# Cross-Discipline Team Leader Review/ Division Summary Review

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| **Date** | March 20, 2023 |
| **From** | Amit Golding, MD (Medical Officer)<br>Raj Nair, MD (Clinical Team Leader)<br>Sanjida Mahjabeen, PhD (Clinical Pharmacology Reviewer)<br>Ping Ji, PhD (CDTL)<br>Ozlem Belen, MD, Deputy Director, DRTM<br>Nikolay Nikolov, MD, Division Director, DRTM |
| **Subject** | Cross-Discipline Team Leader Review<br>Division Summary Review |
| **BLA # and Supplement#** | 761071 Supplement 14 |
| **Applicant** | Sandoz Inc |
| **Date of Submission** | May 20, 2022 |
| **BSUFA Goal Date** | March 20, 2023 |
| **Proprietary Name/Proper Name** | Hyrimoz (adalimumab-adaz) |
| **Reference Product Proprietary Name** | Humira |
| **Strengths and Presentations** | 10 mg/0.1 mL and 20 mg/0.2 mL in a prefilled syringe (PFS); and<br>40 mg/0.4 mL, and 80 mg/0.8 mL in both prefilled syringe (PFS) and autoinjector |
| **Recommended Dosing Regimen** | 40 mg subcutaneously every 2 weeks. No new dosing regimens are proposed with this supplement. |
| **Recommendation on Regulatory Action** | Approval |

## 1. Introduction

The Applicant, Sandoz, submitted Supplement-14 to Biologic License Application (BLA) 761071 to propose a high-concentration formulation (GPN017B1 HCF, 100 mg/mL). Hyrimoz is currently approved as low-concentration formulation (GP2017 LCF, 50 mg/mL). The 100 mg/mL HCF single-dose prefilled glass syringe will include 4 strengths: 10 mg/0.1 mL, 20 mg/0.2 mL, 40 mg/0.4 mL, and 80 mg/0.8 mL. The 100 mg HCF single-dose prefilled pen will include two strengths: 40 mg/0.4 mL and 80 mg/0.8 mL. To support the approval of high-concentration formulation, the Applicant submitted analytical and clinical pharmacokinetics (PK) data. The PK comparability study (CGPN017B12101) compared the PK, safety and tolerability of GPN017B1 HCF and GP2017 LCF administered to healthy subjects. This

memorandum provides an overview of the supplement with a focus on the data relevant to whether the supplement is approvable under section 351(k) of the Public Health Service Act.

## 2. Background and Regulatory History

Adalimumab- adaz (Hyrimoz) is a recombinant human immunoglobulin (Ig) G1 monoclonal antibody (mAb) against tumor necrosis factor (TNF)-alpha. Adalimumab- adaz was approved as a biosimilar to US-licensed Humira (US-Humira) under BLA 761071 on Oct 30, 2018 (see CDTL Review, dated Oct 30, 2018) under section 351(k) of the Public Health Service Act, for the treatment of:

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 PsA.
4. Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.
5. Crohn's Disease (CD): treatment of moderately to severely active Crohn's disease in adults.
6. Ulcerative Colitis (UC): treatment of moderately to severely active ulcerative colitis in adult patients. Limitations of Use: Effectiveness has not been established in patient show have lost response to or were intolerant to TNF blockers.
7. Plaque Psoriasis (Ps): 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.

In the original BLA, Hyrimoz was approved in the following presentations:

- 40 mg/0.8 mL solution in a single-dose prefilled syringe (PFS) and
- 40 mg/0.8 mL solution in a single-dose Sensoready autoinjector (AI)

On March 28, 2022, the CMC supplement (BLA 761071 Supplement 11) was approved for the 10 mg/0.2 mL pre-filled syringe (PFS) for pediatric polyarticular juvenile idiopathic arthritis (pJIA) patients who weigh 10 kg to less than 15 kg (see Clinical Review/CDTL Review/Division Director Summary Review dated March 28, 2022).

On July 27, 2022, the efficacy supplements (761071/S-010 and S-012) were approved to expand the indications of Juvenile Idiopathic Arthritis (JIA) and Crohn's Disease (CD) that were previously under orphan exclusivity to 2 years of age and older for JIA and 6 years of age and older for CD (see Clinical Review/CDTL Review/Division Director Summary Review dated July 27, 2022).

On July 02, 2019, a BPD Type 2 meeting included discussion on the single-dose comparative PK study CGPN017B12101 in healthy adult male subjects to demonstrate PK comparability between Hyrimoz-HCF (100 mg/mL) and Hyrimoz-LCF (50 mg/mL). The meeting also discussed the in vitro characterization of Hyrimoz-HCF, the analytical comparability between Hyrimoz-HCF and Hyrimoz-LCF, analytical similarity between Hyrimoz-HCF and US-Humira-HCF, and the need to conduct nonclinical in vivo studies.

On October 16, 2020, a BPD Type 2 meeting included discussion on the demonstration of analytical similarity given the observed difference in mean protein concentration between Hyrimoz HCF and US Humira HCF. FDA recommended that batches of product manufactured using the proposed commercial process should be used in the PK study comparing Hyrimoz HCF to Hyrimoz LCF.

On March 16, 2021, a BPD Type 2 meeting included discussion on the proposed comparative analytical assessment protocol between Hyrimoz HCF and Humira HCF. FDA provided a list of comparative analytical assessment required to establish analytical similarity.

On April 9, 2022, a BPD Type 2 meeting included discussion on the sBLA structure and the justification needed for demonstrating no differences between the Hyrimoz-LCF (40 mg/0.8 mL) autoinjector and the proposed Hyrimoz-HCF (40 mg/0.4 mL and 80 mg/0.8 mL) autoinjectors in device performance and PK profile. FDA recommended that all specifications and the relevant testing should be provided. Additionally, the meeting discussed the submission of the additional real time stability data during the review phase, allowing extension of the DS/DP shelf-life claims upon approval, to which FDA disagreed and requested all the data submitted at the time of sBLA submission.

On May 20, 2022, the Applicant submitted this supplemental BLA (sBLA) to propose the addition of:

- 10 mg/0.1 mL and 20 mg/0.2 mL in a prefilled syringe (PFS); and
- 40 mg/0.4 mL, and 80 mg/0.8 mL in both prefilled syringe (PFS) and autoinjector

To support these presentations, the Applicant conducted the following assessments:

- Analytical comparability studies between GPN017B1 and GP2017
- A comparative PK study in healthy subjects using GPN017B1 and GP2017
- A comparative analytical assessment (CAA) of US-Humira HCF and GPN017B1 complementing the comparability studies
- A bridging study between the currently approved version of the (b) (4) autoinjector used for GP2017 and the version of the (b) (4) autoinjector proposed for GPN017B1
- Usability engineering activities to support the assessment of the safe and effective use of the GPN017B1 presentations

# 3. Product Quality

*Product Quality Review Team: Xiaoshi Wang/Yan Wang/Patrick Lynch*
*CDRH Review Team: Dunya Karimi/Courtney Evans*
*OPMA Review Team- Madushini Dharmasena/Candace Gomez-Broughton*
*DMEPA Review Team: Neha Kuma/Oluwamurewa Oguntimein*

## 3.1 Product Quality

The product quality review of this supplement included the following assessment:

- The manufacturing process characterization and process validation studies
- The comparability study between GPN017B1 DS and GP2017 DS, a comparability study between GPN017B1 DP and GP2017 DP
- The comparative analytical assessment (CAA) between Hyrimoz HCF and US-licensed Humira HCF
- Critical quality attributes (CQA) of GPN017B1 DP lots
- The additional proposed changes for purity and aggregation by SEC at (b) (4) Chromatography step
- Immunogenicity assay

Compared with the approved GP2017 DP, the major change for GPN017B1 DP is the change of formulation.

The GPN017B1 DP manufacturing process is based on GP2017 DP manufacturing process with modifications to accommodate the higher protein concentration. In addition to the introduction of GPN017B1 DP, the Applicant also proposes several changes to GPN017B1 DS manufacturing process to keep the manufacturing process and control elements of GP2017 DS and GPN017B1 DS harmonized. The GPN017B1 DS and bulk DP will still be manufactured at Sandoz GmbH Schaftenau, Austria (BPS, FEI: 3004828473), which is the same facility for manufacturing GP2017 DS and bulk DP. BPS facility is also the device assembly site for GPN017B1 final combination DP of all four new strengths. The same container closure system will also be used for GPN017B1 bulk DP as the approved GP2017 bulk DP. The product quality team considers that the manufacturing process characterization and process validation studies are sufficient to support the GPN017B1 DS and DP manufacturing processes. All GPN017B1 PPQ DS and DP batches were successfully manufactured, and the results demonstrate that the GPN017B1 DS and DP processes are well controlled, consistent and reproducible.

The product quality team considers that the results from a comparability study between GPN017B1 DS and GP2017 DS, a comparability study between GPN017B1 DP and GP2017 DP are sufficient to demonstrate that the GPN017B1 are comparable with the approved GP2017.

The product quality team considers that the results from a comparative analytical assessment (CAA) between Hyrimoz HCF and US-licensed Humira HCF are sufficient to support that Hyrimoz HCF is highly similar to US-licensed Humira HCF for all four strengths notwithstanding minor differences in clinically inactive components.

The product quality team considers the tested critical quality attributes (CQA) are appropriate and sufficient. The results from GPN017B1 DP lots are all within the justified and defined quality ranges (QR) of the US-licensed Humira HCF lots. The strength of GPN017B1 10 mg/0.1 mL, 20 mg/0.2 mL, 40 mg/0.4 mL and 80 mg/0.8 mL, is the same as that of U.S.-licensed Humira HCF 10 mg/0.1 mL, 20 mg/0.2 mL, 40 mg/0.4 mL and 80 mg/0.8 mL, respectively.

In the current supplement, the Applicant only performed simulated shipping studies to support the commercial shipping and handling conditions. A real time shipping study is needed to verify the results obtained from the simulated validation study for the finished product. During the review cycle, the Applicant agreed the following Post-Marketing Commitment (PMC):

**Perform a real time shipping qualification study to evaluate the impact of commercial shipping and handling conditions of the GPN017B1 finished products on product quality.**

**Final report submission date: 03/2024**

Also, the product quality team considers the following additional proposed changes for purity and aggregation by SEC at (b) (4) Chromatography step acceptable:

(b) (4)

In addition, the product quality team considers that the immunogenicity assays to detect anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) in samples from the clinical study CGPN017B12101 (a clinical study to support PK comparability between Hyrimoz HCF and Hyrimoz LCF) is suitable.

Based on all above assessment, product quality team recommended approval of Supplement-14 from the quality perspective. We agree with the conclusions and the

recommendations by the product quality review team.

The product quality microbiology review team evaluated the sterility assurance and quality microbiology data. The product quality microbiology review team recommended approval of this supplement from a product quality microbiology and sterility assurance perspective. We agree with the product quality microbiology review team's recommendation.

### 3.2 Devices

The device review included the following assessment:

- A bridging study between the currently approved version of the (b) (4) autoinjector used for GP2017 and the version of the (b) (4) autoinjector proposed for GPN017B1

The drug device combination product (DDC) GPN017B1 03 consists of the following components which are all sourced from (b) (4) (Figure 1):

- 1 mL long glass syringe with staked 29G thin wall (TW) ½ inch needle and rigid needle shield. The syringe is pre-filled with either 10 mg/0.1 mL or 20 mg/0.2 mL of GPN017B1 drug product (INN: Adalimumab)
- Plunger rod
- Backstop

**Figure 1. Illustration of GPN017B1 (b) (4) autoinjector**


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Source: CDRH review

The primary container closure (i.e., the PFS closed with the needle shield and the plunger stopper) for the Hyrimoz-HCF (40 mg/0.4 mL and 80 mg/0.8 mL) AI is identical to the one submitted for Hyrimoz-LCF under BLA 761071 (b) (4) The (b) (4) autoinjector consists of 16 components. Of these 16 components, only 2 differ in their dimensions and spring strength to adapt for the different fill volumes (0.4 mL and 0.8 mL) and the different viscosities due to different concentrations (50 mg/mL and 100 mg/mL). One component differs in the ID marking that is printed on each rear subassembly. There are no differences in the materials used for both products.

The CDRH/ODE review team has determined that the device description and design control document that included the performance requirements of the device, functional requirements, and user interface requirements of the device, and a biocompatibility evaluation of the device constituent are adequate.

A pre-approval inspection was required. Given that the facilities inspection was conducted 3/22/2018 to 8/18/2018, which inspection covered drug current good manufacturing practice (CGMP), so the inspection was classified Voluntary Action Indicated (VAI).

The CDRH/ODE review team has determined, and we agree that the device constituent parts of the combination product are approvable.

### 3.2 Division of Medication Error Prevention and Analysis (DMEPA)

The Applicant conducted comparative analyses comparing their proposed high concentration prefilled syringe to US-licensed Humira and their proposed prefilled syringe with needle shield and autoinjector with the approved low concentration Hyrimoz prefilled syringe with needle safety device and autoinjector, respectively. DMEPA reviewed the comparative analyses and determined that the Applicant does not need to submit human factor validation results to support their marketing application for their proposed high concentration prefilled syringe, prefilled syringe with needle shield, and autoinjector. Additionally, the Applicant conducted a HF validation study and supplemental HF study for the proposed high concentration starter packs. The HF validation study included 60 participants and the supplemental HF study included 33 participants. Participants were stratified primarily by distinct user groups (adult patients and adolescent patients). The results showed there were use errors, close calls and use difficulties associated with the critical and non-critical tasks. Based on DMEPA's review of the available participants' subjective feedback, and the Applicant's mitigation strategies and root cause analysis, DMEPA did not identify any additional risk mitigations to address the use errors, close calls, and use difficulties. As such, DMEPA did not have any recommendations for the Applicant. Based on this assessment, DMEPA recommended approval of Supplement-14 from a human factors perspective. We agree with the conclusion by DMEPA.

### 3.4 Office of Study Integrity and Surveillance (OSIS)

On June 30th, 2022, an inspection request was sent to OSIS for both clinical and analytical sites (b) (4) designated for this supplement. As of October 5, 2022, the Division of New Drug Study Integrity (DNDSI) within OSIS determined that an inspection is not needed at this time for the clinical site in Florida. The Office of Regulatory Affairs (ORA) inspected the clinical site in November 2021, which falls within the surveillance interval.

OSIS has conducted a remote regulatory assessment (RRA) of the analytical portion of Study CGPN017B12101 (BLA 761071/S-014) conducted at (b) (4) from (b) (4) The following studies were reviewed:

- Study CGPN017B12101 (BLA 761071/S014): "A randomized, double-blind, parallel, two-arm study to compare PK, safety and immunogenicity of GPN017B1(Hyrimoz® high concentration formulation; 100 mg/mL) with GP2017 (Hyrimoz® low concentration formulation; 50 mg/mL) after a single dose of 40 mg subcutaneous injection in healthy male subjects"
- PK Assay: BA21001-R "Determination of adalimumab in serum samples of healthy male; subjects of clinical study CGPN017B12101 by ELISA GCP"
    - Sample Analysis Period: September 29, 2021 – January 14, 2022

- Anti-drug Antibody (ADA) Assay: BA21002-R "Determination of anti-adalimumab antibodies in serum samples of healthy male subjects of clinical study CGPN017B12101 by ECL GCP"
    - Sample Analysis Period: April 28, 2021 – January 12, 2022
- Neutralizing Antibody (NAb) Assay: BA21003-R "Determination of neutralizing anti-adalimumab antibodies in serum of healthy male subjects of clinical study CGPN017B12101 by ELISA GCP"
    - Sample Analysis Period: September 29, 2021 – January 11, 2022

No issues were noted for the bioanalytical method to determine study drug and ADA assay. However, during initial review, OSIS noted that the firm did not provide adequate data to verify that a validated method was used to determine the presence of neutralizing antibodies (NAb) in healthy human serum samples for study CGPN017B12101 (Analytical Report: BA21003-R). Specifically, a new cut point (4.9% neutralization or ≤ control OD value * 0.951) and new ratio-based acceptance criteria were not applied to the data from the original NAb method validation BA15002-R to ensure that critical parameters (e.g., precision, selectivity, drug tolerance) remained valid. Additionally, there was no partial validation of the NAb assay in healthy human serum.

As part of their response to OSIS inquiry, (b) (4) provided an amendment to method validation BA15002R. The amendment includes- 1) a definition of the new raw data-based acceptance criteria for the NAb assay used in study BA21003R; 2) the data set used to recalculate the NAb assay cut point, sensitivity, and low positive control (LPC) in healthy human serum; 3) the re-evaluation of validation parameters using the new acceptance criteria and cut point; 4) new data demonstrating selectivity of the assay with the new LPC to confirm the suitability of the re-calculated LPC and cut point; and 5) an evaluation of the overall method precision using data from study BA21003. Based on the re-evaluation of the NAb assay parameters using the new acceptance criteria and cut point, (b) (4) considers the Nab method used in study BA21003R fully validated for the detection of neutralizing anti-adalimumab antibodies in healthy human serum.

Based on the evaluation of the firm's response, OSIS indicated that the re-evaluated and additional data provided by (b) (4) were sufficient to ensure that the NAb method used to determine the presence of neutralizing anti-adalimumab antibodies in healthy human serum is valid. Thus, OSIS concluded that all data from study BA21003R are reliable ((Memorandum on Remote regulatory assessment (RRA) of (b) (4) by OSIS; January 18, 2023; DARRTS Ref ID: 5111532)[1].

# 4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA. There are no nonclinical pharmacology/toxicology issues that would preclude approval.

[1] Reference ID: 5111532

# 5. Clinical Pharmacology

*Clinical Pharmacology Primary Reviewer: Sanjida Mahjabeen, PhD*
*Clinical Pharmacology Team Leader: Ping Ji, PhD*

Sandoz submitted this sBLA proposing a new high-concentration formulation (HCF, 100 mg/mL). Study GPN017B12101 was conducted to demonstrate PK comparability between Hyrimoz-HCF (100 mg/mL, 40 mg/0.4 mL, PFS) and Hyrimoz-LCF (50 mg/mL, 40 mg/0.8 mL, PFS).

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under sBLA 761071 (S014) and finds the sBLA approvable. We agree with the clinical pharmacology team's recommendation.

**Clinical Pharmacology Study Design Features**

The study GPN017B12101 was a multicenter, randomized, double-blind, parallel arm, single dose study conducted in three US sites. In this study, 330 healthy male subjects were randomized to receive a single dose of one of the below treatments via SC injection:

- Reference: Hyrimoz-LCF 40 mg/0.8 mL (Presentation: PFS, Lot no. KL7357, Apr-2022)(n=162);
- Test: Hyrimoz-HCF 40 mg/0.4 mL (Presentation: PFS, Lot no. 15931.4, Apr-2022) (n=168)

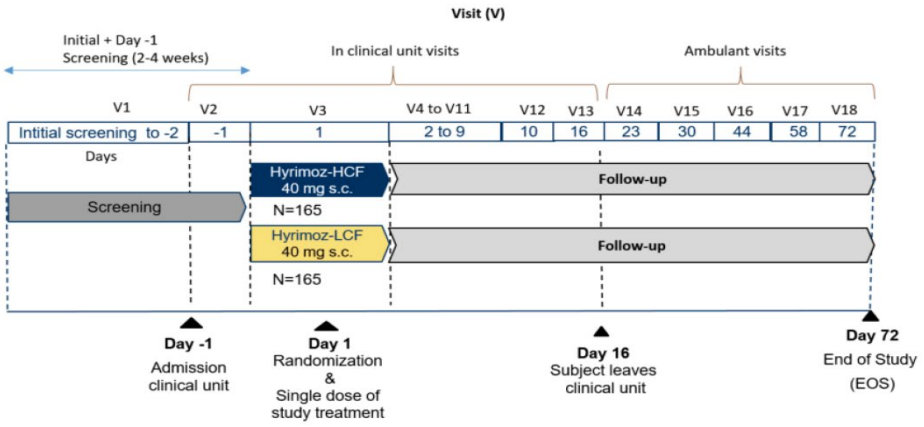
A parallel-arm study design was chosen considering the long terminal half-life (ranging from 11 to 18 days) and the known impact of ADAs on the PK of the study drug.

Blood samples for PK assessment withdrawn on Day 1 (-1 hour (pre-dose)), 6 hours and 9 hours post-dose), daily from Day 2 to Day 10 (included), and at Days 16, 23, 30, 44, 58 and 72. For Immunogenicity assessment, blood samples for ADA quantification were obtained at Day 1 (pre-dose, -1 hour), Post-dose at Days 3, 7, 10, 16, 23, 30, 44, 58, 72, Unscheduled.

All confirmed positive ADA samples were analyzed in the competitive ligand binding assay to evaluate the neutralizing potential of the study drug-specific antibodies.

The sponsor indicated that Study CGPN017B12101 followed the study design used in the PK bridging study M10-867 of US-Humira, comparing PK profiles of the 100 mg/mL concentration formulation to the marketed US-Humira 50 mg/mL formulation. A schematic presentation of the study design is shown in Figure 2.

**Figure 2. Study Design of GPN017B12101**




Source: Clinical study report (Figure 9.1) [2]

## Study Endpoints

In study GPN017B12101, designated primary PK endpoints to establish PK comparability between Hyrimoz HCF and Hyrimoz LCF were Cmax and $AUC_{0-360}$.

## PK dataset

It is of note that total of 331 subjects were randomized in this study, and 330 subjects received at least 1 dose of study treatment and were included in the safety assessment. However, the sponsor's PK population comprised 300 subjects after exclusion of 30 subjects. Among, 30 excluded subjects, 1 subject was randomized by mistake and discontinued the study before receiving study treatment (Subject (b) (6)), this subject's data was not transferred into the database. 18 subjects were excluded from the PK analysis because of major protocol deviations: a. 1 subject with a positive SARS-CoV-2 test result during the study that was not discontinued in error; b. 12 subjects were excluded because they did not complete the study or had a positive SARS-CoV-2 test result during the study. Reviewer's analysis includes all subjects except Subject (b) (6), as the subject was randomized by mistake and the PK concentration data was not transferred to the database. Additionally, a sensitivity analysis was conducted excluding subjects as indicated by the sponsor, the PK comparability conclusion was not affected because of exclusion of subjects.

[2] \\CDSESUB1\EVSPROD\bla761071\0136\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\cgpn017b12101\cgpn017b12101-report-body.pdf)

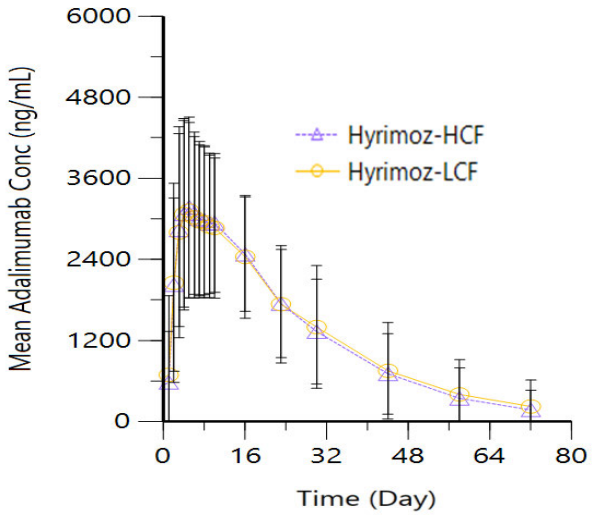
**Bioanalytical PK Method and Performance**

The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated. Serum concentrations of study drug were quantified using an enzyme-linked immunosorbent assay (ELISA). See Appendix 14.4.1 for further details on the bioanalytical method and performance in Study CGPN017B12101.

**PK Assessment**

The serum concentration-time profile of the two products for the PK comparability study (Study CGPN017b12101) is shown below (**Figure 3**). The 90% CI for the geometrics means ratios (GMRs) for the maximum observed drug concentration (Cmax) and area under the serum drug concentration-time curve ($AUC_{inf}$ and $AUC_{360}$) were contained within the prespecified criteria of 80% to 125% (**Table 2**).

**Figure 3. Mean (SD) serum concentration-time profiles or Hyrimoz LCF vs Hyrimoz HCF**




Source: Reviewer's analysis based on ADPC.xpt for CGPN017B12101

**Table 1. Summary of PK parameters in study CGPN017B12101**

| PK parameters | Hyrimoz HCF (Test) (n=162) | | | Hyrimoz LCF (Ref) (n=167) | | |
|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD |
| AUC0-360 (h*ng/mL) | 162 | 981556.79 | 359328.66 | 167 | 960714.84 | 385785.80 |
| AUC0-inf (h*ng/mL) | 158 | 2514051.34 | 1168336.70 | 161 | 2585772.16 | 1432623.82 |

| | | | | | | |
|---|---|---|---|---|---|---|
| AUC0-last (h*ng/mL) | 162 | 2110867.67 | 970565.02 | 167 | 2112058.37 | 1156335.10 |
| Cmax (ng/mL) | 162 | 3521.09 | 1367.20 | 167 | 3501.80 | 1604.80 |
| t1/2 (h) | 158 | 391.34 | 229.10 | 161 | 409.45 | 253.78 |
| tmax (h) | 162 | 153.08 | 98.20 | 167 | 145.06 | 109.88 |

Source: Reviewer's Analysis based on ADPC.XPT, Study CGPN017B12101

**Table 2. Statistical analysis of primary PK comparability between Hyrimoz-HCF vs Hyrimoz-LCF (Ref)**

| PK parameters | LS Geometric Mean (n) | | Point Estimate T/R ratio (90% CI) |
|---|---|---|---|
| | Hyrimoz-HCF (Test) (n=162) | Hyrimoz – LCF (Ref) (n=167) | |
| $C_{max}$ (ng/mL) | 3254.75 | 3170.28 | 102.66 (94.99- 110.95) |
| $AUC_{inf}$ (h*ng/mL) | 2410034 | 2506527 | 96.15 (85.11- 108.61) |
| $AUC_{0-360}$ (h*ng/mL) | 891111.51 | 909997.41 | 101.34 (88.41-116.17) |

Source: Reviewer's Analysis based on ADPC.XPT, Study CGPN017B12101

## Immunogenicity Assessment

### Design features of the clinical immunogenicity assessment

In study GPN017B12101, the immunogenicity assessment was conducted following administration of single equivalent dose of Hyrimoz-LCF and Hyrimoz-HCF in healthy subjects.

As high levels of study drug in the serum samples can interfere with the ADA assay, the drug tolerance of the assays was evaluated during the assay method validation. In addition, study drug concentrations were determined for each ADA sample to assure reliable ADA results. The drug tolerance of the ADA assay was above the highest drug concentration measured in the clinical study.

### Immunogenicity endpoints

The formation of ADA and neutralizing activity of ADA were evaluated for immunogenicity assessment. The immune response after study drug administration was evaluated by a multi-tiered approach:

i) A validated bridging immunogenicity assay was used for the screening, confirmation, and titration of binding ADAs, and
ii) A validated competitive ligand binding assay (CLB assay) was used for assessing the neutralizing capacity of the antibodies (NAb).

Refer to OBP immunogenicity review for more details.

**Immunogenicity data**

The sampling plan is adequate to capture baseline, early onset and dynamic prolife of ADA formation:

- Study GPN017B12101: Serum samples for ADA quantification were obtained at day 1 (pre-dose, -1 hour), post-dose at Days 3, 7, 10, 16, 23, 30, 44, 58, 72.

All confirmed positive ADA samples were analyzed in the competitive ligand binding assay to evaluate the neutralizing potential of study drug-specific antibodies

**Incidence of ADA**

In Study CGPN017B12101, the numbers and proportions of subjects with positive ADA responses and with NAbs were comparable between the Hyrimoz-HCF and Hyrimoz-LCF groups overall as well as at all individual visits (Table 4).

**Table 3. Immunogenicity results for binding ADA and NAb in Study CGPN017B12101**

| Visit | Result | Hyrimoz-HCF (Test) N=162 n (%) | Hyrimoz-LCF (Ref) N=168 n (%) |
|---|---|---|---|
| Day 1 (Pre-dose) | ADA Positive | 1 (0.6) | 0 |
| | NAb Positive | 1 (0.6) | 0 |
| Day 3 | ADA Positive | 0 | 0 |
| | NAb Positive | 0 | 0 |
| Day 7 | ADA Positive | 2 (1.2) | 4 (2.4) |
| | NAb Positive | 2 (1.2) | 4 (2.4) |
| Day 10 | ADA Positive | 2 (1.2) | 5 (3.0) |
| | NAb Positive | 2 (1.2) | 4 (2.4) |
| Day 16 | ADA Positive | 58 (35.8) | 50 (29.8) |
| | NAb Positive | 26 (16.0) | 24 (14.3) |
| Day 23 | ADA Positive | 68 (42.0) | 61 (36.3) |
| | NAb Positive | 34 (21.0) | 40 (23.8) |
| Day 30 | ADA Positive | 43 (26.5) | 47 (28.0) |
| | NAb Positive | 29 (17.9) | 36 (21.4) |
| Day 44 | ADA Positive | 41 (25.3) | 44 (26.2) |
| | NAb Positive | 40 (24.7) | 44 (26.2) |
| Day 58 | ADA Positive | 68 (42.0) | 72 (42.9) |

| | | | |
|---|---|---|---|
| | NAb Positive | 67 (41.4) | 72 (42.9) |
| Day 72 | ADA Positive | 94 (58.0) | 90 (53.6) |
| | NAb Positive | 93 (57.4) | 90 (53.6) |
| Overall (up to Day 72) | ADA Positive | 112 (69.1) | 109 (64.9) |
| | ADA Negative | 49 (30.2) | 59 (35.1) |
| | NAb Positive | 102 (63.0) | 103 (61.3) |
| | Transient | 18 (11.1) | 17 (10.1) |

Source: CSR Study CGPN017B12101 V1: Table 12.5

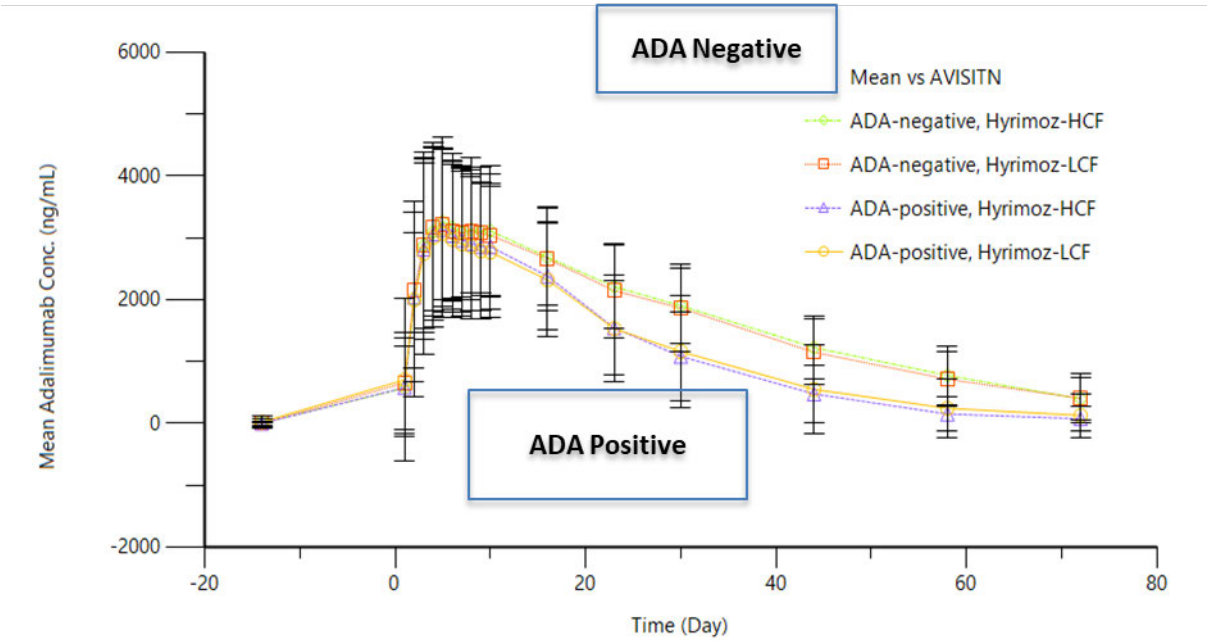
**Incidence of NAb**

In Study CGPN017B12101, the overall incidence of neutralizing antibodies (NAb) formation in the in healthy subjects following single dose of Hyrimoz-HCF (test) vs Hyrimoz-LCF (Ref) were 63.0%, and 61.3%, respectively (Table 4).

**Impact of immunogenicity on PK**

The PK exposure for Hyrimoz HCF and LCF were comparable within ADA positive and negative subgroups (Figure 6, Table 5).

**Figure 4. Impact of ADA status on PK exposure of Hyrimoz-LCF and Hyrimoz-HCF**




Source: Review's analysis using ADPC.xpt from CSR of Study CGPN017B12101

**Table 4. Summary of PK Parameters by Treatment and Overall ADA Status (Study CGPN017B12101)**

| PK parameters | Hyrimoz-HCF (Test) (n=49) | | Hyrimoz-LCF (Ref) (n=58) | |
|---|---|---|---|---|
| | ADA Negative | | | |
| | Mean | SD | Mean | SD |
| Cmax (ng/mL) | 3290257.59 | 1306531.48 | 3127399 | 1359359.62 |
| AUC0-inf (h*ng/mL) | 1026279.56 | 359110.11 | 1001719 | 367189.2106 |
| AUC0-360 (h*ng/mL) | 2797066 | 968694.16 | 2574843 | 1105427.352 |
| AUC0-last (h*ng/mL) | 13.83 | 6.152 | 14.39 | 8.526 |
| t1/2 (h) | 524.7 | 167.6 | 517.575 | 199.431 |
| tmax (h) | 167.54 | 111.46 | 132.851 | 81.68 |
| | ADA Positive | | | |
| **PK parameters** | **Hyrimoz-HCF (Test) (n=109)** | | **Hyrimoz-LCF (Ref) (n=107)** | |
| Cmax (ng/mL) | 2165115 | 910716.48 | 2296904 | 1392161.03 |
| AUC0-inf (h*ng/mL) | 962164 | 359280.8 | 938896 | 395241.29 |
| AUC0-360 (h*ng/mL) | 1813313 | 810325.67 | 1865806 | 1110874.45 |
| AUC0-last (h*ng/mL) | 12.96 | 10.098 | 14.07 | 12.35 |
| t1/2 (h) | 331.39 | 228.3 | 351.77 | 261.53 |
| tmax (h) | 146.8 | 91.68 | 151.55 | 122.11 |

Source: Reviewer's Analysis based on ADPC.XPT, Study CGPN017B12101

## Impact of immunogenicity on Safety

The incidence of treatment-emergent adverse events (TEAEs) was similar between treatment groups in ADA negative and ADA positive subjects (Table 7 and Table 8).

**Table 5. Summary of subjects reporting at least 1 TEAE in ADA population**

| | ADA Negative (Total n=108; 56.5% reported at least 1 TEAE) | | ADA Positive (Total n=222, 51.4% reported at least 1 TEAE) | |
|---|---|---|---|---|
| | **Hyrimoz-HCF (Test)** | **Hyrimoz-LCF (Ref)** | **Hyrimoz-HCF (Test)** | **Hyrimoz-LCF (Ref)** |
| No. and % Subject reporting at least 1 TEAE | 27 (55.1%) | 34 (57.6%) | 53 (46.9%) | 61 (56.0%) |

Source: Adapted from CSR Study CGPN017B12101 V1: Table 14.3.1-3

**Table 6. TEAEs, Injection Site Reactions and Skin and Subcutaneousnous Tissue Disorder By ADA Status (Study CGPN017B12101) (Safety Population)**

| | Hyrimoz-HCF (Test) | | Hyrimoz-LCF (Ref) | |
|---|---|---|---|---|
| | ADA Positive | ADA Negative | ADA Positive N=109 | ADA Negative |

| | N=113 | N= 49 | | N=59 |
|---|---|---|---|---|
| General disorder and administration site conditions | 39 (34.5%) | 16 (32.7%) | 43 (39.4%) | 26 (44.1%) |
| Skin and subcutaneous tissue disorder | 37 (32.7%) | 13 (26.5%) | 42 (38.5%) | 21 (35.6%) |

Source: adapted from CSR of Study CGPN017B12101 Table 14.3.1-3

# 6. Clinical/Statistical-Efficacy

Not applicable.

# 7. Safety

**Deaths**

No deaths occurred in Study GPN017B12101 (Study 101).

**Serious Adverse Events**

No Serious Adverse Events occurred in Study 101.

**Adverse Events Leading to Discontinuation**

Four subjects (1.2%) discontinued the study due to TEAEs, 1 subject (0.6%) in the Hyrimoz-HCF group because of a positive SARS-CoV-2 test and 3 subjects (1.8%) in the Hyrimoz-LCF group because of a positive SARS-CoV-2 test (2 subjects) and increased blood pressure (1 subject).

**Adverse Events of Special Interest (AESI)**

AESIs for Study 101 were injection site reactions and COVID-19-related Adverse Events.

Infusion site reactions (ISRs): ISRs are a common TEAE reported with the use of adalimumab. In Study 101, ISR counts were based on the preferred term (PT) injection site reaction. Overall, for 113 subjects (34.2%), ISRs were reported during this study. There were no clinically relevant differences in the proportions of subjects reporting at least 1 ISR in the Hyrimoz-HCF group (50 subjects, 30.9%) and the Hyrimoz-LCF group (63 subjects, 37.5%).

COVID-19-related adverse events: Overall, 4 subjects (1.2%) were reported with a positive SARS-CoV-2 test during the study, 1 subject (0.6%) in the Hyrimoz-HCF group and 3 subjects (1.8%) in the Hyrimoz-LCF group.

## Common Adverse Events

Treatment emergent adverse events (TEAEs) were generally balanced between the Hyrimoz High Concentration Formulation (HCF) arm and the Hyrimoz Low Concentration Formulation (LCF) arm. The number of subjects with at least one TEAE was 80 out of 162 subjects (49.4%) in the HCF arm and 95 out of 168 subjects (56.5%) in the placebo arm.

The following is a table (Table 9) summarizing common TEAEs in the study:

**Table 7. TEAEs by primary system organ class and preferred term (at least 2% of subjects in either treatment group)**

| Primary system organ class<br>Preferred term | Hyrimoz-HCF<br>N = 162<br>n (%) | Hyrimoz-LCF<br>N = 168<br>n (%) |
|---|---|---|
| Number of subjects with at least 1 event | 80 (49.4) | 95 (56.5) |
| General disorders and administration site conditions | 55 (34.0) | 69 (41.1) |
| Injection site reaction | 50 (30.9) | 63 (37.5) |
| Investigations | 16 (9.9) | 24 (14.3) |
| Hemoglobin decreased | 4 (2.5) | 5 (3.0) |
| ALT increased | 5 (3.1) | 3 (1.8) |
| AST increased | 4 (2.5) | 4 (2.4) |
| Weight decreased | 2 (1.2) | 6 (3.6) |
| Musculoskeletal and connective tissue disorders | 8 (4.9) | 14 (8.3) |
| Back pain | 3 (1.9) | 4 (2.4) |
| Pain in extremity | 1 (0.6) | 6 (3.6) |
| Nervous system disorders | 8 (4.9) | 6 (3.6) |
| Headache | 6 (3.7) | 4 (2.4) |
| Skin and subcutaneous disorders | 10 (6.2) | 4 (2.4) |
| Rash | 4 (2.5) | 1 (0.6) |
| Gastrointestinal disorders | 8 (4.9) | 3 (1.8) |
| Respiratory, thoracic, and mediastinal disorders | 2 (1.2) | 6 (3.6) |
| Eye disorders | 1 (0.6) | 4 (2.4) |
| Injury, poisoning and procedural complications | 4 (2.5) | 1 (0.6) |

Source: Integrated Summary of Safety

## Safety Summary

Overall, the safety profiles were comparable between the two treatment groups in Study 101 and in accordance with the known safety profile of Hyrimoz and of US-Humira.

# 8. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this supplement. There were no findings in this program that would warrant a discussion at an Advisory Committee meeting.

# 9. Pediatrics

Not applicable.

# 10. Other Relevant Regulatory Issues

Not applicable.

# 11. Labeling

*Prescribing Information*

Revisions in the proposed United States Prescribing Information (USPI) update the labeling to include the HCF and to incorporate relevant information, where appropriate, from the US-licensed Humira labeling approved on February 24, 2021 (BLA 125057/S-417). Table 10 presents a high-level summary of the labeling proposal from the Applicant.

**Table 8. Summary of Significant Labeling Changes**

| Section | Labeling Changes |
|---|---|
| Highlights of PI | Revise the language in the Dosage Forms and Strengths section to the following:<br>• Single-dose prefilled pen (Sensoready Pen): 40 mg/0.8 mL, 40 mg/0.4 mL and 80 mg/0.8 mL<br>• Single-dose prefilled glass syringe (with BD UltraSafe Passive™ Needle Guard): 40 mg/0.8mL,40 mg/0.4 mL and 80 mg/0.8 mL<br>• Single-dose prefilled glass syringe: 10 mg/0.2 mL, 10 mg/0.1 mL and 20 mg/0.2 mL |

| | |
|---|---|
| Section 3 | (b) (4) |
| Sections 11 | Addition of language related with HCF |
| Section 16 | Addition of reference and information about supplying and storage/handling of the HCF presentations |
| Section 17 | Addition of instructions to the Instructions on Injection Technique section |
| Medication Guide | Addition to Medication Guide |

# 12. Postmarketing Recommendations

There are no new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement. A postmarketing commitment was requested by OBP and agreed upon with the applicant:

**Perform a real time shipping qualification study to evaluate the impact of commercial shipping and handling conditions of the GPN017B1 finished products on product quality.**

**Final report submission date: 03/2024**

# 13. Risk Evaluation and Mitigation Strategies

The review team did not identify a need for Risk Evaluation and Mitigation Strategies (REMS)

to ensure the safe use of adalimumab-adaz.

# 14. Recommended Regulatory Action

The action for this sBLA is Approval.

The Applicant provided adequate CMC, actual use human factors, device, and PK data to support approval of high-concentration formulation. FDA has also determined that the Applicant has provided adequate data and information to support a demonstration that Hyrimoz HCF is highly similar to US-Humira HCF, notwithstanding minor differences in clinically inactive components. FDA has further determined that the data and information provided by the Applicant in the BLA, including this supplement—including the data submitted from the clinical development program and the analytical similarity and comparability data—support a demonstration of no clinically meaningful differences between Hyrimoz HCF and US-Humira HCF. The conditions of use for GP2017 have been previously approved for US-Humira, and the strength, dosage form, and route of administration of GP2017 HCF are the same as those of US-Humira HCF. The totality of the data and information provided in the BLA, including this supplement, support licensure of GP2017 HCF as biosimilar to US-licensed Humira.

# 15. Division Director Comments

I concur with the team's assessment of the data and information submitted in this supplemental BLA and support approval. I also agree with the PMC as requested by OBP.

# 16. Appendix

### 16.1 Summary of bioanalytical method performance in study CGPN017B12101

A validated enzyme linked immunosorbent assay (ELISA) was used for the quantification of study drug in serum samples. Briefly, a microtiter plate was coated with TNF-α and free binding sites were blocked with a bovine serum albumin-solution. The serum samples were then added to the coated plate and the "adalimumab" contained in them bound to the TNF-α. Unbound substances were subsequently removed by washing. The detection of the TNF-α-adalimumab-complexes was carried out by binding of an enzyme-labeled secondary antibody and a following color reaction. The optical density of the dye correlated with the concentration of study drug in the sample. The method was validated following below studies:

- "[BA17011] Validation study: ELISA for the quantification of adalimumab in human serum – long-term stability evaluation"
- "BA13010-R: Validation Report: ELISA for the quantification of adalimumab in human serum GCP/GCLP"
- "[BA20008] Validation study: Partial validation of ELISA for the quantification of adalimumab in human serum"

- "[BA21009] Validation study: Partial validation of ELISA for the quantification ofadalimumab in human serum (including validation of the Hamilton Microlab Vantage Robotic system)"

The goal of partial validation in [BA21009] validation study, was a partial validation of the ELISA for the quantification of GPN017B1 in human serum of HV using the Hamilton Microlab Vantage Robotic System.

**Table 9. Summary of the bioanalytical method validation**

| | | | |
|---|---|---|---|
| **Bioanalytical method validation report name, amendments, and hyperlinks** | Bioanalytical Validation Report: ELISA for the quantification of study drug in human serum – long-term stability evaluation (BA17011-R, version 1.0) | | |
| **Method description** | A sandwich ELISA format was used for the determination of study drug in human serum | | |
| **Materials used for calibration curve & concentration** | The standard samples (Std) for the calibration curve were prepared by spiking the reference item in defined concentrations in 1:200 diluted human serum pool from healthy donors; Prepared Concentrations are: 0.25 µg/mL, 0.5 µg/mL, 1 µg/mL, 2 µg/mL, 4 µg/mL, 8 µg/mL, 100 µg/mL | | |
| **Validated assay range** | 0.25 µg/mL (LLOQ) to 8 µg/mL (ULOQ) | | |
| **Material used for QCs & concentration** | Prepared at 6 µg/mL, 1.5 µg/mL, 0.75 µg/mL | | |
| **Minimum required dilutions (MRDs)** | 1:200 in blocking buffer (1% D-PBS + 5% BSA) | | |
| **Source & lot of reagents (LBA)** | • Human serum pool from healthy donors; (b) (4); 1066D -70°C 20-Nov-2020<br>• Bovine serum albumin (BSA); (b) (4)<br>• D-PBS (1x); (b) (4)<br>• D-PBS powder; (b) (4)<br>• Goat anti-human IgG (Fc-specific) POD antibody; (b) (4)<br>• 075M4813V, 116M4809V<br>• Sulfuric acid [95-97%]; (b) (4)<br>• TNF-α; (b) (4)<br>• Tween® 20; (b) (4) | | |
| **Regression model & weighting** | A 5 Parameter Fit, Log-Log, fixed weighting (no factor) model was used | | |
| **Validation parameters** | Method validation summary | | Source location (hyperlinked) |
| **Standard calibration curve performance during accuracy & precision** | Number of standard calibrators from LLOQ to ULOQ | 7 | Bioanalytical Method Validation |
| | Cumulative accuracy (%Nominal):<br>LLOQ and ULOQ (Std 1 and 6):<br>Std 2-5: | <br>86 –113%<br>85 – 115% | Bioanalytical Method Validation |
| | Cumulative precision (%CV) from LLOQ to ULOQ: | | Bioanalytical Method Validation |

| | | | |
|---|---|---|---|
| | LLOQ and ULOQ<br>(Std 1 and 6):<br>Std 2-5: | ≤ 25%<br>≤ 20% | |
| **QCs performance during accuracy & precision** | Cumulative accuracy (%Nominal) and Precision in 6 QCs<br>Accuracy(%)<br>Precision (CV%) | <br>90 to 111.0%<br>≤ 16% | Bioanalytical Method Validation<br><br>Appendix 02 to BA17011-R, V 1.0 (Page 2-2) |
| | Inter-batch %CV<br>ULOQ-VS, VS1, VS2, VS3, LLOQ-VS)<br>GP2017-DP (Sandoz) | ≤ 16% | BA13010-r-validation-report.pdf<br>V 02<br>Appendix 4 |
| | Total Error (TE)<br>QCs: | ≤ 30% | BA13010-r-validation-report.pdf<br>V 02<br>BA13010, version 02<br>Appendix 2 |
| **Selectivity & matrix effect** | The potential matrix-related interferences were evaluated using 10 individual human sera of healthy donors.<br>**Acceptance Criteria:** Matrix components did not interfere with the detection of adalimumab if the mean of the measured concentrations per individual serum were between 80% and 120% (75−125% at the LLOQ) of the expected value when measured against a calibration curve. In addition, the precision (% CV) of the mean measured concentrations had to be ≤ 20% (25% at the LLOQ). The acceptance criteria should be fulfilled for at least 80% of the sera.<br>**Result:** In total ten individual human sera were tested with 3 test items (GP2017-DP-Sandoz, US Humira, EU Humira) using two concentration levels (VS1 and LLOQ) per test item and individual sera. Thus, 20 individual values were generated per test item and 60 individual values were generated in total. In total, 93,3% (56/60) of all generated individual values fulfilled the acceptance criteria. By taking both concentration levels per individual human serum together into one calculation, 86.7% (26/30) of 30 samples fulfilled the acceptance criteria. | | BA13010-r-validation-report.pdf<br>V 02<br>Appendix 10 to BA13010, version 02 |
| **Interference & specificity** | Up to 40 µg/mL anti-adalimumab antibody does not interfere with the quantitation of study drug spiked to 6000 ng/mL. | | BA13010-r-validation-report.pdf<br>V 02 |
| **Bench-top/process stability** | *Stability of the analyte was established short-term at 2-8°C (up to 3 days) and room temperature (up to 20 hours)* | | BA13010-r-validation-report.pdf<br>V 02 |
| **Freeze-Thaw stability** | To test the freeze / thaw stability of the test it ems (see Section 4.1.1) three aliquots of two different concentrations (VS1 and VS3) of each test item spiked in 100% HV human serum pool were tested freshly prepared (this value served as a reference value), after 1, 3 and 5 freeze / thaw cycles at ≤ -70°C / room temperature. All freeze / thaw cycles were performed after an initial freeze / thaw cycle in the beginning to imitate "real" study samples which are stored frozen and subsequently could undergo one, three or five | | BA13010-r-validation-report.pdf<br>V 02 |

| | | |
|---|---|---|
| | freeze / thaw cycles. All samples were frozen for at least 24 h before thawing and freezing again. The test items were considered to be stable for up to 05 freeze / thaw cycles. | |
| **Long-term storage** | This long-term stability validation showed that study drug in human serum stored at -70°C<br>is stable for at least 31 months (957 days). | BA13010-r-validation-report.pdf<br>V 02 |

Source: BLA761071; Module 5; BA17011-R, version 1.0; BA13010-r-validation-report.pdf

## Table 10. In-study method performance in Study CGPN017B1

| **Method performance in study CGPN017B1** | | |
|---|---|---|
| **Assay passing rate** | Overall assay pass rate: 196 out of 206 runs are accepted (95.14%) | Bioanalytical Study Report: BA21001-R, V1 |
| **Standard curve performance** | • Cumulative accuracy (% bias) range: -3 to 1%<br>• Cumulative precision (% CV): ≤ 2.0% | Bioanalytical Study Report: BA21001-R, V1 |
| **QC performance** | • Cumulative accuracy (% bias) range: -11 to -1%<br>• Cumulative precision (% CV): ≤ 4.0% | Bioanalytical Study Report: BA21001-R, V1 |
| **Method reproducibility** | Incurred sample re-analysis (ISR): In total, 10% of samples were re-analyzed up to the 1000th sample and 5% of the sum of samples exceeding the 1000th sample.<br>In the present study, 5870 samples were analyzed. Therefore, the number of ISR samples should have been at least (10% of 1000 samples) + (5% of 4870 samples) = 344 samples (rounded up calculation). In total, finally 348 samples (5.9%) were re-analyzed for ISR.<br>Overall, 80.5% of the 348 samples subjected to ISR successfully passed. | Bioanalytical Study Report: BA21001-R, V1 |
| **Stability** | First study sample draw date: 09-Mar-2021 and last analysis date: 14-Jan-2022. Samples were stored at -70°C prior to the analysis. All samples were measured within the above stated stability ranges (maximum storage period before analysis: ≤ 310 days. | Bioanalytical Study Report: BA21001-R, V1 |

Source: BLA761071; Module 5: Bioanalytical Study Report: BA21001-R, V1

## 16.2 Signature Panel

| Discipline and Title or Role | Reviewer Name | Office/Division |
|---|---|---|
| Clinical Pharmacology Reviewer | Sanjida Mahjabeen | OCP/DIIP |
| | Signature: Sanjida Mahjabeen -S (Affiliate) Digitally signed by Sanjida Mahjabeen -S (Affiliate) Date: 2023.03.08 10:36:22 -05'00' | |
| Clinical Pharmacology Team Leader | Ping Ji | OCP/DIIP |
| | Signature: Ping Ji -S Digitally signed by Ping Ji -S Date: 2023.03.08 10:30:24 -05'00' | |
| Clinical Reviewer | Amit Golding | OII/DRTM |
| | Signature: Amit Golding -S Digitally signed by Amit Golding -S Date: 2023.03.08 10:39:49 -05'00' | |
| Clinical Team Leader | Raj Nair | OII/DRTM |
| | Signature: Raj G. Nair -S Digitally signed by Raj G. Nair -S Date: 2023.03.08 10:43:29 -05'00' | |
| Cross-Discipline Team Leader | Ping Ji | OCP/DIIP |
| | Signature: Ping Ji -S Digitally signed by Ping Ji -S Date: 2023.03.08 10:31:02 -05'00' | |
| Designated Signatory Authority | Nikolay Nikolov | OII/DRTM |
| | Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S Date: 2023.03.09 15:28:28 -05'00' | |

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