CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761058Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review/ Division Director Summary Review

Date	*Electronic Stamp Date*
From	Nikolay P. Nikolov, M.D. Badrul A. Chowdhury, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review Division Director Summary Review
BLA #	351(k) BLA 761058
Applicant	Boehringer Ingelheim
Date of Submission	October 27, 2016
BsUFA Goal Date	August 27, 2017
Proprietary Name (Proposed) / Nonproprietary names	Cyltezo BI 695501,[1] adalimumab-adbm
Dosage Forms / Strength	(b) (4) solution in a single-dose prefilled syringe (PFS)
Route of Administration	Subcutaneous
Proposed Indication(s)	• Rheumatoid arthritis (RA) • Juvenile idiopathic arthritis (JIA) in patients 4 years of age and older • Psoriatic arthritis (PsA) • Ankylosing spondylitis (AS) • Adult Crohn's disease (CD) • Adult ulcerative colitis (UC) • Adult plaque psoriasis (PsO)
Recommended:	*Approval*

1) Introduction

Boehringer Ingelheim (referred to as "BI" or "the Applicant" in the rest of this document) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for BI 695501, a proposed biosimilar to Humira (adalimumab). BI is seeking licensure of BI 695501for the following indications for which US-licensed Humira is licensed:[2]

[1] In this document, we generally refer to Boehringer Ingelheim's proposed product by the Applicant descriptor "BI 695501" which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product was determined to be "adalimumab-adbm."
[2] FDA-approved Humira labeling

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

Although the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology and Inborn Errors Products (DGIEP), and the Division of Dermatology and Dental Products (DDDP) during the course of the review.

The application consists of:

- Extensive analytical data intended to support (i) a demonstration that BI 695501 and US-licensed Humira are highly similar, (ii) a demonstration that BI 695501 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet appropriate quality standards and (iii) a justification of the relevance of comparative data generated using the European Union (EU)-approved Humira to support a demonstration of biosimilarity of BI 695501 to US-licensed Humira.

- A single-dose pharmacokinetic (PK) study (Study 1297.8) providing a 3-way comparison of BI 695501, US-licensed Humira, and EU-approved Humira intended to (i) support PK similarity of BI 695501 and US-licensed Humira and (ii) provide a PK bridge to support the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of BI 695501 to US-licensed Humira. Additional single-dose PK study in healthy subjects (Study 1297.1), that used a "trial" (non-commercial) formulation of BI 695501, was also submitted and provided supportive safety data between BI 695501 "trial" formulation, US-licensed Humira, and EU-approved Humira.

- A comparative clinical study (Study 1297.2) between BI 695501 and US-licensed Humira in patients with RA to support a demonstration of no clinically meaningful differences in terms of safety, purity, and potency. This was a 48-week, randomized, double-blind, parallel group study conducted in 645 patients with moderately to severely active RA on stable background methotrexate (MTX). Subjects were randomized 1:1 to BI 695501 or US-licensed Humira at a dose of 40 mg every other week (Q2W) subcutaneously (SC). At Week 24, patients treated with US-licensed Humira were randomized to undergo a single transition to BI 695501 or continue on US-licensed Humira up to Week 48.

- A scientific justification for extrapolation of data to support biosimilarity in each of the additional indications for which BI is seeking licensure, specifically juvenile idiopathic arthritis in patients 4 years of age or older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis and plaque psoriasis.

BI submitted comparative analytical data on the BI 695501 lots used in clinical studies intended to support a demonstration of biosimilarity and on the proposed commercial product. Based on our review of the data provided, BI's comparative analytical data for BI 695501 demonstrates that BI 695501 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components.

BI used a non-US-licensed comparator (EU-approved Humira) in some studies intended to support a demonstration of biosimilarity to US-licensed Humira. Accordingly, BI provided scientific justification for the relevance of data from those studies to support a demonstration of biosimilarity of BI 695501 to US-licensed Humira by establishing an adequate scientific bridge (analytical and PK) between EU-approved Humira, US-licensed Humira, and BI 695501.

The results of the comparative clinical efficacy, safety, immunogenicity, and PK studies indicate that BI's data support a demonstration of "no clinically meaningful differences" between BI 695501 and US-licensed Humira in terms of safety, purity, and potency in the indications studied. Further, the single transition from US-licensed Humira to BI 695501 compared to patients who remained on US-licensed Humira during the second part of Study 1297.2 in patients with RA did not result in different safety or immunogenicity profiles. This

would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to BI 695501.

In considering the totality of the evidence, the data submitted by BI support a demonstration that BI 695501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between BI 695501 and US-licensed Humira in terms of the safety, purity, and potency of the product, in the studied indication of RA.

The Applicant has also provided an extensive data package to address the scientific considerations for the extrapolation of data to support biosimilarity in other conditions of use and potential licensure of BI 695501 for each of the indications for which US-licensed Humira is currently licensed and for which BI is seeking licensure.

2) Background

The BPCI Act

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

Section 351(i) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and

clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and, once the applicant has established that the proposed biosimilar meets the analytical similarity prong of the biosimilarity standard, the amount of residual uncertainty remaining can be assessed with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

The 'totality of the evidence' submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

Reference Product

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with a reference product. When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

Relevant Regulatory History

The first interaction between BI and the FDA on the BI 695501 development program occurred at a pre-IND meeting held on April 28, 2011 with follow up interactions to include a Biosimilar Biological Product Development (BPD) Type 4 meeting held on June 15, 2016. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP). During the pre-submission interactions, FDA provided product quality, nonclinical, and clinical

comments, including recommendations to the Applicant regarding clinical development, such as:

- Design, endpoints, and selection of the similarity margin for the comparative clinical study in RA.
- Assessment of safety and immunogenicity in the setting of patients who undergo a single transition from US-licensed Humira to BI 695501 to provide a descriptive comparison with patients who continue on US-licensed Humira in the RA comparative clinical study.
- Demonstration of PK similarity between BI 695501, US-licensed Humira, and EU-approved Humira.
- Expectations for the scientific justification for extrapolation of biosimilarity.

At the BPD Type 4 meeting, general agreement was reached on the proposed format and content of the BLA, including the Agency's expectation for the information needed to support a demonstration of biosimilarity and extrapolation of data to support the demonstration of biosimilarity for each indication for which licensure is sought.

Of note, in the initial submission, the Applicant submitted data to support an additional presentation. However, during the filing review, the Agency determined that the data package to support this additional presentation was incomplete and the Applicant withdrew this information from the application. This information was not essential for the substantive review of this 351(k) application.

3) CMC/Product Quality

CMC Reviewer: Richard Ledwidge, Ph.D.
CMC Statistical Reviewer: Li Xing, Ph.D.; CMC Statistical Team Leader: Meiyu Shen, Ph.D.; CMC Statistical Supervisor: Yi Tsong, Ph.D.
Immunogenicity Reviewer: Davinna Ligons, Ph.D.
Microbiology Reviewers: Monica Commerford, Ph.D.; Microbiology Team Leader: Maria Reyes Candau-Chacon, Ph.D.;
Facilities Reviewer: Ephren Hunde; Facilities Supervisory Consumer Safety Officer: Zhihao (Peter) Qiu, Ph.D.
OBP Labeling: Vicky Borders-Hemphill, Pharm.D.
Application Technical Lead: Howard Anderson, Ph.D.
Tertiary Reviewer: Susan Kirshner, Ph.D.
OBP Business Regulatory Process Manager: Keith Olin
CDRH Reviewer: Matthew Ondeck; CDRH Branch Chief: Alan M. Stevens

- **General product quality considerations**

BI 695501 (adalimumab-adbm) is an IgG1 subclass humanized proposed biosimilar to the US-licensed Humira monoclonal antibody and is produced in (b) (4) cells using

recombinant DNA technology. It blocks the inflammatory action of Tumor Necrosis Factor alpha (TNFα) by binding soluble and transmembrane TNFα and preventing the cytokine from binding to p55 (TNFR1) and p75 (TNFR2) cell surface receptors.

The BI 695501 drug substance (DS) manufacturing process involves (b) (4) esulting in highly purified BI 695501 DS. Microbial quality of the DS manufacturing process is controlled (b) (4). All DS lots were manufactured at Boehringer Ingelheim Fremont, Inc. (BIFI), 6701 Kaiser Drive, Fremont, California 94555, USA. The stability data support a BI 695501 DS expiration dating period of (b) (4) months when stored at (b) (4) ºC.

BI 695501 drug product (DP), a 40 mg/0.8 mL of BI 695501 is a clear to slightly opalescent and colorless to slightly yellow solution provided by a single-use, 1 mL prefilled glass syringe (PFS) with a fixed 27 gauge, ½ inch needle and a gray inner needle cover (b) (4) The proposed device was reviewed by the Center for Devices and Radiological Health (CDRH), General Devices Branch review team with no outstanding concerns. All the components of the container closure are supplied by (b) (4). The BI 695501 DP is manufactured at BIFI, 6701 Kaiser Drive, Fremont, California 94555, USA. The stability data support BI 695501 DP expiration dating period of 24 months when stored at 5°C ± 3°C.

The BI 695501 final DS and DP processes are fully validated, and the manufactured product is of a consistent quality. The controls that have been established for the routine manufacture of BI 695501 DS and BI 695501 DP meet regulatory requirements. However, the product quality review team recommends post-marketing commitments (PMCs), as detailed in the section on Recommendation for other Postmarketing Requirements and Commitments at the end of this document. We agree with these recommendations.

Significant deficiencies associated with the DP manufacturing at (b) (4) included in the original submission were identified during the BLA review. These deficiencies have been resolved by the removal of (b) (4) as a DP manufacturing facility in a July 24, 2017, amendment to the BLA. With this amendment, the Division of Microbiology Assessment review teams concluded, and we concur, that the DS and the DP are recommended for approval from a quality microbiology perspective with one PMC, as detailed in the section on Recommendation for other Postmarketing Requirements and Commitments at the end of this document.

- **Analytical Similarity Assessment**

To determine whether BI 695501 is highly similar to US-licensed Humira, and to establish the adequacy of the analytical portion of the scientific bridge between BI 695501, US-licensed Humira, and EU-approved Humira, BI evaluated and compared analytical data from 13 BI 695501 DP lots (produced from 13 DS lots), 58 US-licensed Humira lots and 86 EU-approved

Humira lots. The FDA performed confirmatory statistical analysis of the submitted data. All methods were validated or qualified prior to the time of testing and demonstrated to be suitable for intended use.

The commercial formulation of BI 695501 was evaluated in the two clinical studies 1297.2 and 1297.8 and the analytical similarity study. There have been no major process changes during development.

The results from the statistical equivalence testing of the sTNF-α neutralization assay and the TNF-α binding Surface Plasmon Resonance (SPR) assay met the predefined acceptance criteria for the three pair-wise comparisons (BI 695501 v. US-licensed Humira, BI 695501 v. EU-approved Humira, and US-licensed Humira v. EU-approved Humira) and the product quality review team concluded, and we agree, that the data support a demonstration that the proposed biosimilar BI 695501 is highly similar to US-licensed Humira.

The statistical analyses of these highly critical quality attributes also support the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved Humira and the BI 695501 product to support a demonstration of biosimilarity to US-licensed Humira. Further, more than 90% of the BI 695501 lots assessed in the Tier 2 US-licensed Humira quality statistical range met the predefined acceptance criteria for the three pair-wise comparisons (BI 695501, US-licensed Humira, and EU-approved Humira). Minor differences were noted in the Tier 2 statistical attributes for N-linked oligosaccharides (a-fucosylation, a glycosylation, and sialyation), charge variants (CEX assay), size variants (CGE) and aggregates. The differences in all cases were just outside the three standard deviation range. The residual uncertainty raised by these results is addressed by the results of the functional potency assays, specifically complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), showing no meaningful differences between BI 695501 and US-licensed Humira. To the extent these potential mechanisms of action are relevant for adalimumab products, it is likely that the relative role for each of these mechanisms differs between indications. The Applicant conducted functional assays to assess similarity between BI 695501, US-licensed Humira, and EU-approved Humira with regard to each of these potential mechanisms. In each case, the results were similar and met pre-determined similarity criteria between BI 695501, US-licensed Humira, and EU-approved Humira.

Based on the above considerations, the product quality team concluded, and we agree, that the totality of analytical similarity data supports a demonstration that BI 695501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and supports the scientific bridge between the three products to justify the relevance of comparative data generated from the clinical study that used EU-approved Humira to support a demonstration of biosimilarity of BI 695501 to US-licensed Humira. The product quality review team, including Division of Microbiology Assessment and CDRH, further recommended, and we agree, that this BLA be approved from a sterility assurance and microbiology product quality perspective and from a device perspective.

- **Facilities review/inspection**

FDA's Office of Process and Facilities (OPF) conducted an assessment of the manufacturing facilities for this BLA. A pre-license inspection of the DS and DP manufacturing facility at Boehringer Ingelheim Fremont, BIFI (FEI 3005925062) was conducted from March 27 – April 4, 2017 by CDER (DIA, DMA, OBP and ORA). The inspection covered the Quality, Production, Facilities and Equipment, Laboratory Control, and Materials systems. A 10-item FDA-483 was issued. The Applicant's response to the FDA-483 observations was deemed adequate and the inspection was classified as VAI**.** The OPF team recommended that BLA 761058 be approved from the standpoint of facilities assessment. We concur with this recommendation.

4) Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology Reviewer: L. Steven Leshin, D.V.M., Ph.D.
Pharmacology/Toxicology Team Leader: Carol Galvis, Ph.D.

The BI 695501 nonclinical development program was considered adequate to support clinical development. Of note, to support the relevance of the data generated using EU-approved Humira used in the non-clinical program, the Applicant has provided both analytical and PK data to support the scientific bridge between BI 695501, US-licensed Humira, and EU-approved Humira. The animal studies submitted, support a demonstration of similarity between BI 695501 to US-licensed Humira in terms of the nonclinical pharmacology and pharmacokinetics data. The Pharmacology and Toxicology team concluded, and we agree, that the results of these animal studies can be taken together with the data from the analytical bridging studies (refer to the CMC section of this document for details) to support a demonstration that BI 695501 is biosimilar to US-licensed Humira.

5) Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Reviewer: Shalini Wickramaratne Senarath Yapa, Ph.D.
Clinical Pharmacology Team Leader: Anshu Marathe, Ph.D.
Office of Study Integrity and Surveillance (OSIS) Review Team: Himanshu Gupta, Ph.D.; Melkamu Getie-Kebtie, R.Ph., Ph.D.; Seongeun (Julia) Cho, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations**

The objectives of the BI 695501 clinical pharmacology program were to evaluate the pharmacokinetic similarity between BI 695501 and US-licensed Humira, and to support the scientific bridge between BI 695501, US-licensed Humira, and EU-approved Humira in order to justify the relevance of comparative data generated using EU-approved Humira in the non-

clinical program to support a demonstration of the biosimilarity of BI 695501 to US-licensed Humira.

The clinical development for BI 695501 relevant to the submission in the United States (US) included three clinical studies, and the key design features of the studies are summarized in Table 1. Pharmacokinetic (PK) similarity of BI 695501 to US-licensed Humira was evaluated in a pivotal three-way PK similarity study 1297.8 to compare the PK, safety, tolerability, and immunogenicity of BI 695501, US-licensed Humira, and EU-approved Humira in 324 healthy subjects (108/treatment arm). PK and immunogenicity were also assessed for BI 695501 and US-licensed Humira in 645 patients with active rheumatoid arthritis (RA) in Study 1297.2. Additional single-dose PK study in healthy subjects (Study 1297.1), that used a "trial" (non-commercial) formulation of BI 695501, was also submitted and provided supportive safety data between BI 695501 "trial" formulation, US-licensed Humira, and EU-approved Humira. A bioanalytical assay, an enzyme-linked immunosorbent assay (ELISA), was used to quantify plasma concentrations of adalimumab in studies 1297.8, 1297.2 and 1297.1. Based on the bioanalytical inspection report, the bioanalytical portions of study 1297.8 were found acceptable by the OSIS review team.

Table 1. Key Design Features of BI 695501 Clinical Studies

Study ID	Patient population	Design/Objectives	Dose Duration	Sample size Randomization	Treatment arms
PK Similarity Study					
1297.8	Healthy Subjects	R, DB, 3-arm, PG, 3-way PK bridging	40 mg SC Single dose	N=324 1:1:1	BI 695501 PFS (CF) US-Humira[1] EU-Humira[2]
PK study (Supportive for safety)					
1297.1	Healthy Subjects	R, OL, PG, 3-arm PK bridging study	40 mg SC Single dose	N=193 1:1:1	BI 695501 PFS (TF) US-Humira[1] EU-Humira[2]
Comparative Clinical Study					
1297.2	RA	R, DB, PG Comparative Clinical Study	40 mg SC, every 2 weeks, 48 Weeks	N=645 1:1	BI 695501 PFS (CF) US-Humira[1]
Extension Study					
1297.3	RA	OL extension of 1297.2	48 weeks	ongoing	BI 695501

[1] US-licensed Humira, [2] EU- approved Humira
CF-commercial formulation, TF-trial formulation, , RA- Rheumatoid arthritis, R- Randomized, DB-Double blind, PG-Parallel-group, PK-Pharmacokinetics, SD-Single dose, OL-Open-label, SC- subcutaneous

In the pivotal PK study 1297.8, the 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of BI 695501 to US-licensed Humira, BI 695501 to EU-approved Humira, and US-licensed Humira to EU-approved Humira for the tested PK parameters (i.e., C_{max}, $AUC_{0-\infty}$, AUC_{0-last}) were all within the PK similarity acceptance interval of 80-125% as shown in Table 2. These pairwise comparisons met the pre-specified criteria for PK similarity between BI 695501, US-licensed Humira, and EU-approved Humira. Thus, PK similarity was established

between BI 695501 (to-be marketed formulation) and US-licensed Humira and a PK bridge was established to support the relevance of the data generated using EU-approved Humira in the non-clinical program. In study 1297.2, plasma concentrations of adalimumab were assessed at pre-dose, 6 hour post-dose and at Week 1, 2, 4, 12, 24, and 40. Overall, plasma trough concentrations appeared to be comparable between BI 695501 and US-licensed Humira in the initial randomization period (data not shown), supporting the findings of PK similarity between BI 695501 and US-licensed Humira demonstrated in study 1297.8.

Table 2. Statistical Analysis for PK Parameters (Study 1297.8)

Comparison	Parameter	GMR%	90% CI (%)
BI 695501 vs US-licensed Humira	C_{max}	100.85	(95.15, 106.88)
	$AUC_{0\text{-last}}$	107.32	(98.49, 116.94)
	$AUC_{0\text{-}\infty}$	108.62	(98.50, 119.79)
BI 695501 vs EU-approved Humira	C_{max}	96.39	(91.06, 102.03)
	$AUC_{0\text{-last}}$	99.93	(92.15, 108.37)
	$AUC_{0\text{-}\infty}$	101.27	(92.45, 110.94)
US-licensed Humira vs EU-approved Humira	C_{max}	95.93	(90.83, 101.33)
	$AUC_{0\text{-last}}$	93.66	(86.76, 101.11)
	$AUC_{0\text{-}\infty}$	94.02	(86.01, 102.78)
Source: FDA analysis of data from BI 351(k) BLA submission			

Of note, the Applicant had initially conducted study 1297.1, which utilized a formulation of BI 695501, referred to as "trial" formulation, different from the one proposed for commercialization. Thus the results from study 1297.1 were not taken into account for PK similarity assessment although it was reviewed for completeness and assessment of safety. It is noteworthy that the pre-defined acceptance criteria for PK similarity were not met for all 3 treatment comparisons in Study 1297.1. Exploration of the possible causative factors affecting the PK similarity in Study 1297.1 identified high overall variability, influence of body weight on exposure, differences in the protein concentration of the reference and test formulations, and an unexpectedly low exposure of EU-approved Humira. In contrast, the pivotal PK study 1297.8 used the commercial formulation of BI 695501, and controlled for the possible causative factors affecting the PK similarity in Study 1297.1. Based on these considerations, the OCP review team concluded, and we agree, that Study 1297.8 utilizing the commercial formulation of BI 695501 should be used as the pivotal study for assessment of PK similarity.

The Office of Clinical Pharmacology (OCP) has determined, and we agree, that PK similarity has been demonstrated between BI 695501 and US-licensed Humira and that the PK data supported the scientific bridge justifying the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of BI 695501 to US-licensed Humira. The OCP has concluded that the clinical pharmacology results from the BI 695501 program add to the totality of evidence to support a demonstration of no clinically

meaningful differences between BI 695501 and US-licensed Humira. We concur with this assessment. The PK studies have not raised any new uncertainties and the clinical pharmacology data support a demonstration of biosimilarity between BI 695501 and US-licensed Humira.

6) Clinical Microbiology

Not applicable.

7) Clinical/Statistical-Efficacy

Primary Statistical Reviewer: James Travis, Ph.D.
Statistical Team Leader: Gregory Levin, Ph.D.
Primary Clinical Reviewer: Stefanie Freeman, M.D.
Clinical Team Leader: Nikolay Nikolov, M.D.

Overview of the Clinical Program

To support the demonstration of no clinically meaningful differences between BI 695501 and US-licensed Humira, in addition to the PK similarity study in healthy subjects (study 1297.8) discussed in the section on Clinical Pharmacology above, BI submitted clinical safety, immunogenicity, and efficacy data from one comparative clinical study (study 1297.2) in patients with RA, described in detail in this section below. The key design features of these studies are summarized in Table 1 above.

Study 1297.2 was a randomized, double blind, parallel group, multicenter comparative clinical study to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of BI 695501 compared to US-licensed Humira in 645 subjects with moderate to severe RA despite MTX therapy. Patients must also have been receiving and tolerating oral or parenteral methotrexate therapy at a dose of 15 to 25 mg per week. Patients were allowed to have exposure to no more than one biologic agent. The majority of the patients were from sites in Poland, the US and Ukraine; additional patients were recruited from sites in Serbia, the Russian Federation, Korea, Thailand, and Malaysia. The study consisted of two distinct periods:

1) Randomized double blind period up to Week 24 to either BI 695501 or US-licensed Humira. A total of 645 subjects with moderate to severe RA were randomized in a 1:1 ratio to receive BI 695501 (n=324) or US-licensed Humira (n=321).
2) Transition period starting at Week 24: At week 24, patients originally randomized to the US-licensed Humira group were re-randomized in a 1:1 ratio to undergo a single transition to BI 695501 (n=147) or continue on US-licensed Humira (n=148). Subjects originally randomized to the BI 695501 arm continued the same treatment in this stage (n=292). Study objectives in this period were to compare the long-term safety, tolerability, immunogenicity and efficacy of BI 695501 in subjects with RA who

underwent a single transition from US-licensed Humira treatment to BI 695501 to subjects who maintained the US-licensed Humira treatment.

Treatment groups were balanced with respect to demographics and disease characteristics. The amount of discontinuation from the study prior to both Week 12 and Week 24 was low (2% and 3% at Week 12 and 6% and 5% at Week 24 for the BI 695501 and US-licensed Humira arms, respectively).

The pre-specified primary endpoints for this study were the proportion of patients who met the criteria for an American College of Rheumatology 20% (ACR20) response at Week 12 and 24. This endpoint is considered sufficiently sensitive for the assessment of similarity in clinical efficacy. For this study the Applicant selected two different similarity margins for the two ACR20 endpoints. For the Week 12 endpoint the 90% confidence interval of the difference in ACR20 response rates between patients receiving BI 695501 and US-licensed Humira must have been greater than -12% and less than 15%. This was the primary analysis aligning with recommendations from the Agency. For the Week 24 endpoint the 95% confidence interval of the difference must have been between -15% and 15%. The Agency accepted an asymmetric similarity interval of (−12%, 15%) based on pre-submission discussions and the Applicant's justification.

As shown in Table 3, the proportion of patients who achieved an ACR20 response at Week 12 and 24 was similar between BI 695501 and US-licensed Humira, and contained within the similarity margin. Analysis of the per-protocol set further supported the findings from the full analysis set (data not shown).

Table 3. Primary Efficacy: Estimates and CIs for Differences in ACR20 Response Rate at Week 12 and 24, Study 1297.2 (Full Analysis Set)

	Treatment	N	ACR20 Response Proportion (%)	Difference in Proportion (BI 695501 – Humira, %)	
				Estimate	90% CI
Week 12	BI 695501	324	66.4	5.9	(−0.8, 12.7)
	US-licensed Humira	321	60.5		
Week 24	BI 695501	324	68.4	4.4	(−2.3, 11.1)
	US-licensed Humira	321	64.0		
Source: FDA analysis of data from BI 695501 351(k) BLA submission					

The comparative analyses of secondary endpoints, such as ACR components, HAQ-DI scores, and DAS28, also showed similar efficacy between the two treatment groups (data not shown). The proportion of patients meeting the ACR50 and ACR70 response criteria was also similar between groups (Table 4). The small numerical differences observed in the ACR70 response rates at Week 24 are not considered clinically meaningful. These results are likely confounded by the variability in distribution of dichotomized ACR responses. Further, these differences

were not corroborated by the data on ACR responses using different cut-offs, such as ACR20 or ACR50, or by other measures of clinical response, such as DAS28.

Table 4. Estimate for Differences in ACR50 and ACR70 Response Rate at Week 12 and 24 (Study 1297.2)

Parameter	Week	BI 695501 Response (%) N=324	Humira Response (%) N=321	Difference in Proportion (BI 695501 – Humira, %)	
				Estimate	90% CI
ACR50	12	28.9%	30.6%	−1.7	(−8.3, 4.8)
	24	36.5%	36.3%	0.3	(−6.7, 7.3)
ACR70	12	10%	10.9%	−0.9	(−5.3, 3.5)
	24	13.5%	17.7%	−4.3	(−9.2, 0.6)

Source: FDA's analysis of data from 351(k)BLA submission

The design, conduct, and within-group response rates of study 1297.2 were largely similar to those characteristics in historical clinical studies that demonstrated relatively large and consistent treatment effects of adalimumab over placebo, as detailed in the FDA statistical review. Therefore, the totality of available information supports the constancy assumption and the sufficiency of the assay sensitivity of study 1297.2. The FDA's analyses were consistent with those conducted by the Applicant.

The FDA statistical review team concluded, and we concur, that the results from the comparative clinical study 1297.2 support a demonstration of no clinically meaningful differences between BI 695501 and US-licensed Humira.

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL's conclusions**

In summary, the Applicant has provided statistically robust comparative clinical data demonstrating similar efficacy between BI 695501 and US-licensed Humira in patients with moderate-to-severe RA despite methotrexate in study 1297.2. The primary analyses were supported by the analyses of key secondary endpoints and sensitivity analyses accounting for missing data. The FDA statistical and clinical teams concluded, and we agree, that the results from study 1297.2 support a demonstration of no clinically meaningful differences between BI 695501 and US-licensed Humira.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

None.

8) Safety

Primary Clinical Reviewer: Stefanie Freeman, M.D.
Clinical Team Leader: Nikolay Nikolov, M.D.
OBP Immunogenicity Reviewer: Davinna L. Ligons, Ph.D.
OBP Secondary Immunogenicity Reviewer: Howard Anderson, Ph.D.

- **Studies contributing to safety analyses**

The primary safety data were derived from one comparative clinical study in 645 patients with moderate-to-severe RA (Study 1297.2). In Period 2 of the study at Week 24, a total of 146 subjects underwent a single transition from US-licensed Humira to BI 695501 to assess additional risks, if any, in safety and immunogenicity resulting from a single transition from US-licensed Humira to BI 695501 to address the safety of the clinical scenario where non-treatment naïve patients transition to BI 695501. Supportive safety and immunogenicity information was also provided from two single dose PK studies in healthy subjects (Studies 1297.1 and 1297.8). The safety and immunogenicity data were reviewed for each individual study. Overall, the safety database is adequate to provide a reasonable comparative safety assessment to support a demonstration of no clinically meaningful differences between BI 695501 and US-licensed Humira.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Overall, there were no notable differences in adverse events (AEs), serious adverse events (SAEs), or AEs leading to discontinuations between the treatment groups. Infections were the most common AE in all treatment groups (BI 695501, US-licensed Humira, and EU-approved Humira). Adverse events leading to discontinuation were infrequent and balanced between treatment arms. Reports of hypersensitivity and injection site reactions were balanced between treatment arms with a single case of anaphylaxis in a patient receiving US-licensed Humira. An overview of AEs across the controlled studies is summarized in Table 5 and Table 6. No new safety signals were identified in the BI 695501 group compared to the known adverse event profile of US-licensed Humira, as described in the FDA-approved labeling for Humira.[3]

[3] FDA-approved Humira labeling

Table 5. Overview of Safety in Study 1297.2

	Period 1, up to Week 24		Period 2, Weeks 24 to 48		
	BI 695501 (N=324)	US-Humira (N=321)	BI 695501 continued (N=298)	Humira continued (N=148)	Humira to BI 695501 (N=146)
TEAEs, n (%)	134 (42)	147 (46)	50 (17)	40 (27)	51 (35)
SAEs, n (%)	12 (4)	18 (6)	6 (2)	5 (3)	2 (1)
TEAEs leading to discontinuation, n (%)	8 (3)	11 (3)	4 (1)	1 (<1)	2 (1)
Infections, n (%)	71 (22)	83 (26)	36 (21)	23 (16)	28 (19)
Serious Infections, n (%)	1 (<1)	8 (3)	1 (<1)	1 (<1)	1 (<1)
Malignancy, n (%)	0	2 (1)	0	0	0
Injection Site Reaction, n (%)	5 (2)	10 (3)	2 (1)	2 (1)	0
Anaphylaxis, n (%)	0	1 (<1)	0	0	0
Hematological Disorder, n (%)	10 (3)	3 (1)	10 (3)	2 (1)	2 (1)
Drug-induced Liver Injury, n (%)	1 (<1)	0	2 (1)	1 (<1)	0
Death, n	0	0	0	0	0

Source: FDA analysis of data from BI 695501 351(k) BLA submission
AE: adverse event; SAE: serious adverse event, TEAE: treatment emergent adverse events

Table 6. Overview of Safety in Single Dose Healthy Subjects Studies 1297.1 and 1297.8 (Pooled)

	BI 695501 (N=175)	US-Humira (N=170)	EU-Humira (N=172)
TEAEs, n (%)	134 (77)	129 (76)	127 (74)
SAEs, n (%)	3 (2)	3 (2)	2 (1)
TEAEs leading to discontinuation, n (%)	0	0	0
Serious Infections, n (%)	0	2 (1)	0
AESI, n (%)	2 (1)	2 (1)	1 (<1)
Anaphylaxis, n	0	0	0
Death, n	0	0	0

Source: FDA analysis of data from BI 695501 351(k) BLA submission
AE: adverse event; AESI-adverse events of special interest; SAE: serious adverse event

Death

No deaths were reported in studies 1297.1, 1297.2, and 1297.8.

One death was reported in the 120-day safety update in the extension study 1297.3. The patient was a 71 year-old female who had received BI 695501 for approximately 1.5 years. She was initially hospitalized due to an abdominal hernia and acute appendicitis, underwent a

laparoscopic appendectomy and was discharged from the hospital. Approximately one week later she returned to the hospital with abdominal pain and bloody stools. An abdominal X-ray showed signs of intestinal paralysis. She underwent a hemicolectomy at which time she was diagnosed with cecal adenocarcinoma with abdominal metastasis. Her condition worsened and she died as a result of cardiorespiratory failure.

Nonfatal Serious Adverse Events (SAE)

The proportion of patients who experienced at least one SAE was similar between the treatment groups during the controlled period of clinical studies as detailed in Table 5 and Table 6 above. The most frequently reported SAEs were infections, which were overall similar between the treatment groups. SAEs across the system organ classes (SOCs) showed a similar distribution with minor numerical differences between each group. There was no notable difference in the incidence of SAEs following a single transition in Period 2 from US-licensed Humira to BI 695501 in Study 1297.2. The different SOCs of SAEs or the pattern of SAEs in the BI 695501 clinical program were consistent with the known safety profile of US-licensed Humira as presented in the FDA-approved Humira labeling.

Discontinuations due to Adverse Events (AE)

The proportion of patients discontinuing due to an adverse event was similar between BI 695501 and US-licensed Humira as detailed in Table 5 above. Infections and investigations were the most common reason for discontinuation in Study 1297.2. There was no notable difference in the incidence of treatment discontinuation due to adverse events following the single transition from US-licensed Humira to BI 695501 in Period 2 of Study 1297.2.

Adverse Events of Special Interest (AESI)

The selection of AESI was informed by the known safety profile of US-licensed Humira as presented in the FDA-approved Humira labeling and other published data. Overall, the incidence of AESI, including serious infections, anaphylaxis,[4] malignancy, and liver abnormalities, between the BI 695501, US-licensed Humira, and EU-approved Humira treatment arms was similar across the controlled portions of the clinical studies. No increase in AESI was observed following a single transition from US-licensed Humira to BI 695501 in Period 2 of Study 1297.2.

Common AE

Nasopharyngitis, upper respiratory tract infections, headaches, and disease activity were the most common adverse events in Study 1297.2 with event rates similar between BI 695501 and US-licensed Humira. Following the single transition in Period 2 of Study 1297.2, the common adverse event profile remained consistent and similar between subjects who underwent the single transition from US-licensed Humira to BI 695501 and those who continued on US-

[4] Sampson HA et al., J Allergy Clin Immunol. 2006 Feb;117(2):391-7

licensed Humira. The incidence and types of common adverse events were generally similar between the treatment arms and were consistent with the known safety profile of US-licensed Humira as presented in the FDA-approved Humira labeling, further supporting a demonstration that there are no clinically meaningful differences between BI 695501 and US-licensed Humira in the indication studied. A numerical imbalance was noted in the incidence of fractures with seven patients (2.2%) treated with BI 695501 in Period 1 and 2 versus 0 in the US-licensed Humira arm. Three events of fracture were reported as SAEs, including a fracture of the femoral neck, lumbar vertebral fracture and rib fracture. Most of the patients with fractures had significant risk factors such as long-term treatment with glucocorticoids and osteoporosis. Importantly, there was no consistent pattern of fracture type and much of the imbalance appears to be the result of traumatic injuries. Given these considerations, and the degree of analytical and functional similarity between BI 695501 and US-licensed Humira, the numerical differences in fracture incidence do not preclude the conclusion that no clinically meaningful differences exist between BI 695501 and US-licensed Humira.

Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)

No unexpected laboratory findings were reported in the BI 695501 clinical program. A small numerical imbalance in cases of anemia was reported in the BI 695501 group. These cases represented mostly pre-existing laboratory abnormalities and did not result in discontinuation of treatment. Further, the shifts to CTCAE grade 3 or 4 levels for hemoglobin were similar between treatment groups. Also the mean and median group changes for hemoglobin and hematocrit values were similar between treatment groups during the study. In this context, the small imbalance in the cases of anemia does not preclude a demonstration of no clinically meaningful differences between BI 695501 and US-licensed Humira.

- **Immunogenicity**

In the BI 695501 clinical studies, determination of anti-drug antibodies (ADA) consisted of a multi-tiered approach with sequential screening, confirmation, and characterization using validated assays consistent with 2014 FDA Draft Guidance for Validation for Immunogenicity Testing of Therapeutic Protein Products. A titer assay was used to determine ADA levels in positive plasma samples. Positive plasma samples were evaluated for neutralizing activity using a cell base TNF alpha-inducing antibody-dependent cell-mediated cytotoxic (ADCC) assay. The product quality review team concluded, and we agree, that the immunogenicity assays used to evaluate ADA are adequately validated.

Immunogenicity in Study 1297.2

In Study 1297.2, ADAs were assessed at sequential time points starting at baseline (pre-dose), Weeks 1, 2, 4, 12, 24 (in Part 1), and Weeks 24, 40, 48, and 58 (in the single transition Part 2). As shown in Table 7, a similar proportion of patients tested positive for both ADAs and neutralizing antibodies (nAbs) between patients treated with BI 695501 and US-licensed Humira at multiple time points. Further, as shown in Table 8, the incidence of these antibodies

remained similar between the three groups and did not increase following a single transition from US-licensed Humira to BI 695501.

Table 7. Proportion of ADA and nAb Positive Patients Following Repeat Dosing in Study 1297.2 (Part 1)

	ADA positive, n/N (%)		nAb positive, n/N (%)	
Timepoint	BI 695501	US-Humira	BI 695501	US-Humira
Predose	11/322 (3)	21/321 (7)	9/322 (3)	16/321 (5)
Week 1	18/317 (6)	29/311 (9)	10/317 (3)	12/311 (4)
Week 2	32/317 (10)	51/318 (16)	9/317 (3)	26/318 (8)
Week 4	64/319 (20)	62/315 (20)	20/319 (6)	24/314 (8)
Week 12	101/311 (33)	106/304 (35)	39/311 (13)	53/303 (18)
Week 24	127/294 (43)	144/301 (48)	48/294 (16)	61/301 (20)
Source: FDA analysis of data from BI 695501 351(k) BLA submission				

Table 8. Proportion of ADA and nAb Positive Patients Following Repeat Dosing in Study 1297.2 (Part 2)

	ADA positive, n/N (%)			nAb positive, n/N (%)		
Timepoint	BI 695501 continued	US-Humira continued	US-Humira to BI 695501	BI 695501 continued	US-Humira continued	US-Humira to BI 695501
Week 24	125/292 (43)	74/147 (50)	65/146 (45)	46/292 (16)	35/147 (24)	23/146 (16)
Week 40	117/284 (41)	65/140 (46)	61/140 (44)	38/284 (13)	22/140 (16)	25/140 (18)
Week 48	118/282 (42)	69/139 (50)	50/138 (36)	54/282 (19)	30/139 (22)	21/138 (15)
Week 58	21/47 (45)	21/36 (58)	14/34 (41)	16/47 (34)	14/36 (39)	10/34 (29)
Source: FDA analysis of data from BI 695501 351(k) BLA submission						

Immunogenicity in Study 1297.8

Overall a high proportion of subjects developed ADAs with approximately 90% of subjects ADA positive on Day 71 and 60% with nAb in all treatment groups. As summarized in Table 9, a higher frequency of positive ADAs was observed at a very early time point, Day 8, in the BI 695501 group. However, no notable differences in nAbs between treatment arms were observed at that time point (data not shown), and the proportion of subjects with ADAs and nAbs was similar across treatment groups at multiple time points thereafter, from Days 14 through end of testing on Day 71.

Table 9. Incidence of ADAs in Healthy Subjects, Study 1279.8

	ADA positive			nAb positive		
Timepoint	BI 695501 (n=108)	US-Humira (n=108)	EU-Humira (n=108)	BI 695501 (n=108)	US-Humira (n=108)	EU-Humira (n=108)
Baseline	4 (4%)	3 (3%)	4 (4%)	3 (3%)	1 (1%)	2 (2%)
Day 8	35 (33%)	6 (6%)	5 (5%)	2 (2%)	0 (0%)	0 (0%)
Day 14	44 (41%)	38 (35%)	21 (20%)	5 (5%)	5 (5%)	5 (5%)
Day 28	50 (47%)	60 (56%)	40 (37%)	12 (11%)	19 (18%)	9 (8%)
Day 44	62 (58%)	59 (55%)	58 (54%)	27 (25%)	36 (34%)	26 (24%)
Day 56	85 (80%)	82 (77%)	78 (74%)	43 (41%)	57 (53%)	42 (40%)
Day 71 (EOS)	99 (93%)	95 (88%)	91 (84%)	64 (60%)	69 (64%)	63 (58%)

Impact of immunogenicity on clinical endpoints

To investigate the potential impact of the ADA on clinical outcomes, the relationship between ADA, primary efficacy endpoint (ACR20), and select relevant safety outcomes associated with ADA (such as hypersensitivity reactions) was examined in study 1297.2 in RA. We acknowledge that such analyses are exploratory in nature and limited by the small sample sizes within subgroups and the non-randomized nature of comparisons, as ADA status is a post-randomization variable and observed differences in efficacy or safety outcomes (or lack thereof) could be attributable to ADA formation or to other confounding variables.

In study 1297.2 few hypersensitivity reactions were reported, and numbers of hypersensitivity and injection site reactions were similar between BI 695501 and US-licensed Humira groups. Most ADA positive patients did not have any AEs reported for either hypersensitivity or injection site reactions. No patients treated with BI 695501 had events of anaphylaxis. Immunogenicity and hypersensitivity reactions did not increase after a single transition from US-licensed Humira to BI 695501. In the single-dose clinical pharmacology study 1297.8, the frequency of ADAs and antibody titers were similar in BI 695501, US-licensed Humira, and EU-approved Humira groups. Adverse events of hypersensitivity were also similar between the treatment groups. These data did not indicate significant association of immunogenicity and safety issues with either BI 695501 or US-licensed Humira following repeat administration in study 1297.2, or following single dosing of BI 695501, US-licensed Humira, and EU-approved Humira groups in study 1297.8.

Immunogenicity was assessed at the same time as the efficacy endpoint (ACR20) assessment, i.e. at Week 24 in the randomized, double-blind period in study 1297.2. ACR20 response was observed in a majority of the patients despite ADA status. However, higher incidence and titers of ADAs appeared to have an impact on efficacy but effects were similar between the BI 695501 and the US-licensed Humira groups, as summarized in Table 10. Similarly, a higher incidence of nAbs appeared to negatively impact the clinical responses, but this impact was similar between BI 695501 and US-licensed Humira.

Table 10. ACR20 Response by ADA Status at Week 24 (Study 1297.2, Full Analysis Set)

	N		ACR20 Response rate (%)	
	BI 695501	US-Humira	BI 695501	US-Humira
Overall trial population	321	318	69	65
ADA positive	127	144	69	65
Titer: low (Q1)	32	39	75	67
Titer: medium (Q2-Q3)	59	69	73	67
Titer: high (Q4)	36	36	58	58
ADA negative	167	157	78	71
nAb positive	48	61	60	56
nAb negative	246	240	77	71

Source: FDA analysis of data from BI 695501 351(k) BLA submission
Q=quartile

Conclusions about immunogenicity

Immunogenicity data from the single dose healthy subject studies, and study 1297.2 in patients with RA, does not show an increased risk of development of ADAs with treatment of BI 695501 as compared with US-licensed Humira. ADA formation also did not increase following a single transition from US-licensed Humira to BI 695501. Therefore, the data support similar immunogenicity between BI 695501 and US-licensed Humira and further support a demonstration of no clinically meaningful differences between BI 695501 and US-licensed Humira. Further, the product quality immunogenicity review team recommends approval of the BLA from an immunogenicity perspective and we agree with this recommendation.

- **Discussion of primary reviewer's comments and conclusions**

The safety database submitted for BI 695501 is adequate to provide a reasonable descriptive comparison between the BI 695501 and US-licensed Humira. The safety and immunogenicity analysis of the BI 695501 clinical program in the studied condition of use, RA, and in healthy subjects in the PK single dose Study 1297.8, has not identified notable differences in the safety profile between BI 695501, US-licensed Humira, and EU-approved Humira. No new safety signals have been identified compared to the known adverse event profile of US-licensed Humira. Further, the single transition from US-licensed Humira to BI 695501 after Week 24 in Study 1297.2 did not result in an increase in adverse events, supporting the safety of the clinical scenario where non-treatment naïve patients transition to BI 695501. The FDA safety analysis is consistent with the Applicant's analysis.

The primary review team and we are in agreement that the submitted safety and immunogenicity data and analyses are adequate to support the conclusion of no clinically meaningful differences between BI 695501 and US-licensed Humira in the indication studied.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion**

None.

- **Discussion of notable safety issues (resolved or outstanding)**

None.

9) Extrapolation of Data to Support Biosimilarity in Other Conditions of Use

BI is seeking licensure of BI 695501 for the following indications for which US-licensed Humira is licensed (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, UC, and PsO). The BI 695501 clinical program however, provides clinical efficacy and safety data from a comparative clinical study in patients with RA.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data supporting a demonstration of biosimilarity, including data from clinical study(ies) performed in another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: *"Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,"* if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed.[5] The Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

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

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily

[5] Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (April 2015)
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

preclude extrapolation. Consistent with the principles outlined in the above FDA guidance, BI has provided a justification for the proposed extrapolation of data from study in RA to each of the other indications approved for US-licensed Humira for which BI is seeking licensure, as summarized in this section.

First, BI's extensive analytical characterization data support a demonstration that BI 695501 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components, and that the data support a demonstration there are no clinically meaningful differences between BI 695501 and US-licensed Humira in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in RA.

Further, the additional points considered in the scientific justification for extrapolation of data to support biosimilarity in the indications for which BI is seeking licensure (JIA in patients 4 years of age and older, PsA, AS, adult CD, UC, and PsO) include:

- Similar PK was demonstrated between BI 695501 and US-licensed Humira, as discussed in the section on Clinical Pharmacology above. Importantly, BI 695501 was demonstrated to be highly similar to US-licensed Humira, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between BI 695501 and US-licensed Humira in the indications sought for licensure. Thus, a similar PK profile would be expected between BI 695501 and US-licensed Humira in patients across all the indications being sought for licensure.

- In general, immunogenicity of the US-licensed Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used.[6] As stated previously in this document, the Agency has concluded that there is sufficient data to support similar immunogenicity between BI 695501 and US-licensed Humira with repeat dosing in patients with RA, and between BI 695501, EU-approved Humira, and US-licensed Humira after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between BI 695501 and US-licensed Humira in patients with JIA, PsA, AS, adult CD, UC, and PsO.

- A similar clinical safety profile with chronic dosing was demonstrated between BI 695501 and US-licensed Humira in patients with RA, and between BI 695501, EU-approved Humira, and US-licensed Humira following single doses in healthy subjects. As analytical and PK similarity was demonstrated between BI 695501 and US-licensed Humira, a similar safety profile would be expected between BI 695501 and US-licensed Humira in patients with JIA, PsA, AS, adult CD, UC, and PsO.

[6] FDA-approved Humira labeling

- The mechanism(s) of action (MOA) relevant to the extrapolation of data to support biosimilarity in specific indications are summarized in Table 11 and discussed below.

Table 11. Known and Potential (Likely or Plausible) Mechanisms of Action of US-licensed Humira in the Conditions of Use Sought for Licensure of BI 695501

MOA of Humira	RA, JIA	AS	PsA	PsO	CD	UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible

ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; JIA: juvenile idiopathic arthritis; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors[7,8,9]

Extrapolation of Data to Support Biosimilarity in JIA, PsA, AS, PsO

The primary MOA of adalimumab products is direct binding and blocking of TNF receptor-mediated biological activities (see Table 11 above). Adalimumab products bind to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The published scientific literature indicates that this MOA is the primary MOA in RA, JIA, PsA, AS, and PsO. The data provided by BI showed similar TNF binding and potency to neutralize TNF-α, supporting the demonstration of analytical similarity pertinent to this MOA. Therefore, based on the above considerations, it is reasonable to conclude that the data support extrapolating a demonstration of biosimilarity for BI 695501 to US-licensed Humira in JIA, PsA, AS and PsO.

Extrapolation of Data to Support Biosimilarity in Inflammatory Bowel Disease (IBD) Indications

TNF plays a central role in the pathogenesis of the IBD indications (Crohn's Disease

[7] Oikonomopoulos A et al., Current Drug Targets, 2013, 14, 1421-1432.
[8] Tracey D et al., Pharmacology & Therapeutics 117 (2008) 244–279.
[9] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

and ulcerative colitis), and TNF inhibition is important in treating the diseases, as evidenced by the efficacy of the approved TNF monoclonal antibodies, but the detailed cellular and molecular mechanisms involved have not been fully elucidated.[10] However, the available scientific evidence suggests that for TNF inhibitors in IBD, in addition to binding and neutralization of sTNF, other MOA, listed in Table 11 may play a role.[11] Binding to sTNF and tmTNF involves the Fab region of the antibody, while the other plausible mechanisms of action involve the Fc region of the molecule.

As outlined in the section on CMC/Product Quality above, BI provided experimental data supporting a demonstration that BI 695501 and US-licensed Humira are highly similar based on extensive structural and functional analytical characterization. Further, BI addressed each of the known and potential mechanisms of action of US-licensed Humira listed in Table 11 and submitted data to support the conclusion that BI 695501 and US-licensed Humira have the same mechanisms of action for each of the requested indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Thus, the DGIEP review team concluded, and we agree, that based on the totality of the data demonstrating analytical high similarity, PK similarity, and no clinically meaningful differences in RA between BI 695501 and US-licensed Humira, it is reasonable to conclude that the data support extrapolating a demonstration of biosimilarity for BI 695501 to US-licensed Humira in IBD conditions of use.

In aggregate, based on the above considerations, a conclusion that the data support extrapolation of a demonstration of biosimilarity for BI 695501 to US-licensed Humira in JIA, PsA, AS, adult CD, UC, and PsO, to support licensure of BI 695501 for the indications being sought is scientifically justified.

10) Advisory Committee Meeting

An Advisory Committee (AC) meeting was determined not to be necessary as there were no issues where the Agency needed input from the committee.

11) Pediatrics

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, pediatric assessment**

[10] Oikonomopoulos A et al., "Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?", Current Drug Targets, 2013, 14, 1421-1432
[11] Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", Pharmacology & Therapeutics 117 (2008) 244–279

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(m) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred. Thus, if BI 695501 is licensed only as a biosimilar product, it triggers PREA and BI would be expected to address PREA for every indication for which they are seeking licensure.

Following revisions to the initial pediatric study plan (iPSP), based on the Agency's feedback, BI submitted an agreed iPSP and a conforming pediatric assessment under the BLA, to address the PREA requirements for the following indications as detailed below:

- Rheumatoid Arthritis (RA), Polyarticular juvenile idiopathic arthritis (JIA): Polyarticular JIA has been considered the condition of use to address PREA for products approved for RA. With this BLA, BI proposed that the pediatric assessment is complete, for JIA patients between 4 and 17 years old, in part by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to BI 695501. BI requested a deferral of the requirements to submit a pediatric assessment for JIA patients 2 to < 4 years of age (b) (4) Further, the Applicant proposed to develop a pediatric (b) (4) presentation to treat the pediatric population that require lower doses, patients with body weight <30 kg, as indicated in the FDA-approved Humira labeling (b) (4) The Applicant has also submitted requests for waiver of the requirement to submit a pediatric assessment for patients < 2 years old because the condition is rare in this age group and such studies would be impossible or highly impracticable.

- Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA): The Applicant has submitted requests for full waiver of the requirement to submit a pediatric assessment for juvenile AS and juvenile PsA because the studies would be impossible or highly impracticable due to the difficulty of making specific diagnoses of juvenile PsA or juvenile AS in the pediatric age range.

- Plaque Psoriasis: Consistent with the agreed iPSP, with this submission, the Applicant submitted a request for a waiver of the requirements to submit a pediatric assessment for patients with pediatric chronic severe plaque psoriasis ages 0 to 17 years old due to (b) (4) However, the current view by the DDDP and the Division of Pediatric and Maternal Health (DPMH) is that a full waiver should be granted for pediatric studies in patients with plaque psoriasis based on the rationale that the product fails to

represent a meaningful therapeutic benefit[12] over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients, as described below:

- BI695501, a TNF-alpha inhibitor, does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients. Another TNF-alpha inhibitor is an approved product for the treatment of pediatric patients 4 years and older with moderate to severe plaque psoriasis. In addition, as a class, TNF-alpha inhibitors are generally not currently the most recommended approved therapies for the treatment of patients with moderate to severe psoriasis; more narrowly-targeted agents such as ixekizumab, secukinumab, and ustekinumab are recommended as first-line therapeutic options for children with psoriasis who are in need of treatment with a systemic agent. In addition, apremilast, an inhibitor of phosphodiesterase type 4, is an approved systemic drug product for the treatment of moderate to severe psoriasis.

  Based on the above considerations, DDDP has concluded, and DPMH agrees, that BI695501 would not provide for the meaningful therapeutic benefit over these existing therapies for pediatric patients.

- BI695501 is not likely to be used in a substantial number of pediatric patients because, based on DDDP's evaluation of use data for the time period from January 1, 2009 to June 30, 2015, TNF-alpha inhibitors were used to treat psoriasis in only a very limited number of pediatric patients (0.2% share of total use of all TNFs). For adalimumab, the reported number of uses was even lower (approximately (b) (4)).[13]

- Crohn's Disease: The Applicant requested a deferral of the requirements to submit a pediatric assessment for patients with Crohn's disease 6 to 17 years of age (b) (4) As a scientific matter, based on emerging epidemiologic data, the Agency has determined that under PREA, pediatric studies would be required for patients with CD down to 2 years of age. However, the Agency has also determined that dedicated studies for patients with CD limited to ages 2 to <6 years old would be impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age. Thus, the Applicant requested a waiver of the requirement to submit a pediatric assessment for patients <6 years old.

- Ulcerative Colitis: The Applicant requested a deferral of the requirements to submit a pediatric assessment for patients with ulcerative colitis 5 to 17 years of age (b) (4) As a scientific matter, based on emerging epidemiologic data, the Agency has determined that under PREA, pediatric

[12] See section 505B(c) of the FD&C Act.
[13] Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Jan 2009 - Jun 2015. Extracted September 2015

studies would be required for patients with UC down to 2 years of age. However, the Agency has also determined that dedicated studies for patients with UC limited to ages 2 to <5 years old would be impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age. Thus, the Applicant requested a waiver of the requirement to submit a pediatric assessment for patients < 5 years old.

The BI 695501 pediatric study plan was discussed at the Pediatric Review Committee (PeRC) meeting on July 19, 2017. The PeRC agreed with the requested waivers and deferrals for RA, JIA, AS, PsA, CD, and UC. For the pediatric assessment for PsO, PeRC recommended that waiver of the requirements to submit a pediatric assessment for patients with pediatric chronic severe plaque psoriasis ages 0 to 17 years old is appropriate because BI 695501 would not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested (0 to ≤17 years of age). PeRC also recommended that PREA post-marketing requirements (PMR) be issued for BI to submit a pediatric assessment for patients with JIA 2 to <4 years of age, patients with CD 6 to 17 years of age, patients with UC 5 to 17 years of age, and for BI to develop an age appropriate presentation so that this product may be accurately administered to pediatric patients down to 2 years of age with pJIA. We agree with PeRC's recommendations.

12) Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted, no issues.
- **Exclusivity**— There is no unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Humira (adalimumab) (BLA 125057; AbbVie Inc.) that would prohibit the approval of BI 695501.
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **OSI audits—**Two clinical sites that enrolled patients in the comparative clinical study 1297.2 in RA were selected for inspection. The inspections showed the clinical sites to be in compliance with Good Clinical Practices. The Applicant was also inspected. The OSI investigators concluded that the data submitted were acceptable to support the current BLA.
- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—Not applicable.

13) Labeling

- **Proprietary name**

The Applicant submitted the proposed proprietary name Cyltezo for review. The name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by

the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be conditionally acceptable. We agree with this assessment.

- **Non-proprietary/Proper name**

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for BI's Cyltezo product is necessary to distinguish this proposed product from Humira (adalimumab). As explained in FDA's Guidance for Industry, Nonproprietary Naming of Biological Products, FDA expects that a nonproprietary name that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance of biological products.[14]

The Applicant submitted a list of suffixes to be used in the nonproprietary name of BI 695501 along with supporting analyses intended to demonstrate that the proposed suffixes satisfied the factors described in section VI of the Guidance for Industry, Nonproprietary Naming of Biological Products. The DMEPA review concluded, and we agree, that BI's proposed distinguishing suffix "adbm" is acceptable and the nonproprietary name "adalimumab-adbm" should be reflected in the product label and labeling accordingly.

- **Important issues raised by brief discussion of OPDP and OSE Division comments**

None

- **Physician labeling**

The Applicant-proposed labeling is closely tracking the labeling of US-licensed Humira.

During the BLA labeling review, revisions were made for consistency with the Guidance for Industry, Labeling for Biosimilar Products (January 2017). Additionally, references to orphan-protected indications and related protected information were omitted from the BI 695501 labeling and it was determined that such information was not essential for the safe and effective use of BI 695501 for the remaining non-protected conditions of use.

The proprietary name "Cyltezo" and the non-proprietary name "adalimumab-adbm" should be reflected in the product labeling as appropriate.

- **Carton and immediate container labels**

As discussed above in the DMEPA review and recommendations, the proprietary name "Cyltezo" and the non-proprietary name "adalimumab-adbm" should be reflected in the product Patient labeling/Medication guide as appropriate.

[14] See the FDA Guidance for Industry on Nonproprietary Naming of Biological Products (January 2017). The guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

- **Patient labeling/Medication guide**

The Applicant proposed a Patient labeling/Medication guide closely tracking that of US-licensed Humira. The proprietary name "Cyltezo" and the non-proprietary name "adalimumab-adbm" should be reflected in the product Patient labeling/Medication guide as appropriate.

14) Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

We recommend approval of the 351(k) BLA 761058 for BI 695501 to receive licensure as a biosimilar product to US-licensed Humira for each of the following indications for which US-licensed Humira is currently licensed and BI is seeking licensure of BI 695501: RA, JIA in patients 4 years and older, PsA, AS, PsO, Adult CD, and UC.

- **Totality of the Evidence**

The conclusion of the comparison of the structural and functional properties of the clinical and commercial product lots of BI 695501 and US-licensed Humira was that they were highly similar, notwithstanding minor differences in clinically inactive components.

BI provided extensive analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Humira to support a demonstration of biosimilarity of BI 695501 to US-licensed Humira.

The submitted pivotal clinical pharmacology study is adequate to (1) support the demonstration of PK similarity between BI 695501 and US-licensed Humira, and (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved Humira.

The results of the clinical development program indicate that Applicant's data meet the requirement for a demonstration of no clinically meaningful differences between BI 695501 and US-licensed Humira in terms of safety, purity, and potency in the indication studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included the use of a chronic dosing regimen of BI 695501 and US-licensed Humira in patients with RA, adequately support a demonstration that there are no clinically meaningful differences between BI 695501 and US-licensed Humira in RA. The single transition from US-licensed Humira to BI 695501 during the second part of Study 1297.2 did not result in different safety or immunogenicity profile. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to BI 695501.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity of BI 695501 to US-licensed Humira to conditions of use not directly studied to support licensure of BI 695501 for each of the indications for which US-licensed Humira is currently licensed and for which BI is seeking licensure of BI 695501.

In considering the totality of the evidence submitted, the data submitted by the Applicant show that BI 695501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between BI 695501 and US-licensed Humira in terms of the safety, purity, and potency of the product. The information submitted by the Applicant demonstrates that BI 695501 is biosimilar to US-licensed Humira and should be licensed.[15]

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

None.

- **Recommendation for other Postmarketing Requirements and Commitments**

Postmarketing Requirement (PMR):

As currently presented, BI 695501 presentations are not designed to allow for accurate administration of doses less than 40 mg, which impacts children who weigh less than 30 kg. For accurate weight-based dosing of patients that are less than 30 kg, an age-appropriate presentation is required under PREA. Therefore, I recommend a PREA PMR for the development of a presentation that can be used to accurately administer BI 695501 to pediatric patients who weigh less than 30 kg. Also, under PREA, BI is required to submit a pediatric assessment for patients with JIA 2 to <4 years of age, patients with CD 6 to 17 years of age, patients with UC 5 to 17 years of age. Thus, to address the PREA requirements, I recommend the following PREA PMRs:

1. Assessment of Cyltezo (adalimumab-adbm) for the treatment of pediatric ulcerative colitis in patients 5 to 17 years of age.

   Final Report Submission Date: December 2020

2. Assessment of Cyltezo (adalimumab-adbm) for the treatment of pediatric Crohn's disease in patients 6 years to 17 years of age.

   Final Report Submission Date: September 2021

[15] The proposed BI 695501 labeling states: "Biosimilarity of CYLTEZO has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

3. Assessment of Cyltezo (adalimumab-adbm) for the treatment of juvenile idiopathic arthritis (JIA) in patients ages 2 to <4 years of age.

   Final Report Submission Date: September 2021

4. Develop a presentation that can be used to accurately administer Cyltezo (adalimumab-adbm) to pediatric patients who weigh less than 30 kg.

   Final Report Submission Date: September 2021

Postmarketing Commitments (PMC):

We concur with the post-marketing commitments recommended by the OBP, product quality review team, as listed below:

1. Develop a comprehensive and robust control strategy to control for effector function of BI 695501.

   Final Report Submission: December 2018

We concur with the post-marketing commitments recommended by the DMA, microbiology review team, as listed below:

2. Conduct the bioburden in-process and release method qualification using two additional batches of BI 695501.

   Final Report Submission: August 2018

- **Recommended Comments to Applicant**

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NIKOLAY P NIKOLOV
08/25/2017

BADRUL A CHOWDHURY
08/25/2017
I concur