CDTL/Division Summary Memo

DRTM/OII/CDER

Cross-Discipline Team Leader/Division Summary Review

Date	See stamped date
From	DRTM: Juwaria Waheed, MD and Nadia Habal, MD (Team Lead) OCP: Sojeong Yi, PhD, and Ping Ji, PhD OBP: Rachel Lokanga, PhD, and Ian McWilliams, PhD OBP Labeling: Liming Lu, PharmD OPMA/Micro: Reyes (Maria) Candauchacon, PhD, and Virginia Carroll, PhD DMEPA: Teresa McMillan, PharmD, and Idalia Rychlik, PharmD DMEPA HF: Matthew Barlow, PharmD, and Oluwamurewa Oguntimein, PhD, MHS, CPH, MCHES CDRH: Dunya Karimi, BS in BME, Lead Reviewer, OPEQ/OHT3/DHT3C, and Courtney Evans, Team Lead, Injection Team, OPEQ/OHT3/DHT3C
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 761058 Supplement-016 (IND 110467)
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc. (BI)
Date of Submission	July 22, 2022
BSUFA Goal Date	May 22, 2023
Proprietary Name/ Proper name/Code name	Cyltezo/ Adalimumab-adbm (BI 695501)
Formulation(s)/Presentation(s)	AI: 40 mg/0.8 mL
Recommended Action	Approval

1 Introduction

BI 695501 (Cyltezo, adalimumab-adbm) is a recombinant human monoclonal antibody approved as a biosimilar to US-licensed Humira (adalimumab) on August 25, 2017, and as an interchangeable biosimilar to US-licensed Humira (adalimumab) on December 15, 2021. BI 695501 40 mg/0.8 mL, 20 mg/0.4 mL, 10 mg/0.2 mL in a single pre-filled syringe (PFS) is approved under a 351(k) BLA (BLA 761058).

The Applicant submitted an efficacy supplement (S-16) BLA for Cyltezo (adalimumab-adbm) BI 695501 to extend its licensure for use in an autoinjector (AI) presentation, 40 mg/0.8 mL pen, manufactured (b) (4) process. Of note, a previous supplement BLA (sBLA (b) (4) for an AI using (b) (4) process was submitted on October 31, 2017, and received a complete response on December 30, 2019, due to deficiencies found on inspection of manufacturing facility. This Application was subsequently withdrawn on December 30, 2019 to focus on the (b) (4) autoinjector development.

The proposed labeling changes include the addition of the 40 mg/0.8 mL AI presentation.

2 Background and Regulatory History

As noted above, the Applicant submitted supplement (b) (4) to support licensure of an AI (b) (4) process in October 2017 which was CR'd due to facility inspection deficiencies. To support the autoinjector form of Cyltezo, BI conducted a clinical program that included two PK studies (Studies 1297.6 and 1297.13) and one real life handling study (Study 1297.11). See Table 1 below.

Table 1. Key Design Features of Clinical Studies

Protocol	Patient population	Design/Objective	Duration	Treatment arms: sample size
1297.6	Healthy male subjects	R, OL, P, PK, safety bridging PFS to AI (abdomen)	Single dose	BI 695501 AI: 35 BI 695501 PFS: 36
1297.13	Healthy subjects	R, OL, P, PK safety bridging PFS to AI (thigh)	Single dose	BI 695501 AI: 81 BI 695501 PFS: 81
1297.11*	Rheumatoid Arthritis	OL, Real –life patient handling of AI	50 weeks – AI phase (7 weeks) followed by PFS extension phase (42 weeks)	BI 695501 AI: 77 (Auto-injector phase) PFS phase: 72

*AI portion of study 1297.11 submitted with original BLA

Data from these studies was reviewed under supplement (b) (4) and found acceptable. Please refer to the CDTL review dated August 31, 2018, for details.

3 Chemistry and Manufacturing/Device

Summary of OPQ and CDRH Assessments (Reviews)

OPQ/OBP Final Recommendation: Approval

The efficacy supplement was submitted to register Cyltezo (adalimumab-adbm) 40 mg/0.8 mL autoinjector (AI) pen manufactured (b) (4) To support the registration of the AI, the Applicant provided the manufacturing process validation data, release and stability data, and shipping validation data of the AI presentation, including assessment of impact of AI assembly on product quality and functionality of the AI. The data support no impact to BI 695501 product quality with the manufacture, storage, and shipment of the AI presentation. The stability data support the labeled storage of the AI at 2°C to 8°C for 24

months and at room temperature (25°C) for up to 14 days. To address variability in room temperature conditions (e.g., 30°C) during storage, the Applicant revised the stability commitment to include testing DP at the end of shelf-life for an additional 14 days at 30°C. Immunogenicity assays were previously assessed and are fit-for-purpose. Facility and microbiological assessment is deferred to OPMA. Assessment of device related information is deferred to CDRH.

The commercial AI manufacturing process and the associated controls were adequately described, and the manufacturing and shipping conditions for the AI adequately validated. Batch analysis of various biochemical attributes at release and during stability studies demonstrated that the manufacturing process (b) (4)) for the AI does not impact product quality and stability of the PFS DP. In addition, the ADA and nAb immunogenicity assays are the same as those previously reviewed and are fit-for-purpose. Therefore, OBP recommends approval for this PAS.

CDRH Final Recommendation: Device Constituent Parts of the Combination Product are Approvable with PMC.

CDER/OPQ consulted CDRH to assess the device constituent parts of the combination product, specifically the pharmaceutical development, manufacturing, functional performance, and stability of the automated autoinjector presentation of Cyltezo. During this review cycle, CDRH recommended a Pre-Approval Inspection (PAI). Inspection was conducted 8/16/2018 to 8/24/2018. The inspection covered both drug CGMPs and medical device (b) (4) (abbreviated) and was classified as voluntary action indicated (VAI). The overall outcome of the inspection was acceptable.

CDRH recommended a post marketing commitment regarding audible feedback from the device to accurately identify the start of the injection, and a verification testing to ensure device performance for the new requirement. See Section 9 PMC for details.

OPQ/OPMA Product Quality Microbiology/Facility Assessment Recommendation:
Approval
This Prior Approval Supplement was reviewed from a sterility assurance perspective and is recommended for Approval. Manufacturing Facility Assessment Recommendation: Approval. See reviews from the respective review divisions for additional details.

4 Human Factors

The Applicant submitted comparative analyses under IND 110467 for Cyltezo AI, a proposed interchangeable to US licensed Humira. DMEPA reviewed the comparative analyses and determined that additional data from a comparative use human factors study (CUHF) was needed to support interchangeability with US-licensed Humira.[1] In response, the Applicant submitted a

[1] Barlow, M. Comparative Analyses Review for Cyltezo (IND 110467 & BLA 761058/S-016). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JUNE 16. RCM No.: 2020-336.

meeting package with their Type 1 BPD meeting request on August 26, 2022. The meeting package included a comparison of the needle cover force along with button activation force between the proposed Cyltezo AI and US-licensed Humira. Based on the additional information provided along with the labeling and task similarities, DMEPA reconsidered their initial determination and no longer found that CUHF data was needed for the proposed Cyltezo AI. This efficacy supplement included a summary of human factors (HF) validation study results; however, DMEPA previously reviewed HF validation data for the proposed AI under BLA 761058/S-(b) (4) and found the results acceptable.[2] Although the summary of HF validation study results included data DMEPA has not previously reviewed, DMEPA notes the user interface has not changed. Therefore, DMEPA's determination that CUHF data is not needed to support a demonstration of interchangeability for this supplement has not changed. In conclusion, this sBLA is acceptable for approval of the proposed AI presentation of Cyltezo from DMEPA's perspective.

5 Pharmacology/Toxicology

Not applicable. This supplement does not include non-clinical studies.

6 Clinical Pharmacology

Clinical Pharmacology Primary Reviewer: Sojeong Yi, PhD
Clinical Pharmacology Team Leader: Ping Ji, PhD

To support the Cyltezo 40 mg/0.8 mL autoinjector (AI), two relative bioavailability studies, i.e., Study 1297.6 (with abdomen as injection site) and Study 1297.13 (with thigh as injection site), were conducted.

Both studies were previously submitted in sBLA(b) (4), which were reviewed by the Agency. See the CDTL/Division Summary Review by Dr. Nadia Habal dated Aug 31, 2018, in DARRTS (reference ID: 4315132). Study 1297.6 was later updated with additional 5 subjects and reviewed by the Agency. See the Clinical Pharmacology Review by Dr. Shalini Wickramaratne Senarath Yapa, dated Oct 31, 2017, in DARRTS (reference ID: 4297469).

Briefly, comparable bioavailability of adalimumab-adbm was established between AI and PFS following a single subcutaneous injection, and the sBLA-(b) (4) was acceptable for approval for the AI presentation from a clinical pharmacology standpoint.

The clinical pharmacology data submitted in sBLA-016 is the same as what was previously submitted and reviewed in sBLA-(b) (4) consisting of Study 1297.6 and Study 1297.13.
In conclusion, this sBLA is acceptable for approval of the proposed AI presentation of Cyltezo from a clinical pharmacology standpoint.

[2] Mena-Grillasca, C. Label, Labeling, and Human Factors Review for Cyltezo (BLA 761058/S(b) (4)). Silver Spring (MD); FDA, CDER, OSE, DMEPA (US); 2018 AUG 08. RCM No.: 2017-2578 and 2017-2580

7 Safety

No new clinical data were submitted to support this supplement.
In pre-BLA communication, the Applicant was asked to provide information to justify the relevance of the clinical data generated with the AI manufactured [redacted] process (studies 1297.6, 1297.13, and 1297.11) to support approval of the AI manufactured [redacted] process.

To justify the relevance of the clinical data generated with the AI manufactured [redacted] process (studies 1297.6, 1297.13, and 1297.11) to support approval of the AI manufactured [redacted] process, the Applicant conducted a comparison between the [redacted] processes. The outcome of this comparison is that the [redacted] autoinjector used in the clinical studies are representative of the commercial product. In addition, to the risk assessment and comparability, the Applicant executed a real-time [redacted] transport study and supplemented it with a [redacted] assembled AI (n=3) simulated shipment study for the worst-case ISO 11608-1 pre-conditionings drop, shake, impact testing.

The Applicant also presented results which concluded that the [redacted] and [redacted] processes manufacture AIs of the same quality without impacting the functionality of the AI, performance of the AI, or quality attributes of the final formulated drug substance. Therefore, clinical studies and the real-time transport qualification performed using autoinjector batches from the [redacted] process can be leveraged to support submission of the AI.

The review team found the justification reasonable.

8 Labeling

Product labeling was updated to reflect the addition of the auto injector - CYLTEZO Pen; Injection: 40 mg/0.8 mL in a single-dose pen. Minor formatting and editorial changes were made consistent with best labeling practices.

Labeling changes included updates to the following sections of the PI:

Section 2 Dosage and Administration:

- Language adding Cyltezo pen in section 2.8 – General Considerations for Administration

Section 3 Dosage Forms and Strengths:

- Addition of: Pen (CYLTEZO Pen) Injection: 40 mg/0.8 mL in a single-dose pen

Section 11 Description

- Addition of single-dose, prefilled pen (CYLTEZO Pen)

Section 16 How Supplied/Storage and Handling

- Addition of information about the CYLTEZO® Pen Prefilled Pen including the contents of PFS cartons, number of units per carton, and NDC number

Section 17 Patient Counseling Information

- Updates to Instructions on Injection Technique with information about using the Cyltezo Pen

The medication guide (MG) was updated with minor revisions in alignment with the updated prescribing information.

Instructions for Use (IFU) were added for Cyltezo Pen.

The Division of Medication Error Prevention and Analysis review team has found the proposed PI acceptable. On May 9, 2023, an IR was communicated to the Applicant requesting for the Applicant to implement revisions to the Carton labeling and Blister Tray. On May 11, 2023, the Applicant agreed to implement the revisions as outlined in that Information Request by submitting a CBE labeling supplement within 14 days of the Autoinjector sBLA action date.

The CMC labeling team has also found the container labels and carton labeling and the prescribing information/medication guide/instructions for use acceptable.

9 Postmarketing Commitment (PMC)

Your device labeling indicates an audible feedback feature (“Click”) indicating the start of injection. However, the verification test reports provided do not include any testing conducted on audible feedback for your device indicating the start of injection as recommended in ISO 11608-1:2014 Needle-based injection systems for medical use - Requirements and test methods – Part 1: Needle-based injection systems, section 5.5, General design requirements. Your device should have a requirement for audible feedback which indicates clear requirements regarding loudness of the audible feedback (in decibels) and accuracy (+/- x seconds) indicating the start of injection. Your intended user may solely rely on the audible feedback to indicate the initiation of injection. Therefore, to ensure users can adequately identify the start of injection by audible means, 1) define a specification for start of injection click timing for your autoinjector, and 2) provide updated verification testing to include a requirement for audible feedback (as specified above) to confirm the devices performance.

10 Regulatory Action

- **Recommended regulatory action:** Approval

The recommended action for this supplement is approval. As determined by the respective review teams, the Applicant has provided sufficient information for Cyltezo, an interchangeable biosimilar to US-licensed Humira (adalimumab), for use in an autoinjector presentation, 40 mg/0.8 mL pen. CDRH recommended a pre-approval facility site inspection, and the outcome of the inspection was acceptable. The proposed labeling changes include the addition of the auto injector – “CYLTEZO Pen; Injection: 40 mg/0.8 mL in a single-dose pen.” The proposed

labeling changes are acceptable for the review team and there will be a Changes Being Effected" (CBE) labeling supplement implementing revisions to the carton labeling and blister tray within 14 days of approval as noted above. A PMC will be issued to address the device's performance as noted above. Please see respective discipline reviews for additional details.

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

/s/

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