-1 requiring the development of a presentation to accurately administer etanercept-szzs to pediatric patients who weigh less than 63 kg.

Sandoz has demonstrated that GP2015 LYVI has the same recoverable content as U.S.-licensed Enbrel LYVI. Based on the comparative data between GP2015 LYVI and US-Enbrel LYVI, GP2015 LYVI has the same total content of drug substance in units of mass in a container as US-licensed Enbrel LYVI.

In summary, the product quality review team recommends approval of this supplement.
We agree with the conclusions and recommendations by the product quality review team.

For more detailed information, refer to the review memo by the Product Quality team (6/9/2022).

- **Product Quality Microbiology/Clinical Microbiology/Facilities inspections**

The product quality microbiology review team evaluated the sterility assurance and quality microbiology data. Manufacturing facility inspections were conducted at Novartis Technical Operations S.A. Alcon-Couvreur N.V and (b) (4) From a microbiology product quality and facilities perspective, the OPQ/OPMA team recommends approval (Product Quality Microbiology/Facility Assessment Memorandum). We agree with the conclusions and recommendations by the microbiology review team.

4 Pharmacology/Toxicology

Primary Pharmacology/Toxicology Reviewer: Ijeoma Uzoma, Ph.D.
Pharmacology/Toxicology Team Leader: Tim Robison, Ph.D.

No new pharmacologic/toxicologic data was submitted or needed for this Supplemental Application.

5 Clinical Pharmacology

Clinical Pharmacology Primary Reviewer: Lei He, PhD
Clinical Pharmacology Team Leader: Ping Ji, PhD

Sandoz submitted this prior approval supplement (PAS) to fulfill PREA postmarketing requirement (PMR) 3110-1, i.e., "*Develop a presentation that can be used to accurately administer etanercept-szzs to pediatric patients who weigh less than 63 kg*". The proposed presentation is a 25 mg lyophilized powder in multiple dose vial for reconstitution (Erelzi LYVI) with an administration kit (GP2015 LYVI kit). One PK similarity study, Study CGP2015_2106, was conducted to compare PK of the proposed Erelzi LYVI and US-licensed Enbrel lyophilized powder for injection (25 mg lyophilized powder in a multiple-dose vial for reconstitution) (US-Enbrel LYVI).

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) have reviewed the clinical pharmacology data submitted under BLA 761042 Supplement 18. The submission is recommended for approval from a clinical pharmacology perspective.

The clinical team agrees with the conclusions and recommendations by the clinical pharmacology review team.

Clinical Pharmacology Study Design Features

Study CGP2015_2106 is a single center, randomized, open-label, two-period, crossover (at least 35-day washout period) study in 56 healthy male subjects (**Error! Reference source not found.**). Eligible subjects were randomized on Day -1 of Treatment Period I to receive either the

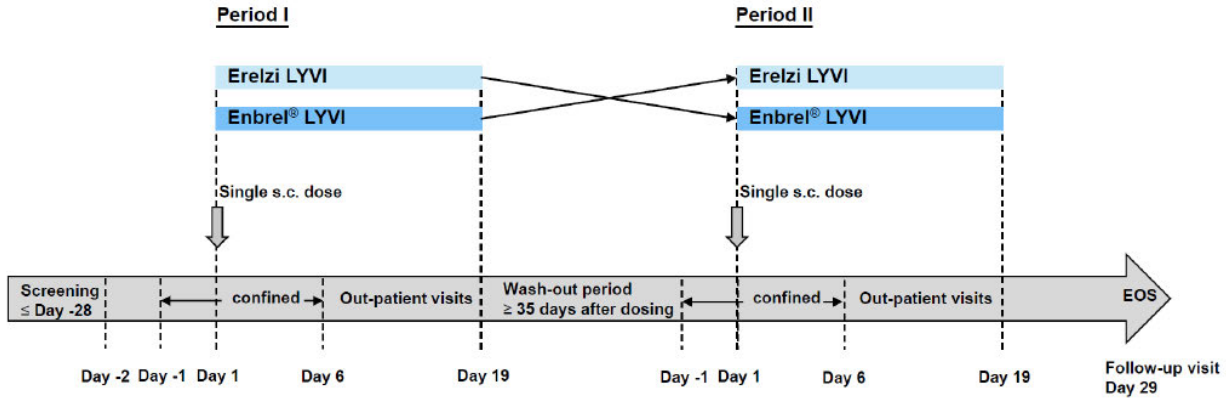
treatment sequence, Erelzi LYVI in Treatment Period I and US-Enbrel LYVI in Treatment Period II, or the treatment sequence, US-Enbrel LYVI in Treatment Period I and Erelzi LYVI in Treatment Period II. On the morning of Day 1 of Treatment Period I and Treatment Period II, subjects received either a single subcutaneous (SC) injection of Erelzi LYVI (18 mg) or a single SC injection of US-Enbrel LYVI (18 mg).

As the proposed administration kit (GP2015 LYVI kit) was not available at the time of study initiation, the administration syringes used in Study CGP2015_2106 was different from the proposed GP2015 LYVI kit. Briefly, Erelzi and US-licensed Enbrel lyophilizates were reconstituted with 1.00 mL of the sterile water for injection, USP (0.9% benzyl alcohol), leading to a study drug concentration of 22.5 mg/mL. 1 mL syringes ([redacted] (b) (4)) with 25G needles were used to transfer the diluent into the vials and therewith reconstitute Erelzi LYVI and US-Enbrel LYVI. A new syringe and 25G needle were used for extraction of 0.8 mL of reconstituted Erelzi LYVI and US-Enbrel LYVI. The 25G needle was then be replaced by a 27G needle for SC administration.

In each treatment period, blood samples were collected pre-dose on Day 1 and at 6, 12, 24, 36, 48, 60, 72, 84, 96, 120, 168, 216, 264, 336, 432 hours or 672 hours (Treatment period II only) post-dose for PK assessment. In each treatment period, blood samples were also collected at baseline (pre-dose on Day 1) and Days 15 and 29, or early termination visit for immunogenicity assessment.

Note that the biopharmaceutical inspection was requested for the clinical site of Study CGP2015_2106. Office of Study Integrity and Surveillance (OSIS) determined that the final classification the requested inspection was No Action Indicated (NAI). Refer to the review memo by Dr. James Lumalcuri dated September 16, 2021.

Figure 1. Study design of Study CGP2015_2106



Source: Figure 9-1 of Study CGP2015_2106 CSR

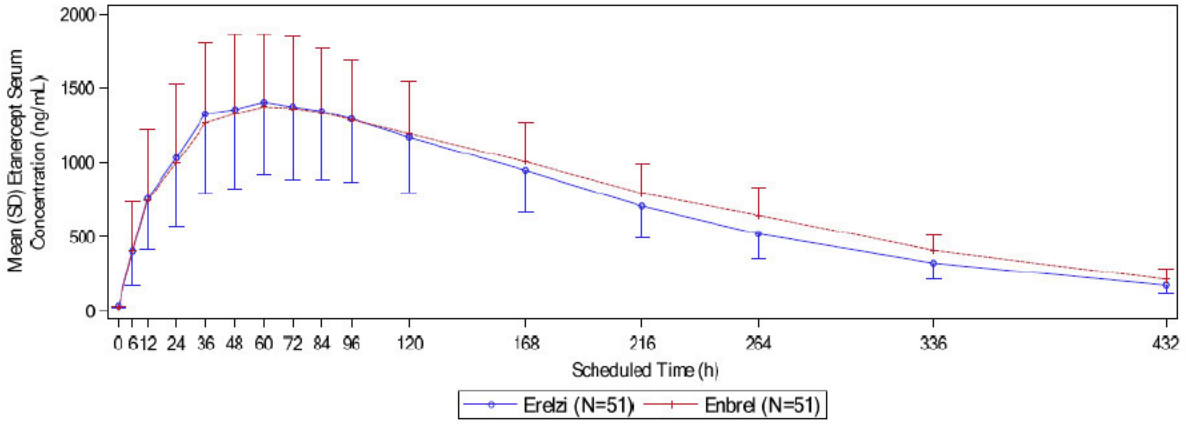
PK Assessment

A total of 56 healthy subjects were randomized to receive either the treatment sequence, Erelzi LYVI in Treatment Period I and US-Enbrel LYVI in Treatment Period II, or the treatment

sequence, US-Enbrel LYVI in Treatment Period I and Erelzi LYVI in Treatment Period II. 5 subjects were considered as treatment discontinuations and excluded in PK analysis as they only received dosing during Treatment Period I due to ICF withdrawal (Subject (b) (6)), personal reasons (Subjects (b) (6) and (b) (6)), or COVID-19 pandemic (Subjects (b) (6) and (b) (6)).

PK analysis showed that, following a single SC injection of 18 mg Erelzi LYVI or US-Enbrel LYVI, the systemic exposure (Cmax, AUC0-t, and AUC0-inf) is comparable between Erelzi LYVI and US-Enbrel LYVI (Figure 2, Table 1).

Figure 2. Arithmetic mean (SD) study drug serum concentration-time profiles (linear scale, Study CGP2015_2106)



Source: Adapted from Figure 11-3 of Study CGP2015_2106 CSR

Table 1. Statistical analysis for PK parameters (Study CGP2015_2106)

PK Parameters	Geometric LS Means		Ratio of Test/Reference (%)	
	Erelzi LYVI (Test, n=51)	US-Enbrel LYVI (Reference, n=51)	Geometric mean ratio	90% CI
Cmax (ng/mL)	1402	1387	101.07	(95.05, 107.47)
AUC0-t (h*ng/mL)	304085	336639	90.33	(85.42, 95.52)
AUC0-inf (h*ng/mL)	327524	360129	90.95	(86.24, 95.91)

Source: FDA analysis)

Immunogenicity Assessment

In Study CGP2015_2106, one subject was detected positive for anti-drug antibodies (ADA) after US-Enbrel LYVI administration in treatment period II at follow-up visit (Day 29) but tested negative for neutralizing antibodies (NAb) (Table 2).

Table 2. Summary of immunogenicity results (safety analysis set, Study CGP2015_2106)

Visit	Erelzi (test) N=53 n (%)	Enbrel (reference) N=54 n (%)
ADA		
Day 1, pre-dose	0	0
Day 15	0	0
Day 29	0	1 (1.9)
Total (# of subjects with at least one positive result)	0	1 (1.9)
NAb		
Total (# of subjects with at least one positive result)	0	0

N = number of subjects exposed per treatment.
n = number of positive results.
%=Number of subjects with a positive result (confirmatory assay) as a percentage of number of subjects exposed per treatment.
NAb was only analyzed on confirmed positive ADA samples.
Source: Table 12-8 of Study CGP2015_2106 CSR

Bioanalytical PK method and performance

An enzyme linked immunosorbent assay (ELISA) was validated and used for analysis of study drug in human serum in study CGP2015_2106. All PK samples from Study CGP2015_2106 were stored at -70°C and analyzed within <9 months after the sample collection, which is within the demonstrated 24-month long-term stability duration at -70°C. Therefore, the bioanalytical method validation and PK sample analysis for Study CGP2015_2106 are acceptable. Refer to Appendix for more detailed information regarding the bioanalytical method validation.

6 Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Stefanie Freeman, M.D.
Clinical Team Leader: Raj Nair, M.D.

Study CGP2015_2106 is entitled, A randomized, open-label, two-period, crossover study to determine the pharmacokinetics of reconstituted lyophilized Erelzi and Enbrel (US-licensed) following a single subcutaneous injection in healthy male subjects. The study was a single center pharmacokinetics (PK) study conducted in the Netherlands. The study was conducted in accordance with 21 CFR 312.120 and with Good Clinical Practice. The objective of the study was to demonstrate PK similarity of Erelzi LYVI and US-Enbrel LYVI and to assess immunogenicity, safety, and local tolerance. The study was not designed to assess effectiveness.

Table 3: Key Design Features of Clinical Study

Protocol	Patient population	Design/Objective	Doses Administered	Treatment arms: sample size
CGP2015_2106	Healthy male subjects	R, OL, 2-period, cross-over Primary Objective: PK comparability between of reconstituted lyophilized Erelzi and Enbrel (US) - (AUC_{inf}, AUC_{last}, C_{max}) Secondary Objective: Investigate safety/tolerability	1 dose SC Erelzi LYVI and 1 dose SC US-Enbrel LYVI 35-day washout between periods	Total N=56

Abbreviations: R: randomized, OL: open label, PK: pharmacokinetic, SC.: subcutaneous

Study CGP2015_2106 was a single center, open-label, 2-period, single-dose, cross-over study in healthy male subjects designed to address the PMR to develop and appropriate dose-adjustable presentation for use in pediatric patients weighing < 63 kg (138 pounds). The study was designed to evaluate the PK similarity, safety, and immunogenicity of Erelzi LYVI and US-Enbrel LYVI in 56 healthy male volunteers. Subjects were randomized on Day -1 of Treatment Period I to receive 1 of the following treatment sequences:

- Erelzi LYVI in Treatment Period I (TP1) followed by US-Enbrel LYVI in Treatment Period II (TP2)
- US-Enbrel LYVI in TP1 followed by Erelzi LYVI in TP2

Both Erelzi LYVI and US-Enbrel LYVI formulations were provided as 25 mg lyophilizate in vials. Vials were reconstituted with water for injection (USP) containing 0.9% benzyl alcohol which were provided to the investigator. As the finished administration kit was not available at the time of study initiation, the administration syringe used in the study was different from that present in the current (to-be-marketed) Erelzi LYVI kit. In order to assess and identify any differences based on the administration syringe used in the clinical study CGP2015_2106 and the LYVI kit an additional risk assessment was performed.

In study CGP2015_2106, Erelzi LYVI and US-Enbrel LYVI were provided as lyophilizate cakes in 25 mg vials (25 mg in 1.00 mL after reconstitution). The study assessed PK similarity using a single dose of 18 mg.

On Day 1 of TP1 and TP2, subjects received either a single SC injection of Erelzi LYVI (18 mg) or a single SC injection of US-Enbrel LYVI (18 mg) in a fixed dosing volume of 0.8 mL. All doses were to be administered by the same investigator whenever possible in each of the two treatment periods. Subjects were discharged from the clinical unit after the post-dose assessments were completed on Day 6 of Treatment Periods 1 and 2. Following Day 6 subjects returned to the clinical unit on an out-patient basis for scheduled pharmacokinetic, safety, and immunogenicity assessments. Between TP1 and TP2 there was a wash-out period of at least 35 days between the investigational product administrations. A follow-up examination was performed on Day 29 after the last investigational product application which included blood sampling for immunogenicity analysis Figure 1.

The SC injections were administered in the abdominal region while subjects were in a supine position. The SC injection for TP2 was administered in the equivalent location on the contralateral side.

PK similarity was assessed comparing the main PK variables: $AUC_{0\text{-}tlast}$, C_{max} and $AUC_{0\text{-}inf}$ as the primary endpoints. PK similarity was defined by the 90% CIs for the ratios of geometric means of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ between treatments were contained within the margins of 0.80 to 1.25.

A total of 56 healthy male subjects were enrolled in the PK study CGP2015_2106 and 50 subjects completed the study. The population characteristics were comparable between treatment arms. The majority of subjects were White (82.1%), followed by Multiple (5.4%), American Indian and Alaskan Native (5.4%), Asian (3.6%) and Black or African American (3.6%). The mean age of subjects was 34.8 ± 11.06 years and mean BMI was 24.90 ± 2.983 kg/m^2.

In study CGP2015_2106, five (5) subjects received dosing only during TP1 and were considered as treatment discontinuations. Reasons for discontinuation included informed consent form withdrawal (1 subject), personal decision (2 subjects), and early study termination due to COVID-19 (2 subjects). These subjects were excluded from the PK analysis set. The PK analysis set therefore comprised 51 subjects. One subject discontinued in TP2 after completion of the second dosing and was considered a study discontinuation but was included in the PK analysis set.

Study CGP2015_2106 was initially halted on Oct 5, 2018 (prior to first subject first treatment) due to the finding of a difference in the actual protein content of Erelzi LYVI compared to US-licensed Enbrel LYVI. The study was re-started on Jun 13, 2019, following release of a new Erelzi LYVI investigational medicinal product (IMP) batch. The initial due date of the PMR was December 2019. A deferral with a new submission due date for the PMR of May 2021 was granted based on the foregoing.

Due to the COVID-19 pandemic, the second dosing in study CGP2015 was temporarily halted for 2 subjects and safety follow-ups were performed via telephone instead of by in person visit to ensure subject safety. The study was terminated early on May 13, 2020, due to the impact of the COVID-19 outbreak on study conduct. The last two subjects who were about to start TP2 of the study were unable to complete dosing due to the COVID-19 pandemic, but the majority of subjects had already completed both periods with 51 subjects with evaluable PK. Therefore, the impact of COVID-19 pandemic on the study design and conduct was considered minimal and without impact to the interpretability of the study data.

PK analysis (as described above) showed that, following a single SC injection of 18 mg Erelzi LYVI or US-Enbrel LYVI, the systemic exposure (Cmax, AUC0-t, and AUC0-inf) of study drug is comparable between Erelzi LYVI and US-Enbrel LYVI.

No new efficacy data were submitted or required to support this supplement; however, the data and information summarized in the review by the Product Quality team, (6/9/2022), and Section 5 by Clinical Pharmacology establish the relevance of the data submitted in the BLA 761042 for Erelzi (including the data submitted from the clinical development program) to the evaluation of this supplement under section 351(k) of the PHS Act. The safety from the clinical studies and clinical considerations for this application are discussed in the next section, Safety.

7 Safety

In study CGP2015_2106 fifty-six (56) subjects received at least one dose of either Erelzi LYVI or US Enbrel LYVI and safety and tolerability was evaluated. As described above: Subjects were randomized on Day -1 of TP1 to receive a single 18 mg dose SC administration in one of the following treatment sequences:

- Erelzi LYVI in TP1 followed by US-Enbrel LYVI in TP2
- US-Enbrel LYVI in TP1 followed by Erelzi LYVI in TP2

Adverse events in study CGP2015-2106 were coded using MedDRA Version 23.0. Treatment emergent adverse events (TEAEs) were assigned to each study period based on the following:
Period 1: Adverse events (AEs) starting after the first period dosing of investigational product but before the second period dosing of the investigational product.
Period 2: AEs starting after the second period dosing of investigational product.

Of the 56 subjects enrolled in the CGP2015_2106 study, 53 subjects were exposed to a single 18 mg SC dose of Erelzi LYVI/US, and 54 subjects were exposed to a single 18 mg SC dose of US-Enbrel LYVI administered on Day 1 of Treatment Periods 1 and 2.

As shown below in Table 4 the number of subjects with TEAEs was similar between the treatment arms. The majority of reported TEAEs were mild in severity with two moderate TEAEs reported during the US-Enbrel LYVI period, and no severe TEAEs. The moderate TEAEs reported during the US-Enbrel LYVI treatment period included an event of ALT increased and an upper respiratory tract infection. No SAEs or deaths were reported in the study. No TEAEs led to discontinuation of the study or of the study treatment. Reported AEs were consistent with TEAEs reported in other clinical studies of Erelzi.

A higher number of subjects in the Erelzi LYVI treatment group (18 subjects, 34.0%) experienced injection site reactions (ISR) compared to subjects in the US-Enbrel LYVI treatment group (8 subjects, 14.8%).

A summary of safety is presented in Table 4.

Table 4: Study CGP 2015_2106 Safety Summary

	Study CGP 2015_2106	
	Erelzi LYVI N= 53 n (%)	US Enbrel LYVI N=54 n (%)
Number (%) of subjects with TEAEs Total number of TEAEs	29 (54.7%) 64	28 (51.9%) 55
Number of subjects with SAEs	0	0
Severity		
Mild	29 (54.7%)	28 (51.9%)
Moderate	0	2 (3.7%)
Severe	0	0
Number (%) of subjects with AEs leading to discontinuation	0	0
Number (%) of subjects with Injection site reactions**	18 (34.0%)	8 (14.8%)

Abbreviations: TEAE=treatment emergent adverse events, SAE=serious adverse events, ** injection site reactions included events: “erythema”, “bruising”, “pain”, “swelling”, and “other”

Source: Adapted from Applicant’s clinical study report Table 14.3.1-1, 14.3.1-6

Deaths
No deaths were reported in the clinical study.

Serious Adverse Events
No serious adverse events were reported.

Adverse Events Leading to Discontinuation
No adverse events led to discontinuation of the study drug.

Adverse Events of Special Interest (AESI)
While no events were designated as AESIs in the study protocol, injection site reactions (ISR) were evaluated to assess local tolerance of Erelzi LYVI. In Study CGP 2015_2106 subjects evaluated the local reaction using a visual analysis scale (VAS) and investigators also evaluated the injection sites using ISR scores. Any ISR score greater than 1 (mild) were to be reported as an AEs.

A total of 18 subjects (34.0%) receiving Erelzi LYVI and 8 subjects (14.8%) receiving US-Enbrel LYVI reported ISRs. All ISRs were mild in severity and were reported as local reactions. One ISR after receiving Erelzi LYVI required treatment with 1 dose of paracetamol. All ISR resolved by study end without need for further treatment. The reported ISR symptoms for Erelzi

LYVI and US-Enbrel LYVI included event terms “erythema”, “bruising”, “pain”, “swelling”, and “other” (sensitivity, itching, tingling and warm feeling). ISR related to pain were similar in both treatments with 2 subjects reporting ISR events of pain following the injection of the Erelzi LYVI and US-Enbrel LYVI. ISR events of erythema and bruising were higher following the Erelzi LYVI injection. Six patients reported events of erythema following the Erelzi LYVI injection and one patient reported erythema following the US-Enbrel LYVI injection. Seven patients reported bruising following the Erelzi LYVI and three patients had bruising following US-Enbrel LYVI injection. A higher number of ISRs was reported in treatment period 1, with increased frequency for Erelzi LYVI (Erelzi LYVI: 14; US-Enbrel LYVI: 3). The frequency of ISR events was similar between the arms in treatment period 2 (Erelzi LYVI: 4; US-Enbrel LYVI: 5). The types of ISR reported were similar between Erelzi LYVI and US-Enbrel LYVI and were similar to ISR events observed in other clinical studies with Erelzi. The reported frequency of ISR in the study is consistent with ISR reported for Enbrel[2] in placebo-controlled trials in rheumatologic indications although the reported frequency of ISR in this clinical study for Erelzi LYVI is higher than that reported in other healthy volunteer (HV) studies for Erelzi. Across the other pooled HV clinical studies to support the original BLA conducted with Erelzi the pooled HV patients with ISR was 5.3% for Erelzi vs. 5.4% for US-Enbrel and 7.5% for EU-Enbrel. Results for the reported VAS scores for injection sites in Study CGP 2015_2016 were similar between the Erelzi LYVI and US-Enbrel LYVI. All Erelzi LYVI ISR were mild and the significance of the increased ISR observed with Erelzi LYVI only during TP1 is unclear. Therefore, the differences in ISRs between the Erelzi LYVI and the Enbrel LYVI in Study CGP 2015_2106 do not preclude a demonstration of no clinically meaningful differences.

The study was conducted during the COVID-19 pandemic. During the study one subject (24-year-old male) developed a respiratory infection after dosing in the second study treatment period. The subject developed symptoms of a cough and back pain and the infection was considered suspicious for COVID-19. The subject was never tested for COVID-19 and remained in quarantine until resolution of the event. The event was considered non-serious and moderate in severity. The AE resolved without sequelae.

Common Adverse Events

TEAEs in study CGP2015_2106 to either Erelzi LYVI or US-Enbrel LYVI were reported most commonly in the primary System Organ Classes (SOCs) of General disorders and administration site conditions (n=25 [44%]), Gastrointestinal Disorders (n=12 [21.4%]), nervous system disorders (n=12 [21.4]), musculoskeletal and connective tissue disorders (n=11 [19.6%]) and Infections and Infestations (n=9 [16.1%]).

TEAEs in the Erelzi dosing period were most commonly reported in the primary System Organ Class (SOC) of General Disorders and Administration Site Conditions, Gastrointestinal Disorder, and Infections and Infestations.

[2] Enbrel USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103795s5582lbl.pdf

- General Disorders and Administration site conditions: 19 subjects, (35.8%) reported events with Erelzi LYVI and 9 subjects (16.7%) reported events in the US-Enbrel LYVI period.
- Gastrointestinal disorders: 8 subjects (15.1%) with Erelzi LYVI and 6 subjects (11.1%) with US-Enbrel LYVI
- Infections and infestations: 7 subjects Erelzi LYVI (13.2%) and 3 subjects (5.6%) US-Enbrel LYVI.

Within the SOC for General Disorders and Administrative conditions the most common preferred terms corresponded to ISRs.

The most frequently reported TEAEs by preferred term are shown below in **Table 5**.

Table 5. Study CGP2015_2106 Summary of Most Common TEAEs (Reported Preferred Terms, for TEAEs occurring in 2 or more subjects)

	Erelzi LYVI N= 53 n (%)	**US Enbrel LYVI N=54 n (%)**
Number of subjects with at least one TEAE	**29 (54.7)**	**28 (51.9)**
Injection site reaction	18 (34.0)	8 (14.8)
Diarrhea	5 (9.4)	2 (3.7)
Rhinitis	3 (5.7)	1 (1.9)
Abdominal pain	2 (3.8)	1 (1.9)
Erythema	2 (3.8)	0
Fatigue	2 (3.8)	1 (1.9)
Headache	2 (3.8)	9 (16.7)
Nasopharyngitis	2 (3.8)	1 (1.9)
Oropharyngeal pain	2 (3.8)	1 (1.9)
Arthralgia	1 (1.9)	1 (1.9)
Back pain	1 (1.9)	3 (5.6)
Constipation	1 (1.9)	1 (1.9)
Cough	1 (1.9)	2 (3.7)
Flatulence	1 (1.9)	1 (1.9)
Gastrointestinal sounds abnormal	1 (1.9)	1 (1.9)
Hematoma	1 (1.9)	1 (1.9)
Myalgia	1 (1.9)	1 (1.9)
Musculoskeletal pain	0	2 (3.7)
Nasal congestion	0	2 (3.7)

TEAE: Treatment Emergent Adverse Event; A patient with multiple occurrences of an AE is counted only once.
Source: Adapted from Applicant's Clinical Overview Table 5-5, CSR 14.3.1-2

Clinical Laboratories

Clinical laboratories were evaluated and included chemistry, hematology, and urinalysis. Samples were collected at screening, Day -1, Study Days 2, 6, 15, and 29. In Study GCP2015_2106 mean and median changes in laboratory parameters and laboratory abnormalities

were generally similar between US-Enbrel LYVI and Erelzi LYVI treatment. One patient had a clinically significant chemistry finding of elevated ALT which occurred during the US-Enbrel LYVI treatment period. The AE was considered moderate in severity. No other clinically significant laboratory changes were identified in the study.

Vital Signs and ECGs
Physical examinations were conducted at screening, Study Days -1, 2, and follow-up (Day 26). Vital signs were evaluated at Screening, Study Days 1, 2, 3, 4, 8, 15 and follow-up (Day 26). ECGs were evaluated at Screening, Day -1 (predose), and at the follow-up visits (Day 26). No clinically significant changes in vital signs, physical examinations, or ECGs were identified in the CGP2015_2106 study.

Immunogenicity
Sampling for anti-drug antibodies were conducted pre-dose on Study Day 1 and post dose on Study Day 15 and at follow-up (Study Day 26).

In study CGP2015_2106 all patients had negative ADA results on Day 1 of both treatment periods. One subject randomized to the Erelzi LYVI/US-Enbrel LYVI treatment sequence had a positive ADA result that occurred 29 days after US-Enbrel LYVI treatment (follow-up visit). The sample was negative for neutralizing antibodies. During the study the subject reported 5 mild AEs: myalgia, abdominal discomfort, rhinitis, ISR, and dry mouth. All AEs had recovered at the follow-up visit (at the time of the positive ADA result). The results of the immunogenicity assessment do not preclude a determination of no clinically meaningful differences.

Safety Summary
The safety profile of Erelzi was evaluated in the original BLA submission. The current supplement is for pediatric formulation of Erelzi LYVI. Erelzi LYVI was evaluated in study CGP2015_2106. In this study PK, safety, and tolerability of a single-dose of Erelzi LYVI was compared to US-Enbrel LYVI in a cross-over study conducted in 56 healthy adult male volunteers. In this study the overall TEAE profile of Erelzi LYVI and US-Enbrel LYVI were similar. More ISR were noted in the Erelzi LYVI arm of the study compared to US-Enbrel LYVI. The types of ISRs were similar to those observed with US-Enbrel LYVI and previously described for Erelzi. The ISRs following administration of Erelzi LYVI were all mild in severity. The majority of the ISR events in the Erelzi LYVI arm were observed when Erelzi was used in TP1. A more similar frequency of events between the Erelzi LYVI and US-Enbrel LYVI arms was observed in TP2. The most common ISRs in the Erelzi LYVI were events of bruising and erythema. Although an increased frequency of mild events was noted following the Erelzi LYVI dose compared to the US-Enbrel LYVI dose, the events are within the current labeled frequency of ISR in the USPI for clinical trials in RA. Also given the increase is observed only in patients treated in TP1 the significance of the increase is unclear. The final administration kit was not used in the clinical study, however the gauge and needle size used in the clinical study CGP2015_2106 are the same as that to be included in the final kit. The changes in the final kit would therefore not be expected to demonstrate a different safety profile than that observed in the clinical study. The differences in ISRs between the Erelzi LYVI and the US-Enbrel LYVI in Study CGP 2015_2106 do not preclude a demonstration of no clinically meaningful differences.

Device Considerations
The Applicant supported this submission with the results from a comparative analysis and use-related risk analysis. The Applicant provided a comparative analysis to identify user interface differences that may impact the ability of the intent users, including patients and caregivers, to use the proposed 25 mg vial kit safety and effectively as compared to the US-licensed Enbrel 25 mg vial kit. The Division of Medication Error Prevention and Analysis (DMEPA 1) reviewed the submitted materials and identified minor differences between the proposed Erelzi 25 mg kit and US-licensed Enbrel 25 mg kit and determined that the differences are unlikely to impact users' ability to complete the critical tasks that may be impacted by design (DMEPA review, 2/8/22). We agree with this assessment.

8 Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this supplement.

9 Pediatrics

A presentation that could be used to directly and accurately administer Erelzi to pediatric patients ages 2-17 years who weigh less than 63 kg (as required by the Pediatric Research Equity Act [PREA]) was not included in the original 351(k) biosimilar application. At that time only the 25 mg/0.5 mL and 50 mg/mL pre-filled syringe and auto-injector (PFS/AI) were available, and development of the pediatric presentation for patients weighing <63 kg was deferred. At the time of the approval, a postmarketing requirement (PMR) for a pediatric presentation was issued, PMR 3110-1. The Applicant has fulfilled the PREA PMR with the development and submission of the current supplement for Erelzi (etanercept-szzs) 25 mg lyophilized powder in multiple dose vial for reconstitution.

10 Other Relevant Regulatory Issues

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that the final classification for the requested bioanalytical site inspection and clinical site inspection was No Action Indicated (NAI). See the review memo by Dr. James Lumalcuri dated September 16, 2021.

During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies appear to have been conducted in accordance with accepted ethical standards. The Applicant submitted financial disclosure statements which showed no disclosable financial interests reported by the clinical investigators in study CGP2015_2106. There are no other unresolved relevant regulatory issues.

11 Labeling

The labeling has been updated to include the proposed presentation. The labeling has been reviewed by DMEPA, OPDP and DMPP and their recommendations which pertain to consistency, improving readability and clarity of the labeling including the package insert/medication guide, instructions for use, carton and container labels have been agreed to with the Applicant.

The labeling for the strength of Erelzi's LYVI will be the same as that of the US-licensed Enbrel 25 mg lyophilized powder. For additional detailed information, refer to the memorandum to file from the Office of Immunology and Inflammation.

12 Regulatory Action

- **Recommended regulatory action**

Approval. In summary based on the review of the information in the BLA, including the current supplemental application, Erelzi (etanercept-szzs) 25 mg LYVI is highly similar to US-licensed Enbrel LYVI and there are no clinically meaningful differences between GP2015 LYVI and US-licensed Enbrel LYVI.

- **Recommendation for Postmarketing Risk Management Activities**

A REMS is not recommended for this application.

13 Appendix: Summary of the Bioanalytical Method

An ELISA was used for analysis of etanercept in human serum in study CGP2015_2106. The assay was initially validated (Reports BA120008-R and BA14011-R) and reviewed in the original BLA submission (refer to BLA 761042 Clinical Pharmacology Review dated July 25, 2016). Since the initially used lot numbers of the reagents were not available any more for study sample analysis of Study CGP2015_2106, adaptions were performed to the original assay, including concentrations of coating and detection antibodies, incubation times, and others. The adapted assay was then re-validated (Report BA20007-R) to analyze etanercept concentrations in healthy subject serum in Study CGP2015_2106. However, in the new validation report BA20007-R, stability assessment (including bench-top, freeze-thaw, short- and long-term stability) was not conducted but referenced the previous stability assessment results from Reports BA12008-R and BA13005-R (**Error! Reference source not found.**).

Per the Agency's information request, Sandoz submitted additional information on October 29, 2021 regarding the detailed changes of assay reagents and assay process in Report BA20007-R and justified that these changes would not affect the stability assessment, such as bench-top, freeze-thaw, short- and long-term stability, as demonstrated in the bioanalytical validation Reports BA12008-R and BA13005-R, and an additional study assessing the long-term stability of etanercept in healthy subject serum (Report BA18020-R).

The review team requested the biopharmaceutical inspection for the bioanalytical site of Study CGP2015_2106, (b) (4) and also submitted a consult to OSIS regarding the acceptability of the bioanalytical assay validation. OSIS determined that the final classification for the requested bioanalytical site inspection was NAI (refer to the review memo by Dr. James Lumalcuri dated September 16, 2021). OSIS also concluded that "*the extended long-term stability of 24 months at -70°C reported in the method validation Report BA18020-R should be applicable retrospectively for sample analysis in bioanalytical report BA19003-R for Study CGP2015_2106*" (**Error! Reference source not found.**) (refer to the review memo by Dr. Yiyue Zhang dated November 30, 2021).

All PK samples from Study CGP2015_2106 were stored at -70°C and analyzed within <9 months after the sample collection, which is within the demonstrated 24-month long-term stability duration at -70°C. Therefore, the bioanalytical method validation and PK sample analysis for Study CGP2015_2106 are acceptable.

Table 6. Validation summary of the bioanalytica PK assay used for Study CGP2015_2106 (Report BA20007-R)

Validation parameter	Specification	Validation result	Evaluation
Selectivity	10 individual sera were measured unspiked, and spiked with GP2015-LYVI / Enbrel®-LYVI at VS1 and LLOQ-VS level. 80% of sera had to fulfill following acceptance criteria: VS1 Precision CV (%) ≤ 20 Accuracy: 80% - 120% LLOQ-VS Precision CV (%) ≤ 25 Accuracy: 75% - 125% 90% of blank individual sera had to be below the LLOQ.	**GP2015-LYVI** 100% of the individual sera fulfilled the acceptance criteria. Accuracy / Precision VS1: 89% - 101% / 1% - 5% LLOQ-VS: 77% - 108% / 1% - 11% **Enbrel®-LYVI** 100% of the individual sera fulfilled the acceptance criteria. Accuracy / Precision VS1: 88% - 105% / 1% - 6% LLOQ-VS: 91% - 125% / 1% - 13% 100% of blank individual sera were below LLOQ.	Passed
Intra-assay precision	Five sets of VS (ULOQ-VS, VS1, VS2, VS3, LLOQ-VS) were analyzed on one day Intra-assay precision CV (%) ≤ 20; at LLOQ & ULOQ ≤ 25	**Intra-assay precision GP2015 LYVI:** ULOQ-VS: 3% VS1: 3% VS2: 3% VS3: 2% LLOQ-VS: 3% **Intra-assay precision Enbrel®-LYVI:** ULOQ-VS: 4% VS1: 4% VS2: 4% VS3: 3% LLOQ-VS: 4% **Intra-assay precision GP2015.02WST:** ULOQ-VS: 1% VS1: 4% VS2: 3% VS3: 4% LLOQ-VS: 3%	Passed
Inter-assay precision	Three sets of VS (ULOQ-VS, VS1, VS2, VS3, LLOQ-VS) were analyzed per day on six different days (18 sets in total) Inter-assay precision CV (%) ≤ 20;	**Inter-assay precision GP2015 LYVI:** ULOQ-VS: 4% VS1: 4% VS2: 5% VS3: 5% LLOQ-VS: 6%	Passed

Validation parameter	Specification	Validation result	Evaluation
	at LLOQ & ULOQ ≤ 25	**Inter-assay precision Enbrel®-LYVI:** ULOQ-VS: 5% VS1: 5% VS2: 5% VS3: 4% LLOQ-VS: 6% **Inter-assay precision GP2015.02WST:** ULOQ-VS: 4% VS1: 5% VS2: 4% VS3: 4% LLOQ-VS: 5%	
Accuracy	Intra- / inter-assay accuracy 80% - 120%; at LLOQ & ULOQ 75% - 125%	**Intra / inter-assay accuracy GP2015-LYVI:** ULOQ-VS: 98% / 97% VS1: 98% / 97% VS2: 100% / 100% VS3: 103% / 102% LLOQ-VS:107% / 102% **Intra / inter-assay accuracy Enbrel®-LYVI:** ULOQ-VS: 101% / 99% VS1: 102% / 100% VS2: 107% / 104% VS3: 107% / 106% LLOQ-VS: 106% / 103% **Intra / inter-assay accuracy GP2015.02WST:** ULOQ-VS: 99% / 100% VS1: 99% / 103% VS2: 106% / 108% VS3: 111% / 109% LLOQ-VS: 108% / 110%	Passed
	Intra- / inter-assay total error ≤ 30%; at LLOQ & ULOQ ≤ 40%	**Intra / inter-assay total error GP2015-LYVI:** ULOQ-VS: 5% / 7% VS1: 5% / 7% VS2: 3% / 5% VS3: 5% / 7% LLOQ-VS: 10% / 8% **Intra / inter-assay total error Enbrel®-LYVI** ULOQ-VS: 5% / 7% VS1: 6% / 5% VS2: 11% / 8% VS3: 10% / 9% LLOQ-VS: 9% / 9% **Intra / inter-assay total error GP2015.02WST** ULOQ-VS: 2% / 4% VS1: 4% / 8% VS2: 8% / 12% VS3: 15% / 13% LLOQ-VS: 10% / 15%	

Validation parameter	Specification	Validation result	Evaluation
Calibration curve / Linearity	Calculation of inter-assay precision and accuracy of all calibrator concentrations of all valid experimental runs. Linear regression of expected versus determined concentrations. Inter-assay precision CV (%) ≤ 20; at LLOQ & ULOQ ≤ 25 Inter-assay accuracy 80% - 120%; at LLOQ & ULOQ 75% - 125% Coefficient of determination (r^2) ≥ 0.980	Inter-assay precision (CV (%)): 0% - 4% Inter-assay accuracy: 97% - 101% Coefficient of determination (r^2) = 1.000	Passed
Assay range	The calibration curve consists of 7 calibration curve samples, ranging from 15.0 ng/mL to 400.0 ng/mL.	All calibration curve samples of all validation runs passed the acceptance criteria.	n/a
Robustness	The impact of three different wash devices, different analysts, and three different microtiter plate readers were evaluated as part of the inter-assay precision parameter. Acceptance criteria: see inter-assay precision and accuracy section.	Execution of the assay by three different analysts and use of different devices/equipment had no impact on inter-assay precision. See inter-assay precision and accuracy results.	Passed
Freeze / thaw stability	[Module 5.3.1.4 BA12008-R] (HV) [Module 5.3.1.4 BA13005-R] (Psoriasis)	5 cycles 5 cycles	n/a
Short-term stability at 2-8°C	[Module 5.3.1.4 BA12008-R] (HV) [Module 5.3.1.4 BA13005-R] (Psoriasis)	3 days 3 days	n/a
Short-term stability at RT	[Module 5.3.1.4 BA12008-R] (HV) [Module 5.3.1.4 BA13005-R] (Psoriasis)	4 hours 20 hours	n/a
Long-term stability at -20°C	[Module 5.3.1.4 BA12008-R-Amendment 1] (HV) [Module 5.3.1.4 BA13005-R] (Psoriasis)	6 months 8 months	n/a

Validation parameter	Specification	Validation result	Evaluation
Long-term stability at -70°C	[Module 5.3.1.4 BA12008-R- Amendment 1] (HV) [Module 5.3.1.4 BA13005-R] (Psoriasis)	6 months 13 months	n/a
Dilution linearity	Five dilution series (8,000.0 ng/mL to 25.0 ng/mL) Mean precision of nominal concentration after multiplication with the dilution factor CV (%) ≤ 20 Mean accuracy of nominal concentration after multiplication with the dilution factor 80% - 120% Lack of hook effect: Concentrations > ULOQ (8,000 ng/mL, 1,600 ng/mL) measured > ULOQ	**GP2015-LYVI** Nominal conc. / CV (%) / Accuracy (%) 8,000.0 / n/a / n/a 1,600.0 / n/a / n/a 300.0 / 2 / 95 150.0 / 2 / 98 75.0 / 2 / 99 25.0 / 3 / 105 8,000.0 & 1,600.0 ng/mL > ULOQ **Enbrel®-LYVI** Nominal conc. / CV (%) / Accuracy (%) 8,000.0 / n/a / n/a 1,600.0 / n/a / n/a 300.0 / 5 / 112 150.0 / 4 / 113 75.0 / 3 / 116 25.0 / 6 / 119 8,000.0 & 1,600.0 ng/mL > ULOQ	Passed
Comparability	Ratio of mean etanercept concentrations determined in inter-assay measurements at ULOQ, VS1, VS2, VS3, and LLOQ levels for each pair of test items 1 - 3: 0.8 - 1.25 Inter-assay precision CV (%) ≤ 20; at ULOQ & LLOQ ≤ 25 Inter-assay accuracy 80% - 120%; at ULOQ & LLOQ 75% - 125%	**Ratio of GP2015-LYVI to Enbrel®-LYVI** ULOQ-VS: 0.98 VS1: 0.96 VS2: 0.96 VS3: 0.97 LLOQ-VS: 0.99 **Ratio of GP2015-LYVI to GP2015.02WST** ULOQ-VS: 0.96 VS1: 0.94 VS2: 0.93 VS3: 0.94 LLOQ-VS: 0.93 **Ratio of Enbrel®-LYVI to GP2015.02WST** ULOQ-VS: 0.98 VS1: 0.97 VS2: 0.96 VS3: 0.96 LLOQ-VS: 0.94 See inter-assay precision results. See inter-assay accuracy results.	Passed

Validation parameter	Specification	Validation result	Evaluation
Target tolerance	Tumor necrosis factor alpha (TNF-α) concentration which did not prevent quantification of the drug with following predefined acceptance criteria Accuracy: 80% - 120% at VS1 and VS3, 75% - 125% at LLOQ-VS	**GP2015-LYVI target tolerance:** 80 pg/mL at VS1, VS3, and LLOQ-VS **Enbrel®-LYVI target tolerance:** 80 pg/mL at VS1, VS3, and LLOQ-VS	Determined
ADA tolerance	ADA / drug (= test item) mass ratio which did not prevent quantification of the drug with following predefined criteria Accuracy: 80% - 120% at VS1 and VS3, 75% - 125% at LLOQ-VS	**GP2015-LYVI ADA tolerance level:** VS1: 2.0 VS3: 2.2 LLOQ-VS: 2.3 **Enbrel®-LYVI ADA tolerance level:** VS1: 2.0 VS3: 2.2 LLOQ-VS: 6.7	Determined
Incurred sample reanalysis of study CGP2015_2106	The concentration obtained for the initial analysis and the concentration obtained by reanalysis should be within 30% of their mean (± 15% of their mean) for at least 67% of the repeats.	140 samples of 1743 samples (8%) were re-analyzed. 139 of 140 samples (99%) fulfilled the acceptance criteria.	Passed

ULOQ: 400 ng/mL; VS1: 300 ng/mL; VS2: 120 ng/mL; VS3: 45 ng/mL; LLOQ: 15 ng/mL

Source: [Module 5.3.1.4 BA20007-R-Table 3-1], Module 5.3.1.4 BA19003-R-Section 3.7.1], Module 5.3.1.4 BA19003-R-Section 4.5]

Source: Table 1-1 of Summary of biopharmaceutic studies

Table 7. Summary of the established long-term stability of etanercept by (b) (4) in human serum from healthy volunteers and patients

Method Validation Number	Dates of Conduct	Matrix	Storage condition	Established LTS Duration
BA12008-RA01	(b) (4)	human serum (healthy)	-20°C and -70°C	6 months (-20°C and -70°C)
BA13005-R		human serum (psoriasis)	-20°C and -70°C	8 months (-20°C); 13 months (-70°C)
BA15026-R		human serum (RA)	-20°C and -70°C	1 months (-20°C); 18 months (-70°C)
BA20007-R		human serum (healthy)	NA	Not tested
BA18020-R		human serum (healthy)	-70°C	24 months

Source: Table in page 2 of the OSIS review memo by Dr. Yiyue Zhang dated November 30, 2021.

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