CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761058Orig1s000

PHARMACOLOGY REVIEW(S)

Pharmacology and Toxicology Secondary Review for BLA 761058

Date: July 27, 2017

To: **BLA 761058**
BI695501 (proposed biosimilar to adalimumab)
Boehringer Ingelheim, Inc.

From: Carol M. Galvis, PhD
Acting Pharmacology and Toxicology Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Recommendation

I concur with the primary reviewer, Dr. Lawrence Steven Leshin, that the nonclinical development program is adequate and the application is recommended for approval from the nonclinical pharmacology and toxicology perspective (refer to Dr. Leshin's review dated June 14, 2017). There are no outstanding nonclinical issues.

Background

Boehringer Ingelheim Inc. submitted BLA 761058 on October 27, 2016, to support registration of BI695501, under section 351(k) of the Public Health Service Act, as a biosimilar to adalimumab (US-licensed Humira). Adalimumab is a monoclonal antibody against tumor necrosis factor alpha (TNFα) and blocks interaction of TNFα with the TNF receptors.

US-licensed Humira was developed by Abbot Laboratories under BLA 125057 and is currently indicated for Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) in patients 2 years of age and older, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), adult and pediatric Crohn's Disease, Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Hidradenitis Suppurativa (HS), and Uveitis (UV). The applicant seeks approval of BI695501 for all the approved non-exclusive indications (RA, JIA 4 years of age and older, PsA, AS, adult Crohn's Disease, UC, and Ps) using the same approved dosing regimens. BI695501 is formulated in a solution for subcutaneous injection.

Summary of Pharmacology and Toxicology Data with BI695501

The nonclinical pharmacology and toxicology program included in vitro pharmacology studies, a non-GLP pharmacokinetic study in cynomolgus monkeys using BI695501 and US-licensed Humira, and a 5-week repeat-dose toxicity study in cynomolgus monkeys using BI695501 and EU-approved Humira. An adequate scientific bridge based on analytical similarity was demonstrated

between BI695501, US-licensed Humira, and EU-approved Humira; therefore, the repeat-dose toxicology study could be used to assess the safety of BI695501.

Collectively, there was no evidence in the nonclinical studies to indicate potential safety concerns associated with BI695501 administration. The toxicokinetic and toxicology profiles of BI695501 were considered reasonably similar to that of US-licensed Humira in cynomolgus monkeys.

Labeling

The nonclinical sections of the label mirrored the approved labels for US-licensed Humira and Amjevita (approved adalimumab biosimilar).

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/s/

CAROL M GALVIS
07/27/2017

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

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761058
Supporting document/s:	SD-1
Applicant's letter date:	October 27, 2016
CDER stamp date:	October 27, 2016
Product:	BI 695501 (Adalimumab biosimilar)
Indication:	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, and Plaque Psoriasis
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	L. Steven Leshin, D.V.M., Ph.D.
Acting Team Leader:	Carol Galvis, Ph.D.
Division Director:	Badrul A. Chowdhury, M.D., Ph.D.
Project Manager:	Sadaf Nabavian

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The applicant is seeking licensing approval to market BI 695501, as a biosimilar to US-licensed Humira® (adalimumab) under the 351(k) pathway of the Public Health Service Act. Humira, approved in 2002 (BLA 125057), was developed by Abbot Laboratories and is now owned by AbbVie. Adalimumab is a monoclonal antibody against tumor necrosis factor alpha (TNFα) and exerts its therapeutic effects by blocking TNFα interaction with the TNF-receptors TNFR1 and TNFR2. The applicant is seeking the same indications for BI 695501 as indicated for Humira and that are not covered by orphan exclusivity. These indications are rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis. One adalimumab biosimilar, Amjevita (adalimumab-atto) injection (BLA 761024) was recently approved on September 23, 2016.

The BI 695501 drug product will be provided as solution for subcutaneous (SC) injection, 40 mg/0.8 mL, in a single-use 1 mL pre-filled syringe (PFS). (b) (4)

Most nonclinical studies to support the clinical development were previously reviewed under IND 110467 and that review is included in the Appendix. The nonclinical program was discussed with the applicant during the IND development.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical studies included pharmacology, pharmacokinetic, and a 5-week repeated dosing toxicity study in cynomolgus monkeys. The studies used either or both US-licensed and EU-approved Humira as comparators to BI 695501.

Pharmacology: BI 695501 is a human monoclonal immunoglobulin (IgG1 κ subtype) against human TNFα. The applicant provided qualitative and quantitative data to demonstrate similarly of BI 695501 to US-licensed and EU-approved Humira with regard to the pharmacological parameters listed below. Refer to the extensive analysis of these parameters by the Product Quality reviewers.

- Binding to soluble TNF-α (measured in 3 assay formats)
- Binding to membrane bound TNF-α using a cell based assay
- Binding to a panel of Fc receptors by surface plasmon resonance (CD16a, CD16b, CD32a, CD32b/c, CD64, FcRn)
- Inhibition of TNF-α induced apoptosis
- Complement-dependent Cytotoxicity (CDC)
- Binding to C1q by ELISA
- Antigen-dependent cellular cytotoxicity (ADCC)
- Inhibition of TNF-α induced induction of adhesion molecule expression (ICAM-1, ELAM-1, and VCAM-1).

Pharmacokinetics: A non-GLP pharmacokinetic (PK) study was conducted in cynomolgus monkeys that compared PK parameters of BI 695501 and US-licensed Humira. BI 695501, formulated in the intended commercial formulation, and US-licensed Humira were administered subcutaneously at 0.8 mg/kg. Similar PK parameters were obtained after adjustment for the differences in actual protein concentration administered. All animals developed immunogenicity, which affected PK after 216 hours postdose.

Physicochemical and functional pharmacologic data generally indicated similarity among multiple lots of BI 695501, EU-approved Humira, and US-licensed Humira and also established that BI 695501 drug substance from early manufacturing processes and used in the nonclinical studies, was similar to the proposed clinical trial batch using an improved manufacturing process. This enabled bridging of safety from the toxicology studies to the batch of BI 695501 to be used in the proposed clinical trial.

Toxicology: In a repeated-dose study, cynomolgus monkeys were administered either vehicle, BI 695501 (157 mg/kg), or EU-approved Humira (157 mg/kg), IV, once weekly for 5 weeks (n=5/sex/group), followed by an 8-week recovery period (n=2). Both BI 695501 and Humira produced a mild reversible increase in globulin levels, and associated reductions in the albumin/globulin ratios, thought to be attributed to the amount of IgG administered. Both BI 695501 and Humira similarly reduced the size and number of germinal centers of the spleen and reduced lymphoid follicle activation in the mesenteric and mandibular lymph nodes. Similar toxicokinetic profiles resulted from BI 695501 and Humira administration. Based on this study, BI 695501 and EU-Humira were toxicologically similar.

A GLP-compliant cross-reaction study with human tissues comparing an early formulation of BI 695501 to US-licensed Humira produced similar results. Staining, however, was widespread likely due to solubility and diffusion of TNF and technical considerations. Therefore, although similar results were obtained, the study was not appropriate for inclusion in the regulatory assessment of biosimilarity. Additional non-GLP-compliant studies assessed the effects of cytokine release, complement activation and off-target cytokine binding. Similar findings were observed in these studies, but due to non-GLP compliancy, these studies were not used in the overall assessment of biosimilarity.

The presented studies did not raise any safety concerns for BI 695501. Collectively, the pharmacology and toxicology studies demonstrated reasonable biosimilarity between BI 695501 and US-licensed Humira either by direct comparison or through bridging of EU-approved Humira to US-licensed.

1.3 Recommendations

1.3.1 Approvability

BLA 761058 is recommended for approval from the nonclinical Pharmacology and Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

There are no additional nonclinical recommendations.

1.3.3 Labeling

The applicant's label is based on Humira's latest approved label of June 30, 2016. It has been slightly modified to coincide with the label for the recently approved adalimumab biosimilar Amjevita (BLA 761024). When risk information conveyed by the reference product is also necessary for label inclusion for the safe use of the biosimilar, the term "adalimumab product" was used as described in the Draft Guidance for Industry: Labeling for Biosimilar Products (March 2016).

It should be noted that the pregnancy risk statement indicates a level of major birth defects for the RA populations, such that the second paragraph statement "The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown" now conflicts with the first paragraphs statement. However, this sentence is in US-licensed Humira and its biosimilar products labels, (b) (5) The recommended changes to the Applicant's proposed label are indicated by additions that are underlined and by deletions that are strikethroughs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited clinical data are available from ~~the adalimumab~~ a Pregnancy Registry conducted with adalimumab. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations].* In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended the human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *[see Data]*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to adalimumab products *in utero [see Use in Specific Populations (8.4)].*

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with adalimumab, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of adalimumab was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mothers's clinical need for TRADE NAME and any

potential adverse effects on the breastfed child from TRADE NAME or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab products bind specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab products also lyse surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab products do not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In Ps, treatment with adalimumab products may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

Adalimumab products also modulate biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies of adalimumab products have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

2 Drug Information

2.1 Drug

Generic Name	Adalimumab (biosimilar)
Code Name	BI 695501
Chemical Name	Adalimumab-xxxx
Molecular Formula Molecular Weight	$C_{6448}H_{9964}N_{1732}O_{2020}S_{42}$, based on amino acid sequence without post -translational modifications ~145 kDa
Structure or Biochemical Description	This is a human monoclonal IgG1 (κ subtype) glycosylated immunoglobulin composed of two heterodimers, each composed of a heavy and light polypeptide chain. The four polypeptide chains of the antibody molecule are linked together by 4 disulfide bonds. The two heavy chains (HC) each are composed of 451 amino acids and the two light chains (LC) each contain 214 amino acids. Each

	HC contains a single N-glycosylation site at asparagine 297. BI 695501 is produced from (b) (4) cells
Pharmacologic Class	Tumor necrosis factor (TNF) blocker

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 110467 for BI 695501
BLA 125057 for Humira (adalimumab), approved December 31, 2002
BLA 761024 for Amjevita (adalimumab biosimilar), approved September 23, 2016

2.3 Drug Formulation

BI 695501 will be provided as a sterile solution for subcutaneous injection with a unit strength of 40 mg/0.8 mL in a single-use 1 mL pre-filled syringe (PFS). The drug product formulation is presented in Table 1 and has a pH of (b) (4). The container closure system consists of a 1 mL ready-to-fill, staked needle syringe ((b) (4) glass type (b) (4), a (b) (4) stopper and a rigid needle shield. The entire container closure system is discarded after a single use.

Table 1: Composition of BI 695501 Solution for Injection in a Pre-filled Syringe

Components	Concentration [mmol/L]	Concentration [g/L]	Nominal amount [mg/syringe][1] V = 0.8 mL	Purpose of component	Compend-ial Grade
BI 695501 DS	0.34	50	40	Active Pharmaceutical Ingredient	NA
Sodium acetate Trihydrate	22.3	3.03	2.43	(b) (4)	USP, Ph.Eur.
Glacial acetic acid	2.7	0.16	0.13		USP, Ph.Eur.
Trehalose Dihydrate	215	81.3	65.0		USP, Ph Eur.
Polysorbate 80	0.76	1.0	0.80		USP, Ph Eur.
Water for injection (WFI)	---	---	ad 0.8 mL		USP, Ph.Eur.

[1] The amounts stated do not include the overfill.

Manufacturing batches for nonclinical studies

The (b) (4) L scale batch #6004380 was used for nonclinical studies (single-dose pharmacokinetic study in monkeys and a subcutaneous and intramuscular irritancy study in rabbits). Earlier batches (#93850 and #93852) manufactured at (b) (4) L scale

were used for the initial nonclinical and clinical studies. Batch #6004851 was used for clinical study 1297.8, and batch #6004906 was used for the proposed clinical study. Comparability studies were conducted with material produced at different scales (including process modification) and different sites. The results indicated the batches were similar (refer to the Product Quality review for further information).

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

There were no process-related impurities or degradants identified in the BI 695501 drug substance that required toxicological evaluation (refer to the product quality review by Dr. Richard Ledwidge).

Leachables and extractables were assessed from contact with manufacturing machinery and components in the drug substance, and storage bags for the drug substance. Identified leachables and extractables were below their qualification limits and therefore did not require additional toxicity evaluations (refer to the CDRH review by Dr. Matthew Ondeck).

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indications are based on those currently approved for Humira. These include Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, and Plaque Psoriasis. BI 695501 is proposed to be administered at the same dosing regimens as US-licensed Humira.

2.7 Regulatory Background

This BLA application was submitted on October 27, 2016 (SD-4). (b) (4)

BI 695501 was developed under IND 110467 which was submitted on January 21, 2015. Prior to this, three pre-IND meetings were held with the applicant to discuss proposed product quality, nonclinical, and clinical development plans for BI 695501 [April 28, 2011 (Meeting Minutes dated May 25, 2011), July 1, 2013 (Meeting Minutes dated July 30, 2013), and July 29, 2014 (Meeting Minutes dated September 22, 2014)]. Pertinent to nonclinical development, topics related to the comparison of BI 695501 and approved Humira, US-licensed and EU-approved Humira, for in vitro pharmacology, in vivo toxicology, and pharmacokinetics, and the support for an initial clinical study were

covered at the meeting on April 28, 2011. With the submission of additional information, the adequacy of bridging between adalimumab products was discussed at the September 22, 2014 meeting.

Humira (adalimumab) was approved on December 31, 2002 (BLA 125057). It was developed by Abbot Laboratories and is now owned by AbbVie. There is one adalimumab biosimilar, Amjevita (adalimumab-atto) injection (BLA 761024) approved on September 23, 2016.

3 Studies Submitted

3.1 Studies Reviewed

Report Number	Title
Secondary Pharmacology	
11r164	Inhibition of Adhesion Molecule Induction (revised report)
12i004	Inhibition of Adhesion Molecule Induction (revised report)
13i011	Inhibition of Adhesion Molecule Induction (revised report)
10r148	A tissue cross-reactivity study of BI 695501 with normal human tissues
Pharmacokinetics	
Assay Validation	
13i044-dm-12-1010	Validation of an ELISA Method used for the Determination of Humira® and BI 695501 in Cynomolgus Monkey Plasma (K_2 EDTA)
13i045-dm-12-1011	Validation of a Qualitative Electrochemiluminescent Method for the Detection of Anti-Humira® and Anti-BI695501 Antibodies in Cynomolgus Monkey Plasma (K2 EDTA)
Absorption	
13I036 Final Report and Amendment No. 1	Pharmacokinetics of BI 695501 Following Subcutaneous Dose Administration to Non-Human Primates
Toxicology	
10r090	A 5-week intravenous injection study in Cynomolgus monkeys with an 8-week recovery period comparing Humira and BI 695501
12i001 Final Report and Amendment No. 1	BI 695501: A Tissue Irritancy Study following a Single Intramuscular and Subcutaneous Injection in the Rabbit
13i001 amendment 1 amendment 2	BI 695501: A Tissue Irritancy Study following a Single Intramuscular and Subcutaneous Injection in the Rabbit
Special Toxicology	
13i001	BI 695501: A Tissue Irritancy Study following a Single Intramuscular and Subcutaneous Injection in the Rabbit
11r162	Cytokine binding analysis (revised report)

11r176 revision	BI 695501: Determination of Complement Activation and Cytokine Release in an *In Vitro* Biocomparability Assessment of BI 695501 and Humira (Revised Version)
10r148	A tissue cross-reactivity study of BI 695501 with normal human tissues

3.2 Studies Not Reviewed

Pharmacology studies, as preliminary summaries, were reviewed for the IND (see Attachment 1). With submission of the BLA, complete studies were submitted as listed below, and these were reviewed by product quality (refer to the product quality review by Dr. Richard Ledwidge).

Report Number	Title
Primary Pharmacology	
TNFα Binding	
16i012	TNFα Binding SPR (affinity) - Data Report for Similarity Assessment of BI 695501
16i007	TNFα Binding SPR (affinity) - Qualification Report
15i030	TNFα Binding SPR (affinity) - Method
mTNFα Competitive Binding	
15i036	mTNFα Competitive Binding Assay - Data Report for Similarity Assessment of BI 695501
15i041	mTNFα Competitive Binding Assay – Validation Report
Antibody-Dependent Cell-Mediated Cytotoxicity	
16i040	Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Assay - Cross Qualification Report
14i033	Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Assay - Data Report For Similarity Assessment of BI 695501
14i037	Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Assay - Method for Adalimumab/BI 695501
Antibody-Dependent Cellular Phagocytosis	
15i035	Antibody-Dependent Cellular Phagocytosis (ADCP) Reporter Assay - Data Report for Similarity Assessment of BI 695501
15i040	Antibody-Dependent Cellular Phagocytosis (ADCP) Reporter Assay - Method and Validation Report
Complement-Dependent Cytotoxicity	
16i041	Complement-Dependent Cytotoxicity (CDC) Assay– Cross Qualification Report
14i034	Complement-Dependent Cytotoxicity (CDC) Assay– Data Report For Similarity Assessment of BI 695501
14i039	Complement-Dependent Cytotoxicity (CDC) Assay-Method for Adalimumab/BI 695501
FcRn	
16i011	FcRn Binding SPR (Affinity) - Data Report for Similarity Assessment
16i003	FcRn Binding SPR (Affinity) – Qualification Report
15i033	FcRn Binding SPR (affinity) – Method
C1q	

14i035	C1q Binding Assay–Data Report For Similarity Assessment of BI 695501
16i066	C1Q Binding Assay – Cross Qualification Report
14i041	C1q Binding Assay-Method for BI 695501
CD16a	
16i008	CD16a Binding SPR (affinity) - Data Report for Similarity Assessment of BI 695501
16i004	Qualification of the CD16a Binding Assay using a Biocore T200
16i091	CD16a binding SPR (cRLCA)
15i031	BI 695501 Similarity: Binding to CD16a by SPR
CD16b and CD32bc	
16i009	CD16b and CD32bc Binding SPR (Affinity) – Data Report for Similarity Assessment of BI 695501
16i005	CD16b and CD32b/c Binding SPR (Affinity) – Qualification Report
15i032	CD16b and CD32b/c Binding SPR (affinity) – Method
CD64 and CD32a	
16i010	CD64 and CD32a Binding SPR (affinity) - Data Report for Similarity Assessment of BI 695501
16i006	CD64 and CD32a Binding SPR (Affinity) – Qualification
15i034	CD64 and CD32a Binding SPR (affinity) – Method

The two pharmacokinetic studies listed below were conducted with early batches of the drug substance and did not provided information essential for the approval of the clinical product.

Pharmacokinetics	
dm-11-1034	A Single Dose Comparative Pharmacokinetics Study of BI 695501 and Humira Administered Subcutaneously in Cynomolgus Monkeys
dm-12-1067 Final Report and Amendment No. 1	A Comparative Pharmacokinetics Study of BI 695501 in an Alternative Formulation and Humira Administered Subcutaneously in Cynomolgus Monkeys

3.3 Previous Reviews Referenced

IND 110,467 for BI 695501, Pharmacology and Toxicology review dated February 19, 2015 (see Attachment)

4 Pharmacology

BI 695501 is a humanized monoclonal antibody directed against human tumor necrosis factor - alpha (TNFα). Binding to TNFα prevents TNFα interaction with p55 and p75 cell surface TNF receptors, thus blocking the effect of TNFα to induce inflammatory and immune responses that consist of inhibition of cellular cytotoxicity, blockage in the induction of cytokines and adhesion molecules, induction of apoptosis, antibody dependent cellular cytotoxicity, and complement dependent cytotoxicity.

Pharmacological studies compared BI 695501 with EU-approved and US-licensed Humira reference products with regards to physicochemical characterization and pharmacological activity for the known functional domains of the adalimumab molecule that included Fab mediated activities (binding to TNFα and neutralization of TNFα and induction of apoptosis) and Fc mediated activities (ADCC, CDC, C1q binding, Fc receptor interaction).

5 Pharmacokinetics/ADME/Toxicokinetics

There were no nonclinical ADME studies submitted to the BLA. Toxicokinetics of the nonclinical monkey studies were reviewed for IND 110467 (see Attachment).

6 General Toxicology

There were no nonclinical toxicology studies submitted to the BLA. Toxicology studies conducted were reviewed for IND 110467 (see Attachment).

7 Genetic Toxicology

Genetic toxicity studies were not conducted.

8 Carcinogenicity

Carcinogenicity studies were not conducted.

9 Reproductive and Developmental Toxicology

Developmental and reproductive toxicology studies were not conducted.

10 Special Toxicology Studies

LOCAL TOLERANCE

Study title: BI 695501: A Tissue Irritancy Study following a Single Intramuscular and Subcutaneous Injection in the Rabbit

Study no.:	131001
Study report location:	Module 4.2.3.6
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 30, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BI 695501, Lot E3712S01 , Purity 99% by HP-SEC, by IEC the main peak comprised (b) (4)%, with APG (b) (4)% and BPG (b) (4)% (APG and BPG refer to the acid and basic peak groups, respectively).

Key Study Findings:

- In rabbits injected intramuscular or subcutaneous with 0.9% saline vehicle or 40 mg BI 695501, there were no BI 695501-related clinical findings, signs of local irritation, and no macroscopic and microscopic findings due to BI 695501.

Methods
Male New Zealand White rabbits (n=4/treatment group), were administered one injection of 0.8 mL of vehicle (0.9% sodium chloride) or 40 mg (0.8 ml of 50 mg/mL) of BI 695501, intramuscularly to the lumbar region and subcutaneously to the interscapular area of the back. The intramuscular route was used determine the irritation potential of misdosing the intended clinical subcutaneous injection into the muscle. Each injection site was observed for redness and swelling before each injection, immediately following the injection, and at 1, 2, 4, and 6 hours following each injection, and then twice daily until day 5 and scored using a modified Draize scale. Animals were then sacrificed and injection sites tissues were examined.

Table 2: Modified Draize Score

Score	Erythema (Redness)
0	No erythema
1	Very slight erythema (barely perceptible)
2	Well-defined erythema
3	Moderate erythema
4	Severe erythema (beet redness to slight eschar formation, injuries in depth)
Score	**Edema (Swelling)**
0	No edema
1	Very slight edema (barely perceptible)
2	Slight edema (edges of area are well-defined by definite raising)
3	Moderate edema (raised approximately 1 mm)
4	Severe edema (raised more than 1 mm and extending beyond area of exposure)

Results
There were no mortalities and no BI 695501-related clinical observations. All scores were <2. Skin redness at the interscapular and intramuscular injection sites and skin flaking at the interscapular injection site were observed in both controls and BI 695501-treated animals. There was no irritation at the injection sites related to BI 695501-treatment. Also, macroscopic and histopathology findings were similar between control and BI 695501. Macroscopic findings consisted of were dark areas at the injection sites that correlated with the presence of scabs and skin redness. Histopathologic findings consisted of minimal inflammation and/or hemorrhage of the epidermis at the interscapular and/or lumbar injection site, and dermis fibrosis and focal myofiber degeneration at the lumbar sites.

CYTOKINE ASSESSMENT

Study title: BI 695501: Determination of Complement Activation and Cytokine Release in an *In Vitro* Biocomparability Assessment of BI 695501 and Humira (Revised Version)

Study no.:	11R162 (and 11R176 updated version)
Study report location:	Module 4.2.3.7
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 19, 2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	BI 695501, Drug Substance Lot E0712F02 (drug product lot 102192), Purity 99.5% by HP-SEC, by IEC the main peak comprised (b) (4)%, with APG (b) (4)% and BPG (b) (4)% (APG and BPG refer to the acid and basic peak groups, respectively). Humira (EU-approved), Lot 87497XD01, Abbott Laboratories

Key Study Findings:

- BI 695501 and EU-approved Humira did not activate complement when incubated in human serum and did not cause cytokine release when incubated with whole human blood in vitro.

Methods

BI 695501 and EU-approved Humira were tested for their ability to produce cytokine release and when incubated with whole human blood in vitro and to activate complement when incubated in human serum.

Complement Activation: Blood samples were obtained from 6 normal volunteers (1 male and 5 females) and stored frozen (-80°C). The doses of BI 695501 and Humira tested were 1.19, 5.81, or 11.63 µg/mL. Controls included vehicle (Dulbecco's phosphate buffered saline), a positive control (heat aggregated gamma globulin), and C3 depleted serum. Complement activation was determined by the concentration of terminal complement complexes (TCC) (represented in CH50-equivalent units, a measure of complement classical pathway activity) in human serum using an enzyme-linked immunosorbent assay (ELISA).

Cytokine Release: Whole blood from 6 normal volunteers (3 males and 3 females) and was incubated for 24 hours in presence of RPMI, EU-approved Humira®, BI 695501 and the positive control (LPS) at 37°C and 5% CO_2. The doses of Humira and BI 695501 were 2, 20, or 200 µg/mL. Following incubation, plasma was separated and

stored frozen until assayed for cytokines (IL-2, IL-6, IL-8, IFNγ and TNFα) using a Luminex multiplex assay.

Results
The TCC values for Humira and BI 695501 were similar to C3 depleted serum negative controls (< 40 CH50 U Eq/mL), indicating that neither EU-approved Humira nor BI 695501activated complement in human serum. Positive controls produced values of ~97 to 142 CH50 U Eq.mL.

Both BI 695501 and EU-approved Humira increased levels of IL-6 from one donor in each treatment. An increase in IL-8 occurred from 2 male donors at a mid-dose of BI 695501. The IL-6 and IL-8 responses when whole blood was incubated with the isotype control were substantially greater than those observed after incubation with Humira and BI 695501. t Therefore the increases in IL-6 and IL-8 concentration after incubation of whole blood with BI 695501 and EU-approved Humira were not considered treatment related, but reflect variability in donor sensitivity.

TISSUE CROSSREACTIVITY

Study title: A tissue cross-reactivity study of BI 695501 with normal human tissues

Study no.:	10r148
Study report location:	Module 4.2.3.7.7
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 19, 2011
GLP compliance:	Yes, with exceptions for quantifying stability and concentrations during procedures used.
QA statement:	Yes
Drug, lot #, and % purity:	BI 695501, Drug Substance Lot E0712F02, Purity 99.4% by HP-SEC, by IEC the main peak comprised (b) (4)%, with APG (b) (4)% and BPG (b) (4)% (APG and BPG refer to the acid and basic peak groups, respectively). Humira (EU sourced), Lot 87497XD01, Abbott Laboratories Humira (US sourced), Lot 870049A40, Abbott Laboratories

Key Study Findings:

- BI 695501, EU-approved Humira, and US-licensed Humira had similar distribution patterns, bound to similar cellular and tissue sites, and were qualitatively similar.

Methods
Human tissues from at least 3 donors were obtained at autopsy or biopsy and were considered essentially normal. They were prepared unfixed embedded with Tissue Tek in molds and frozen at -85°C to -70°C until used. Positive controls included TNFα UV-resin spot slides and human Crohn's disease colon (HT278-2). The negative controls included human hypercalcemia of malignancy peptide, amino acid residues 1-34, UV-resin spot slides, designated PTHrP 1-34. BI 695501 and Humira antibodies were incubated with cryostat-cut, acetone-fixed tissues at concentrations of 2 and 10 µg/mL. Tissue bound antibodies were detected using a biotin-anti human IgG secondary antibody followed by avidin-peroxidase and then visualized with DAB reacton.

Results
Negative controls were not stained with BI 695501, or EU-approved and US-licensed Humira. All three antibodies stained tissues qualitatively similarly. Staining occurred in cellular cytoplasm, cytoplasmic filaments, and/or cytoplasmic granules in the following cell types and tissues:

- Mononuclear cells (generally macrophages) in spleen as well as infrequent mononuclear cells in urinary bladder
- Variably frequent stromal cells (likely dendritic cells, fibroblasts/fibrocytes, and/or myofibroblasts) and/or smooth myocytes in multiple tissues
- Variably frequent myoepithelium in breast, salivary gland, and sweat glands in skin
- Infrequent striated (skeletal) myocytes in esophagus and eye
- Infrequent keratinocytes (stratified squamous epithelium) in skin (hair follicle)
- Infrequent cells in upper spinosum in cervix (either stratified squamous epithelium or Langerhans' cells)
- Infrequent endometrial epithelium in uterus
- Infrequent transitional cell epithelium in urinary bladder

The applicant indicated the locations of tissue reactivity correspond with published reports of TNFα locations and reactivity.

11 Integrated Summary and Safety Evaluation

BI 695501 is a human monoclonal immunoglobulin (IgG1 κ subtype) against human TNFα. BI 695501 was developed as a biosimilar to US-licensed Humira. Studies were conducted to compare effects produced with BI 695501 to that of EU-approved Humira or US-licensed Humira.

Pharmacology
The sponsor provided summary data from studies that assessed pharmacologic properties of BI695501 and EU-approved and US-licensed Humira. These studies were:

- Binding to soluble TNF-α (measured in 3 assay formats)
- Binding to membrane bound TNF-α using a cell based assay
- Binding to a panel of Fc receptors by surface plasmon resonance (CD16a, CD16b, CD32a, CD32b/c, CD64, FcRn)

- Inhibition of TNF-α induced apoptosis
- Complement-dependent Cytotoxicity (CDC)
- Binding to C1q by ELISA
- Antigen-dependent cellular cytotoxicity (ADCC)
- Inhibition of TNF-α induced induction of adhesion molecule expression (ICAM-1, ELAM-1, and VCAM-1).

The reviewer defers to the Product Quality Reviewer for judgments concerning the appropriateness of the analysis and the determination of chemical and functional similarity among the 3 drug products.

For the IND, it was necessary to determine if the safety established in the nonclinical studies with older lots of BI 695501 drug substance were 1) adequately bridged to the new lots for the proposed clinical study, and 2) EU-approved Humira was adequately bridged to US-licensed Humira, since EU-approved Humira was used as the comparator in some pivotal nonclinical studies, including the repeat-dose monkey toxicology study. For the purpose of safety, there was sufficient information to reasonable assure BI 695501 was comparable to the approved US-licensed and EU-approved Humira products and clinical studies could proceed.

Pharmacokinetics
A non-GLP pharmacokinetic study was conducted in cynomolgus monkeys that compared BI 695501 pharmacokinetics with US-licensed Humira. BI 695501, formulated in the intended commercial formulation, and US-Humira were administered subcutaneously at 0.8 mg/kg. Both compounds resulted in similar pharmacokinetic parameters after adjustment for the actual protein concentration administered. All animals developed immunogenicity, which affected pharmacokinetics after 216 hours postdose.

Toxicology
In a repeated dose study, cynomolgus monkeys were administered either vehicle, BI 695501 (157 mg/kg), or EU-approved Humira (157 mg/kg), IV, once weekly for 5 weeks (n=5/sex/group) followed by a 8 week recovery period (n=2). Both BI 695501 and Humira produced mild reversible increases in globulin levels, and associated reductions in the albumin/globulin ratios, thought to be attributed to the amount of IgG administered. Both BI 695501 and Humira similarly reduced the size and number of germinal centers of the spleen and reduced lymphoid follicle activation in the mesenteric and mandibular lymph nodes. Similar toxicokinetic profiles resulted from BI 695501 and EU-approved Humira administration. There were no sex differences in exposure and there was similar low amount of drug accumulation (~1.4 to 2.6-fold) over the dosing period. No anti-drug antibodies were detected, but it is probable that sufficient drug was present even at prolonged sampling times and this interfered with the anti-drug antibody assay. Based on this study, BI 695501 and EU-approved Humira were toxicologically similar.

Bridging of Nonclinical to Clinical Lots for Clinical Support

The 5-week toxicology study in cynomolgus monkeys was conducted to determine the safety of BI 695501 compared to EU-approved Humira. Toxicology findings were similar between BI-695501 and EU-approved Humira and there were no safety concerns for BI-695501 observed in this study. Physicochemical and functional pharmacologic data generally indicated similarity among multiple lots of BI 695501, EU-approved Humira, and US-licensed Humira and also established that BI 695501 drug substance from early manufacturing processes used in the nonclinical studies was similar to the proposed clinical trial batch using an improved manufacturing process. This enabled bridging of safety from the toxicology studies to the batch of BI 695501 to be used in the proposed clinical trial.

Recommendation

The overall nonclinical safety (data from repeat-dose toxicity studies), immunogenicity, and toxicokinetic data submitted in support of this BLA demonstrated the nonclinical similarity (i.e., comparable nonclinical efficacy, exposures, and safety profiles) between BI 695501 and US-licensed Humira. The BLA is recommended for approval from the nonclinical perspective. No additional animal studies are required. There are no outstanding issues from the nonclinical Pharmacology/Toxicology perspective.

12 Appendix/Attachments

IND 110467 Pharmacology-Toxicology Review dated February 19, 2015.

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

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	110467
Supporting document/s:	15
Sponsor's letter date:	January 21, 2015
CDER stamp date:	January 21, 2015
Product:	BI 695501, adalimumab (Humira®) biosimilar
Indication:	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, and Plaque Psoriasis
Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
Review Division:	Division of Pulmonary, Allergy and Rheumatology Products
Reviewer:	L. Steven Leshin, D.V.M., Ph.D.
Supervisor/Team Leader:	Marcie Wood, Ph.D.
Division Director:	Badrul A. Chowdhury, M.D., Ph.D.
Project Manager:	Sadaf Nabavian

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1 Executive Summary

1.1 Introduction

The sponsor is developing BI 695501 under the 351(k) pathway of the PHS Act as a biosimilar to US-licensed Humira (adalimumab). Humira is a monoclonal antibody against tumor necrosis factor alpha (TNFα) and is indicated for use in numerous immunologic-mediated diseases (rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis). The sponsor is seeking the same indications for BI. Phase 1 PK similarity clinical studies were previously conducted in the UK in healthy subjects. In this initial IND study, the sponsor proposes to conduct a Phase 3 study in patients with moderate to severe rheumatoid arthritis to assess similarity in efficacy, safety, and immunogenicity of BI 695501 and Humira.

The nonclinical studies summarized and reviewed here include data to support the biochemical, pharmacological, toxicological, and toxicokinetic similarity between BI 695501, US-licensed Humira, and EU-licensed Humira

1.2 Brief Discussion of Nonclinical Findings

BI 695501 is human monoclonal immunoglobulin (IgG1 κ subtype) against human TNFα. Studies were conducted to compare the pharmacology, pharmacokinetics, and toxicology of BI 695501 to that of EU-sourced Humira or US-sourced Humira.

*Pharmacology*The sponsor provided summary data from studies that assessed the pharmacologic properties of BI695501 in comparison to EU- and US-Humira. These studies were :

- Binding to soluble TNF-α (measured in 3 assay formats)
- Binding to membrane bound TNF-α using a cell based assay
- Binding to a panel of Fc receptors by surface plasmon resonance (CD16a, CD16b, CD32a, CD32b/c, CD64, FcRn)
- Inhibition of TNF-α induced apoptosis
- Complement-dependent Cytotoxicity (CDC)
- Binding to C1q by ELISA
- Antigen-dependent cellular cytotoxicity (ADCC)
- Inhibition of TNF-α induced induction of adhesion molecule expression (ICAM-1, ELAM-1, and VCAM-1).

Since only study summaries were presented in the nonclinical sections, the reviewer defers to the Product Quality Reviewer for judgments concerning the appropriateness of the statistical analysis and similarity among the 3 drug products regarding these comparisons. In general, similarity appeared to exist for most parameters. . A final determination of "highly similar," necessary for approval, will be undertaken for the BLA review by the appropriate review team members.

Pharmacokinetics
A non-GLP pharmacokinetic study was conducted in cynomolgus monkeys that compared BI 695501 pharmacokinetics with US-Humira. BI 695501, formulated in the intended commercial formulation, and US-Humira were administered subcutaneously at 0.8 mg/kg. Both compounds resulted in similar pharmacokinetic parameters after adjustment for the actual protein concentration administered. All animals developed immunogenicity, which affected pharmacokinetics after 216 hours postdose.

Toxicology
In a repeated dose study, cynomolgus monkeys were administered either vehicle, BI 695501 (157 mg/kg), or EU-Humira (157 mg/kg), IV, once weekly for 5 weeks (n=5/sex/group), followed by an 8-week recovery period (n=2). Both BI 695501 and Humira produced a mild reversible increase in globulin levels, and associated reductions in the albumin/globulin ratios, thought to be attributed to the amount of IgG administered. Both BI 695501 and Humira similarly reduced the size and number of germinal centers of the spleen and reduced lymphoid follicle activation in the mesenteric and mandibular lymph nodes. Similar toxicokinetic profiles resulted from BI 695501 and Humira administration. There were no sex differences in exposure and similar low level of drug accumulation (~1.4 to 2.6-fold) over the dosing period. No anti-drug antibodies were detected, but it is probable that sufficient drug was present even at prolonged sampling times to interfere with anti-drug antibody detection. Based on this study, BI 695501 and EU-Humira were toxicologically similar.

The presented studies raised no safety concerns for BI-695501. Toxicology findings were similar between BI-695501 and EU-Humira. Physicochemical and functional pharmacologic data generally indicated similarity among multiple lots of BI 695501, EU-Humira, and US Humira and also established that BI 695501 drug substance from early manufacturing processes and used in the nonclinical studies, was similar to the proposed clinical trial batch using an improved manufacturing process. This enabled bridging of safety from the toxicology studies to the batch of BI 695501 to be used in the proposed clinical trial.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: Yes

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor):

None

2 Drug Information

2.1 Drug

Generic Name	Adalimumab (Humira®) biosimilar
Code Name	BI 695501, 695501 , 695501-01

Molecular Weight	~148 kDa
Structure or Biochemical Description	This is a human monoclonal IgG1 (κ subtype) glycosylated immunoglobulin composed of two heterodimers, each composed of a heavy and light polypeptide chain. The four polypeptide chains of the antibody molecule are linked together by disulfide bonds. The two heavy chains (HC) each are composed of 451 amino acids and the two light chains (LC) each contain 214 amino acids. Each HC contains a single N-glycosylation site at asparagine 297. BI 695501 is produced from (b) (4) cells.
Pharmacologic Class	Human monoclonal antibody against TNFα

2.2 Relevant INDs, NDAs, BLAs and DMFs

BLA 125057 for Adalimumab (Humira)

2.3 Drug Formulation

BI 695501 (50 mg/mL adalimumab) is provided in a buffered, isotonic, preservative-free solution in a pre-filled syringe for subcutaneous administration. The formulation of BI 695501 is presented in the table below. BI 695501 has a unit strength of 40 mg/0.8 mL.

Table 1: Composition of BI 695501 Solution for Injection in Pre-filled Syringe

Components	Concentratio [mmol/L]	Concentratio [g/l]	Nominal Amount [mg/syringe] V = 0.8 ml	Function	Compendial Grade
BI 695501	0.34	50	40	API	USP, EP
Sodium acetate Trihydrate	22	3.0	2.4	(b) (4)	USP, EP
Acetic acid*	2.7	0.16	0.13		USP, EP
Trehalose Dihydrate	215	81	65		USP, EP
Polysorbate 80	0.76	1.0	0.80		USP, EP
WFI (water for injection)	--	--	ad 0.8 mL		USP, EP

* (b) (4)

Table 2: Formulation of BI 695501 DP and EU / US reference product
(from p 14, SD-9, Mod 1 US-information package (for meeting)

	BI 695501 DP (IFF)*	Humira® (BI 695501 TF)	Function
Adalimumab	50 mg/mL	50 mg/mL	API
Monobasic sodium phosphate dihydrate	-	5.53 mmol/L	(b) (4)
Dibasic sodium phosphate dihydrate	-	8.57 mmol/L	
Sodium citrate dihydrate		1.16 mmol/L	
Citric acid monohydrate	-	6.19 mmol/L	
Sodium acetate trihydrate	22 mmol/L	-	
Acetic acid 100%	2.7 mmol/L	-	
Mannitol	-	65.87 mmol/L	
Trehalose dihydrate	215.0 mmol/L	-	
Sodium chloride	-	105.45 mmol/L	
Polysorbate 80 (Tween 80)	0.1%	0.1%	
Water for Injection	ad 0.8 mL	ad 0.8 mL	

*Final formulation intended for clinical and commercial use

Manufacturing for nonclinical and clinical studies

Initial nonclinical and clinical studies were conducted with drug substance manufactured at (b) (4) L scale and included the nonclinical BI 695501 batches #93850 and #93852, and (b) (4) L scale manufacturing batch #104600 used for the first clinical study 1297.1. The process was later improved and a (b) (4) L scale batch #6004380 was used for nonclinical studies (single dose pharmacokinetic study in monkeys and a subcutaneous and intramuscular irritancy study in rabbits), batch #6004851 was used for clinical study 1297.8, and batch #6004906 will be used for the proposed clinical study. Comparability studies were conducted with material produced at different scales (including process modification) and different sites. The results indicated the batches were similar (refer to the Product Quality review for further information).

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

At this stage of development, there are no impurities or degradants of concern. Stability studies are only partially completed. Leachables from the prefilled syringe have not been addressed.

2.6 Proposed Clinical Protocol

Study 1297.2
Title: Efficacy, safety and immunogenicity of BI 695501 versus adalimumab in patients with active rheumatoid arthritis: a randomized, double-blind, parallel arm, multiple dose, active comparator trial. This study will be followed by Study 1297.3, a 1-year open-label extension of study 1297.2.

This is a phase 3, multi-national, multi-center trial in patients with rheumatoid arthritis. The 58-week study includes a 48-week treatment period in patients with active rheumatoid arthritis receiving background methotrexate (MTX) treatment.

The primary objective of this trial is to establish statistical equivalence of efficacy between BI 695501 and US-sourced Humira® in patients with active RA based on the difference in the proportion of patients meeting American College of Rheumatology 20% (ACR20) response rate at Week 12 and ACR20 response rate at Week 24 between BI 695501 and US-sourced Humira®. Safety will be assessed as a secondary objective in this trial.

A total of up to 650 patients, males and females between 18 and 80 years of age, who have a diagnosis of moderately to severely active RA for at least 6 months, will be randomized to receive one single subcutaneous dose of 40 mg/0.8 mL of either BI 695501 or US-sourced Humira every two weeks. A population PK analysis with sparse

sampling will be carried out to assess the pharmacokinetics (PK) of BI 695501 and US-Humira in this trial.

Males and females of reproductive potential will be required to use a reliable means of contraception (intrauterine devices, surgical sterilization, double barrier, or vasectomized partner) throughout trial participation. Females of child-bearing potential must also agree to use an acceptable method of contraception for 5 months following completion or discontinuation from the trial.

At Week 24, all patients will be re-randomized (requested by FDA) to either continue on blinded medication or switch to the BI 695501 self-administration arm in a 1:1 ratio. Patients who participate in the self- administration will, after adequate training, self-inject at least 4 doses. In addition, patients who are originally randomized to US-sourced Humira and not participating in the self- administration arm, will be re-randomized to either continue on US-Humira or to transition to BI 695501 in a blinded fashion in a 1:1 ratio after 24 weeks.

At the conclusion of the trial, all qualified patients will be offered participation in an open-label extension trial with BI 695501.

2.7 Previous Clinical Experience

A single dose PK study in healthy male volunteers (Study 1297.1) used a trial formulation and failed to meet the primary endpoints. A second PK study also conducted with healthy male subjects (Study 1297.8) was conducted with the intended final formulation. These studies compared BI 695501, US-approved Humira, and EU-approved Humira. The results of the second PK study (n = 108/treatment group) indicated similarity among the 3 products (refer to the Clinical Pharmacology Review). The immunogenicity evaluation also indicated similarity. The sponsor indicated that for all treatments, the common adverse reactions reported in greater than 10% of patients included infections (e.g. nasopharyngitis, upper respiratory tract infections, sinus infections), injection site reactions, headache, and rash. Allergic reactions (e.g. allergic rash, anaphylactic reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

2.8 Regulatory Background

Three pre-IND meetings were held with the sponsor to discuss the proposed product quality, nonclinical and clinical development plan for BI 695501, April 28 2011(Meeting Minutes May 25, 2011), July 1 2013 (Meeting Minutes July 30, 2013), and July 29, 2014 (Meeting Minutes Sept 22, 2014).

Pertinent to nonclinical development, topics related to the comparison of BI 695501 and approved Humira products for in vitro pharmacology, in vivo toxicology, and pharmacokinetics, and support for an initial clinical study were covered at the meeting on April 28 2011, and with the submission of additional information, the adequacy of

bridging between adalimumab products was discussed at the September 22, 2014, meeting.

3 Studies Submitted

3.1 Studies Reviewed

Report Number	Title
Primary Pharmacology (only summaries provided)	
Anti-TNFα	
12R107	Determination of competitive binding between anti-TNFα antibodies using a qualified flow cytometry based assay
13i007	Comparative Receptor Occupancy (RO) Analysis of Humira® originator lots and BI 695501 (b) (4)
Fc Receptors	
11R163	Fc Receptor Binding Analysis
13i013	Surface plasmon resonance binding of BI695501 and originator lots to recombinant Fc receptor panel
Complement Binding and Complement Dependent Cytotoxicity	
12i002	Comparative human complement C1q binding analysis for BI 695501 and Humira®
12i005	Comparative Analysis of Complement Dependent Cytotoxicity (CDC) Mediated by Humira® and BI 695501
12R105	Comparative analysis of CDC of Humira originator lots and BI 695501
Antibody Dependent Cell Mediated Cytotoxicity	
12R106	Determination of Antibody dependent Cell-Mediated Cytotoxicity (ADCC) mediated by Anti-TNFα Antibodies using a fluorescence cell based method and Natural Killer Cell Cytolytic activity in freshly isolated human peripheral blood mononuclear cells
13i008	Comparative Analysis of ADCC of Humira originator lots and BI 695501
Adhesion Molecules	
12i004	Inhibition of Adhesion Molecule Induction
13i011	Inhibition of Adhesion Molecule Induction
Comparison of EU- and US-Humira	
14I036	BI 695501 - Scientific Bridging Report of EU vs. US sourced Humira
Phamacokinetics	
Absorption	
13i036	Pharmacokinetics of BI 695501 Following Subcutaneous Dose Administration to Non-Human Primates
non-glp_nca_13i040.pdf	Non-compartmental analysis of pharmacokinetics of BI 695501 and Humira in study 13i036 ((b) (4) study 20040839)
Repeated Dose	
10r090	A 5-week intravenous injection study in Cynomolgus monkeys with an 8-week recovery period comparing Humira and BI 695501

3.2 Studies Not Reviewed

Report Number	Title
11R162	Cytokine Binding Analysis
11R176	Determination of Complement Activation and Cytokine Release DRAFT
10R148	A tissue cross-reactivity study of BI 695501 with normal human tissues
dm-12-1067	A Comparative Pharmacokinetics Study of BI 695501 in an Alternative Formulation and Humira Administered Subcutaneously in Cynomolgus Monkeys
dm-11-1034	A Single Dose Comparative Pharmacokinetics Study of BI 695501 and Humira Administered Subcutaneously in Cynomolgus Monkeys
13i001 amendment 1 amendment 2	BI 695501: A Tissue Irritancy Study following a Single Intramuscular and Subcutaneous Injection in the Rabbit

3.3 Previous Reviews Referenced

None

4 Pharmacology

BI 695501 is a humanized monoclonal antibody directed against human tumor necrosis factor - alpha (TNFα). Binding to TNFα prevents TNFα interaction with p55 and p75 cell surface TNF receptors, thus blocking the effect of TNFα to induce inflammatory and immune responses that consist of inhibition of cellular cytotoxicity, blockage in the induction of cytokines and adhesion molecules, induction of apoptosis, antibody dependent cellular cytotoxicity, and complement dependent cytotoxicity.

Pharmacological studies compared BI 695501 with EU- and US-Humira reference products with regards to physicochemical characterization and pharmacological activity for the known functional domains of the Humira molecule that included Fab mediated activities (binding to TNFα and neutralization of TNFα and induction of apoptosis) and Fc mediated activities (ADCC, CDC, C1q binding, Fc receptor interaction).

4.1 Primary Pharmacology

The pharmacology assays are described in more detail in Module 3 and reviewed by the Product Quality Reviewer. Only summaries were provided in the nonclinical sections. In general, given the variability of some of the cell based assays, similar results were obtained between lots of BI 695501, EU-, and US-Humira. The study below was directed toward a comparison of the collective studies of EU- and US-Humira to enable bridging of safety from EU-Humira, used as the comparator for BI 695501 nonclinical studies, to US-Humira.

Study Title: BI 695501 - Scientific Bridging Report of EU vs. US sourced Humira®
Study No.: 14I036

Study Location: Module 4.2.3.7.7

In this report the sponsor provided a comparative analysis of multiple lots of EU- and US-Humira with regards to physicochemical characterization and pharmacological activity [i.e., affinity to soluble TNF-α by Biacore; affinity to a panel of Fcγ receptors and FcRn; binding to membrane-bound TNF-α (receptor occupancy); inhibition of TNF-α induced adhesion molecules; Complement dependent cytotoxicity (CDC) activity; antibody dependent cellular cytotoxicity (ADCC) activity; and binding to the complement component C1q]. This information is also covered in more detail in the sections of Module 3 that are the subject of the product quality review. There were a number of parameters that did not meet the sponsor's statistical analysis of equivalence and were further analyzed. The sponsor's conclusion was that EU- and US-Humira were similar. The initial examination of means and their variability of the lots tested may indicate similarity between products. A final determination of "highly similar" necessary for approval will be undertaken for the BLA review by the appropriate review team members.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study Title: Pharmacokinetics of BI 695501 Following Subcutaneous Dose Administration to Non-Human Primates

and

Study Title: Non-compartmental analysis of pharmacokinetics of BI 695501 and Humira in study 13i036

Study no:	13i036 (U13-3968-01 n00231308-02)
Study report location:	Module 4.2.2.2
Conducting laboratory and location:	In life: (b) (4)
	Bioanalysis and anti-drug antibody assessment: (b) (4)
Date of study initiation:	May 21, 2013
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	BI 695501, Lot E3712S01 intended commercial or final formulation
	US-Humira, Lot 2006512E

Composition of BI 695501 and US-Humira formulations

Vehicle for BI 695501:	Vehicle for US-Humira:
50 mg/mL BI-695501	50 mg/mL US-Humira

(actual protein concentration 51.3 mg/mL)	(actual protein concentration 43.9 mg/mL)
(b) (4) mM Sodium acetate 215 mM trehalose trihydrate 0.1 M Polysorbate 80 (Tween 80). pH (b) (4)	(b) (4) mM Citrate-phosphate 65.87 mM Mannitol 105.45 mM Sodium chloride 0.1M Polysorbate 80 (Tween 80) pH of 5.2.

Both BI 695501 and US Humira were diluted in their respective vehicles to produce a 5.0 mg/mL dosing solution.

Key Study Findings

- BI 695501, formulated in the same diluent as the intended clinical formulation, and US-Humira had similar pharmacokinetic parameters when administered subcutaneously to cynomolgus monkeys at a dose of 0.8 mg/kg. In addition, no BI 695501-related safety concerns were identified in the study.

Methods

Male cynomolgus monkeys (n=6/treatment group, 2 - 5 yrs of age, 2.5 – 3.5 kg, Chinese origin) were administered either BI 695501 or US-Humira at a dose of 0.8 mg/kg, SC, in the interscapular area of the back. The dose volume was 0.16 mL/kg, and the dose concentration was 5 mg/mL. Blood was collected at predose, and 1, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 288, 336, and 504 h after dosing. Samples for anti-drug antibodies were obtained at predose, and 168, 192, 216, 240, 288, 336, and 504 h after dosing.

Results

There were no adverse clinical signs in either treatment group. The initial analysis found that the exposure (C_{max}, AUC_{0-216}, and $AUC_{0-\tau}$) was not similar between BI 695501 and US-Humira with slightly higher values for BI 695501 (C_{max} ~19% higher, AUC ~ 36% higher). Investigation of this unexpected difference found that dose administration (in mg/kg, based on the nominal drug protein concentration) did not account for differences in the protein concentrations in the 2 drug products. Since there was a difference of approximately 17% between the 2 products, the data were reanalyzed after normalizing for the protein concentration differences. A correction factor of 0.9746 and 1.1390 was applied for plasma concentrations measured in BI 695501 and US-Humira, respectively. Upon reanalysis, the pharmacokinetic parameters were similar between BI 695501 and US-Humira.

All animals eventually developed anti-drug antibodies resulting in steep decreases in plasma concentrations after 216 hrs. There was no difference in anti-drug antibody response between the treatment groups.

Table 3: Pharmacokinetic Summary

	Original Concentrations		Dose Normalized for Protein Concentrations	
PK parameters	**US-Humira (n=6)**	**BI 695501 (n=6)**	**US-Humira (n=6)**	**BI 695501 (n=6)**
t_{max} (h)	96	108	96	108
C_{max} (µg/mL)	5.94	7.10	6.76	6.92
$AUC_{0-\infty}$	1120	1524	1276	1486
AUC_{0-T} (µg-h/mL)	994	1340	1132	1306

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A 5-week intravenous injection study in Cynomolgus monkeys with an 8-week recovery period comparing Humira and BI 695501

Study no.: pk-10-1052

Study report location: Module 4.2.3.2

Conducting laboratory and location: (b) (4)

Date of study initiation: November 22, 2010

GLP compliance: Yes, with exception for characterization and stability of control article and BI 695501, flow cytometry evaluation, and labeling of Humira for assay of plasma concentrations.

QA statement: Yes

Drug, lot #, and % purity: **BI 695501**, Batch E0712F02, Purity 99.4% (HP-SEC) (bulk lot T1HEX-139/140

EU-Humira, Batch 87497XD01, Purity assumed to be 100%

BI 695501 diluent, Batch 93850/93852 dilution buffer formulation

Key Study Findings

- Cynomolgus monkeys were administered either vehicle, BI 695501 (157 mg/kg), or EU-Humira (157 mg/kg), IV, once weekly for 5 weeks (n=5/sex/group) followed by an 8 week recovery period (n=2/sex/group).

- Both BI 695501 and EU-Humira produced mild reversible increases in globulin levels and associated reductions in the albumin/globulin ratios, thought to be attributed to the amount of IgG administered.
- Both BI 695501 and Humira similarly reduced the size and number of germinal centers of the spleen and reduced lymphoid follicle activation in the mesenteric and mandibular lymph nodes.
- Similar toxicokinetic profiles resulted from BI 695501 and Humira administration. There were no sex differences in exposure and there were similar low amounts of drug accumulation (~1.4 to 2.6-fold) over the dosing period. No anti-drug antibodies were detected, but it is probable that drug levels were sufficiently high enough, even at prolonged sampling times, to interfere with anti-drug antibody detection.
- Based on this study, BI 695501 and EU-Humira were toxicologically similar.

Methods

Doses:	0 and 157 mg/kg/dose (BI 695501 and EU-Humira)
Frequency of dosing:	Once weekly (days 1, 8, 15, 22, and 29)
Route of administration:	IV, slow bolus injection (over 2 to 5 minutes)
Dose volume:	3.14 mL/kg
Formulation/Vehicle:	BI 695501 and EU-Humira were prepared in their own diluent, then both were further diluted in BI 695501 diluent

Formulation:

Monobasic sodium phosphate dihydrate	5.53 mmol/L
Dibasic sodium phosphate dihydrate	8.57 mmol/L
Sodium Citrate dihydrate	1.16 mol/L
Citric acid monohydrate	6.19 mmol/L
Mannitol	65.87 mmol/L
Sodium chloride	105.45 mmol/L
Polysorbate 80 (Tween 80)	0.1%

Species/Strain: Cynomolgus monkey (Chinese origin))
Number/Sex/Group: Main: 3/sex/group
Recovery: 2/sex/group
Age: Males: 2.5 to 3.0 years of age
Females: 2.5 to 3.5 years of age
Weight: Males: 2.3 to 2.7 kg
Females 2.2 to 2.7 kg
Study design:

Experimental Design

Group No.	No. of Animals				Test Material	Dose Level (mg/kg/dose)	Dose Concentration (mg/mL)	Dose Volume (mL/kg/dose)
	Main Study (Necropsy Day 30)		Recovery (Necropsy Day 85)					
	Male	Female	Male	Female				
1	3	3	2	2	Control Article	0	0	3.14
2	3	3	2	2	BI 695501	157	50	3.14
3	3	3	2	2	Humira®	157	50	3.14

Deviation from study protocol: There were no deviations that affected the study results and conclusions

Observations and Results

Mortality

Animals were monitored twice daily.

There were no mortalities.

Clinical Signs

Animals were monitored once daily, detailed clinical observations were obtained once weekly, and postdose observations at 3 hours postdose. Veterinary physical exams were conducted prestudy in week -1, on day 2, on day 30 prior to necropsy, and day 84 for recovery animals.

There were no treatment-related clinical observations or changes noted in physical examinations.

Body Weights

Body weights were monitored at weekly intervals.

There were no treatment-related effects on body weights.

Feed Consumption

Feed consumption was qualitatively monitored once daily

There were no treatment-related effects on feed consumption.

Ophthalmoscopy

Eye examinations were conducted prestudy and during week 4.

There were no treatment-related ocular effects.

ECG

ECG and blood pressure were monitored prestudy, day 2, and day 30

There were no treatment-related effects on ECG rhythm or waveform morphology, and no effects on blood pressure were observed.

Hematology

Blood samples were collected on prestudy day -8, and days 2, 30, and 84 and evaluated for standard hematological parameters.
Blood smears were also made but were not examined.
Flow cytometry was used to examine peripheral blood mononuclear cell subpopulations labeled with antibodies to cellular antigens listed in the following table.

Flow Cytometry

Antigen Markers	Cell Population Identified [a, b]
CD45+	All Lymphocytes –For Gating Purposes
CD45+/CD20+	B-lymphocytes
CD45+/CD3+	T-lymphocytes
CD45+/CD3+/CD4+	T-helper lymphocytes
CD45+/CD3+/CD8+	T-cytotoxic/suppressor lymphocytes
CD45+/CD3-/CD16+	Natural-killer cells
CD45+/CD3-/CD14+	Monocytes
CD45+/CD4+/CD25+/FoxP3+	T-helper regulatory lymphocytes
CD45+/CD8+/CD25+/FoxP3+	T-cytotoxic regulatory lymphocytes
CD45+/CD4+/CD25+/FoxP3-	T-helper activated lymphocytes
CD45+/CD8+/CD25+/FoxP3-	T-cytotoxic activated lymphocytes

[a] A lymphocyte purity estimate (CD3+/CD20+/CD16+) and CD45+ were calculated but not reported.
[b] Absolute cell counts and percent of baseline were calculated and reported.

There were no treatment-related effects on hematology.
There were no treatment-related effects on peripheral blood mononuclear cell subpopulations.

Clinical Chemistry

Blood samples were collected on prestudy day -8, and days 2, 30, and 84 and evaluated for standard chemistry and coagulation parameters.

There was an increase (130 to 141%) in globulin levels in BI 695501 and EU-Humira groups compared to control values on day 30 in both males and females which returned to control levels by the end of the recovery phase. There was a corresponding decrease (23 to 36%) in albumin/globulin ratio that also returned to control levels during recovery. These effects were thought to be due to high doses administered (high content of IgG).

There was no effect on total protein or albumin levels, or other clinical pathology and coagulation parameters.

Table 4: Summary of Changes on Clinical Chemistry Parameters

Treatment		**Vehicle**		**BI 695501**		**EU-Humira**	
Dose (mg/kg/week)		**0**		**157**		**157**	
Gender		**M**	**F**	**M**	**F**	**M**	**F**
	Day (n)						
Globulin (g/dL)	**30 (5)**	2.70	2.70	**3.52 (130%)**	**3.52 (130%)**	**3.26 (121%)**	**3.82 (141%)**
	84 (2)	2.55	3.15	2.70	3.15	2.65	3.50
A/G ratio	**30 (5)**	1.50	1.40	**1.06 (71%)**	**1.08 (77%)**	**1.16 (77%)**	**0.90 (64%)**
	84 (2)	1.50	1.30	1.45	1.30	1.45	1.20

Urinalysis

Samples for urinalysis were not collected, thus there was no assessment of urine parameters.

Gross Pathology

All animals were subjected to a complete necropsy after the scheduled euthanasia on day 30 for main study animals and day 85 for recovery animals.

There were no treatment-related effects on macroscopic findings.

Organ Weights

Organ weights listed in the following table were obtained on days 30 or 85 (recovery).

Organs Weighed at Necropsy

Brain Epididymis Gland, adrenal Gland, pituitary Gland, prostate Gland, thyroid Heart Kidney	Liver Lung Ovary Spleen Testis Thymus Uterus

There were no statistically significant differences in mean organ weights. Mean weights for spleen and thymus were often lower compared to controls; however the variation was large due to the few animals studied. The sponsor noted that a female #2502 in the BI 695501 treatment group and female #3503 in the EU-Humira treatment group had reduced spleen weights that correlated with histopathology findings of reduced size/number of germinal centers in splenic follicles. The reduction of spleen weights, while not statistically significant, is consistent with histopathology findings.

	Males			**Females**		
	Vehicle	**BI**	**EU-**	**Vehicle**	**BI**	**EU-**

		695501	Humira		695501	Humira
Dose (mg/kg/week)	**0**	**157**	**157**	**0**	**157**	**157**
N	**3**	**3**	**3**	**3**	**3**	**3**
Spleen						
g	3.775	3.552	3.016	3.749	2.274	2.607
%BW	1.405	1.358	1.181	1.438	0.943	1.076
Thymus						
g	3.666	2.266	3.067	2.496	1.173	1.540
%BW	1.397	0.875	1.217	0.949	0.489	0.440

Histopathology

Adequate Battery
An adequate battery of tissues were obtained and examined, listed below. Additional histology samples were taken from the thymus, spleen, and mesenteric lymph node for possible analysis. Bone marrow smears were also prepared but not evaluated.

Tissue Collection and Preservation

Administration site	Large intestine, cecum
Animal identification	Large intestine, colon
Artery, aorta	Large intestine, rectum
Bone marrow smear	Liver
Bone marrow, femur	Lung
Bone marrow, sternum	Lymph node, mandibular
Bone, femur	Lymph node, mesenteric
Bone, sternum	Muscle, skeletal psoas, and diaphragm
Brain	Nerve, optic[a]
Cervix	Nerve, sciatic
Epididymis	Ovary
Esophagus	Oviduct
Eye[a]	Pancreas
Gallbladder	Skin
Gland, adrenal	Small intestine, duodenum
Gland, lacrimal	Small intestine, ileum
Gland, mammary	Small intestine, jejunum
Gland, parathyroid	Spinal cord
Gland, pituitary	Spleen
Gland, prostate	Stomach
Gland, salivary mandibular	Testis[b]
Gland, seminal vesicle	Thymus
Gland, thyroid	Tongue
Gross lesions/masses	Trachea
Gut-associated lymphoid tissue	Ureter
Heart	Urinary bladder
Kidney	Uterus
	Vagina

[a] Preserved in Davidson's fixative.
[b] Preserved in Modified Davidson's fixative.

Peer Review
A pathology peer review was conducted by the sponsor's veterinary pathologist with documentation included in the report. This is not considered an independent peer review.

Histological Findings

Except for the spleen and lymph nodes, there were no drug-related histopathology findings for most tissues and organs, and there were no consistent differences between male and females. Common findings in multiple tissues were cellular infiltrates, but there were no consistent findings in males or females for the three treatment groups. Injection site findings in all treatment groups included hemorrhage, fibrosis/fibroplasias, and neutrophilic infiltrates.

There was a moderate reduction in the size and number of germinal centers of splenic lymphoid follicles in the BI 695501 and EU-Humira treatment groups compared to controls. With only 2/sex/group recovery animals, by the end of the 8 week recovery period it was not possible to determine any definitive differences between treatment groups, and it appeared that the reduction in size and numbers of germinal centers was still present in some animals.

The lymph nodes had minimal reductions in "reduced activation" compared to vehicle treatment. Although this physiologic term was not defined in terms of histologic findings, it probably indicates reduced mitotic cells or cell size. These changes were still present in recovery animals, including the control group.

Table 5: Microscopic Findings in the Lymph Nodes and Spleens

Treatment		**Vehicle**		**BI 695501**		**EU-Humira**	
Dose (mg/kg/week)		**0**		**157**		**157**	
Gender		**M**	**F**	**M**	**F**	**M**	**F**
	Severity	**3**	**3**	**3**	**3**	**3**	**3**
Spleen							
Germinal Centers size/number							
decreased	moderate	0	0	0	2	0	2
increased	minimal	1	1	2	1	3	1
Recovery, n=2/group							
decreased	minimal	0	0	1	0	0	1
	mild	0	0	0	1	0	0
	moderate	0	0	0	0	0	1
increased	minimal	2	1	0	1	2	0
Lymph Node, Mandibular n		3	3	3	2	3	3
Lymphoid Follicles, reduced activation	minimal	1	0	2	1	3	3
Recovery, n=2/group	minimal	0	2	2	2	0	2

Lymph Node, Mesenteric Lymphoid Follicles, reduced activation	minimal	2	1	3	3	2	3
Recovery, n=2/group	minimal	0	2	1	2	2	1

Toxicokinetics

Plasma samples were analyzed for concentrations of BI 695501 or EU-Humira on days 1 and 22 at predose and 5 min, 1, 7, 24, 72, 120, and 168 hours post-dose. On day 29 for recovery animals, blood samples were collected at the following time points: 1, 24, 336, 672, 1008, and 1320 hours post-dose.

Anti-drug Antibodies:
Blood was collected by venipuncture once prestudy and on day 29 (predose) and day 29 at 336 h (= day 43), 672 h (= day 57), 1008 h (= day 71), and 1320 h (= day 84) postdose. The samples were analyzed for antibodies against BI 695501 and EU-Humira. During assay validation it was found that 50 µg/mL EU-Humira or BI 695501 inhibited the measurement of anti-Humira or anti-BI 695501 antibodies.

There was no difference in the time course of BI 695501 and Humira kinetics and kinetic summary parameters on day 1 or day 22. There were no sex differences in exposure to either of BI 695501 or EU-Humira. There was a mild accumulation of both BI 695501 and EU-Humira (up to 2.5-fold) between days 1 and 22 (4 doses).

Plasma concentrations of BI 695501 or EU-Humira remained high at the 168 h time points, such that $T_{½}$ or $AUC_{0\text{-}inf}$ could not be reported for any animal on days 1 and 22. On day 29, for the recovery animals of both genders, the longer sampling time (to 1320 h) allowed the estimation of the elimination phase. BI 695501 and EU-Humira's half-life estimates ranged from 247 to 335 h for BI695501 and from 258 to 370 h for EU-Humira.

Table 6: Pharmacokinetic Summary

	Dose (mg/kg/week)			
Treatment	**BI 695501**		**EU-Humira**	
Dose (mg/kg/week)	**157**		**157**	
Gender	**M**	**F**	**M**	F
Day 1				
T_{max} (h)	0.083	0.11	0.083	1.00
C_{max} (µg/mL)	4955	4471	3621	3668
$AUC_{0\text{-}168}$ (µg-h/mL)	256562	247965	274042	267779
Day 22				
T_{max} (h)	0.105	0.083	0.083	0.083

C_{max} (µg/mL)	6935	8211	5826	6090
AUC_{0-168} (µg-h/mL)	576138	632786	488780	473241

Anti-drug antibodies:
No blood samples were positive for the presence of anti-drug antibodies. Since all timepoints in all treated animals had plasma concentrations of EU-Humira or BI 699501 that were greater than 50 µg/mL, it is possible that circulating drug interfered with antibody detection. However, there were no changes in concentration-time profiles of individual animals that were indicative of anti-drug antibody mediated clearance.

Dosing Solution Analysis

There was no dosing solution analysis, as the drugs were dosed at the concentrations received and used within previously determined stability limits.

11 Integrated Summary and Safety Evaluation

BI 695501 is human monoclonal immunoglobulin (IgG1 κ subtype) against human TNFα. Studies were conducted to compare effects produced with BI 695501 to that of EU-sourced Humira or US-sourced Humira.

Pharmacology
The sponsor provided summary data from studies that assessed pharmacologic properties of BI695501 and EU- and US-Humira. These studies were:

- Binding to soluble TNF-α (measured in 3 assay formats)
- Binding to membrane bound TNF-α using a cell based assay
- Binding to a panel of Fc receptors by surface plasmon resonance (CD16a, CD16b, CD32a, CD32b/c, CD64, FcRn)
- Inhibition of TNF-α induced apoptosis
- Complement-dependent Cytotoxicity (CDC)
- Binding to C1q by ELISA
- Antigen-dependent cellular cytotoxicity (ADCC)
- Inhibition of TNF-α induced induction of adhesion molecule expression (ICAM-1, ELAM-1, and VCAM-1).

Since only study summaries were presented in the nonclinical sections, the reviewer defers to the Product Quality Reviewer for judgments concerning the appropriateness of the statistical analysis and similarity among the 3 drug products regarding these functions. In general, similarity appeared to exist for most parameters. There were some non-similar cases which the sponsor attributed to inherent variability in assays, particularly cell-based assays, or relatively few lots were compared. In other cases findings were just outside the sponsor's statistical interval for equivalence claiming these differences had little functional significance. A final determination of "highly

similar," necessary for approval, will be undertaken for the BLA review by the appropriate members of the review team.

For the IND, it was necessary to determine if the safety established in the nonclinical studies with older lots of BI 695501 drug substance were 1) adequately bridged to the new lots for the proposed clinical study, and 2) EU-Humira was adequately bridged to US-Humira, since EU-Humira was used as the comparator in some pivotal nonclinical studies, including the repeat-dose monkey toxicology study. In a communication from the product quality reviewer, BI 695501 produced by early manufacturing processes was comparable to BI 695501 produced for use in the proposed clinical study. In addition, preliminary review indicates that EU- and US-Humira appear to be similar, although some parameters did fail to meet the statistical requirements for the sponsor's determination of equivalence. The sponsor concluded the differences are minor and are not expected to have any influence on efficacy and safety of the product. The nonclinical Reviewer defers to the analysis and conclusions of the Product Quality Reviewer.

Pharmacokinetics
A non-GLP pharmacokinetic study was conducted in cynomolgus monkeys that compared BI 695501 pharmacokinetics with US-Humira. BI 695501, formulated in the intended commercial formulation, and US-Humira were administered subcutaneously at 0.8 mg/kg. Both compounds resulted in similar pharmacokinetic parameters after adjustment for the actual protein concentration administered. All animals developed immunogenicity, which affected pharmacokinetics after 216 hours postdose.

Toxicology
In a repeated dose study, cynomolgus monkeys were administered either vehicle, BI 695501 (157 mg/kg), or EU-Humira (157 mg/kg), IV, once weekly for 5 weeks (n=5/sex/group) followed by a 8 week recovery period (n=2). Both BI 695501 and Humira produced mild reversible increases in globulin levels, and associated reductions in the albumin/globulin ratios, thought to be attributed to the amount of IgG administered. Both BI 695501 and Humira similarly reduced the size and number of germinal centers of the spleen and reduced lymphoid follicle activation in the mesenteric and mandibular lymph nodes. Similar toxicokinetic profiles resulted from BI 695501 and EU-Humira administration. There were no sex differences in exposure and there was similar low amount of drug accumulation (~1.4 to 2.6-fold) over the dosing period. No anti-drug antibodies were detected, but it is probable that sufficient drug was present even at prolonged sampling times and this interfered with the anti-drug antibody assay. Based on this study, BI 695501 and EU-Humira were toxicologically similar.

Bridging of Nonclinical to Clinical Lots for Clinical Support

The 5-week toxicology study in cynomolgus monkeys was conducted to determine the safety of BI 695501 compared to EU-Humira. Toxicology findings were similar between BI-695501 and EU-Humira and there were no safety concerns for BI-695501 observed in this study. Physicochemical and functional pharmacologic data generally indicated

similarity among multiple lots of BI 695501, EU-Humira, and US Humira and also established that BI 695501 drug substance from early manufacturing processes used in the nonclinical studies was similar to the proposed clinical trial batch using an improved manufacturing process. This enabled bridging of safety from the toxicology studies to the batch of BI 695501 to be used in the proposed clinical trial.

Recommendation

The clinical protocol is reasonable safe to proceed.

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/s/

LAWRENCE S LESHIN
02/19/2015

MARCIE L WOOD
02/19/2015

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/s/

LAWRENCE S LESHIN
06/14/2017

CAROL M GALVIS
06/14/2017
I concur.