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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cyltezo

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/004319/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADCC	Antibody Dependent Cellular Cytotoxicity
ACR	American College of Rheumatology
ACR20	20% improvement in the ACR score
ADA	Anti-drug antibody
ADCP	Antibody Dependent Cellular Phagocytosis
AESI	Adverse events of special interest
AEX	Anion Exchange
AF	Alternative Formulation
AF4	Asymmetric flow field flow fractionation
AI	Autoinjector
ALT	Alanine amino transferase
anti-CCP	Anti-cyclic citrullinated peptide
APG	Acid Peak Group
API	Active pharmaceutical ingredient
AST	Aspartate amino transferase
AT	Acid Treatment
AUC	Analytical Ultra-Centrifugation
AUC0-∞	Area under the concentration-time curve of the analyte in plasma from zero to infinity
AUC0-tz	Area under the concentration-time curve of the analyte in plasma from 0 to the last quantifiable concentration
BI	Boehringer Ingelheim
BIcMQ	BI-customized MedDRA query
BLA	Biologics License Application
BMI	Body mass index
BPG	Basic Peak Group
BSE	Bovine Spongiform Encephalopathy
C1q	Complement component C1q
CAMs	Cell Adhesion Molecules
CCI(T)	Container Closure Integrity (Testing)
CD	Cluster of Differentiation
CD	Circular Dichroism
CD	Crohn's disease
CD16a	Fc receptor FcγRIIIa
CDC	Complement Dependent Cytotoxicity
CDR	Complementarity Determining Region
CEX	Cation Exchange
CF	Commercial formulation
CFU	Colony Forming Unit
CGE	Capillary Gel Electrophoresis
cGMP	Current Good Manufacturing Practice
CHO	Chinese Hamster Ovaries
CI	Confidence interval
CMA	Critical Material Attribute
Cmax	Maximum measured concentration of the analyte in plasma
CpB	Carboxypeptidase B
CPI	Critical Process Indicator
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRP	C-reactive protein
CTD	Common Technical Document
CV	Variation Coefficient
CZE	Capillary zone electrophoresis
DAS28 -ESR	Disease Activity Score 28, based on erythrocyte sedimentation rate
DF	Diafiltration
DILI	Drug-induced liver injury

DMARD	Disease modifying antirheumatic drug
DNA	Deoxyribonucleic Acid
DSC	Differential Scanning Calorimetry
ELAM-1	Endothelial Cell Leukocyte Adhesion Molecule-1
ELISA	Enzyme linked immunosorbent assay
ESI	Electrospray ionization
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACS	Fluorescence-Activated Cell Sorting
FcRn	Neonatal Fc Receptor
FMEA	Failure Mode Effects Analysis
FT-IR	Fourier-transform infrared (spectroscopy)
gMean	Geometric Mean
HCB	Host Cell Bank
HCCF	Harvested Cell Culture Fluid
HIC	Hydrophobic Interaction Chromatography
HMW	High Molecular Weight
HUVEC	Human Umbilical Vein Endothelial Cells
ICAM	Intercellular Adesion Molecule
ICH	International Conference on Harmonisation
IEC	Ion Exchange Chromatography
IEF	Isoelectric Focusing
IGF	Insulin Like Growth Factor
IgG	Immunoglobulin G
IND	Investigational New Drug (application)
INN	International Non proprietary Name
IPC	In-Process Control
kDa / kD	Kilo Dalton
KPI	Key Process Indicator
KPP	Key Process parameter
LAL	Limulus Amebocyte Lysate
LC	Light Chain
LC-MS	Liquid chromatography - mass spectrometry
LMW	Low Molecular Weight
LOQ	Limit Of Quantification
Mab	Monoclonal Antibody
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Micro Flow Imaging
MI	Multiple imputation
MS	Mass Spectrometry
mTNFα	Membrane spanning form of TNFα
MTX	Methotrexate
MW	Molecular Weight
nAb	Neutralizing antibody
NIST	National Institute of Standards and Technology
NOR	Normal Operating Range
NRI	Non-responder imputation
PAR	Proven Acceptable Range
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PFS	Pre-filled Syringe
Ph.Eur.	European Pharmacopeia
pI	Isoelectric Point
PK	Pharmacokinetics
ppm	Parts Per Million
PPQ	Process Performance Qualification
PPS	Per-protocol set
PS80	Polysorbate 80

PVAC	Process Validation Acceptance Criterion
PVDF	Polyvinylidene fluoride
QA	Quality Attribute
QC	Quality Control
QTPP	Quality Target Product Profile
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RH	Relative Humidity
RLCA	Response Level Correlation Assay
RPN	Risk Priority Number
RPP	Reference Product Pool
RT	Room Temperature
s.c.	Subcutaneous
SAF	Safety analysis set
SCB	Safety Cell Bank
SD	Standard deviation
SPR	Surface Plasmon Resonance
t1/2	Terminal half-life of the analyte in plasma
TEM	Transmission electron microscopy
tmax	Time from (last) dosing to the maximum measured concentration in plasma
TNF	Tumor Necrosis Factor
TOST	Two One-sided Test
TSE	Transmissible Spongiform Encephalopathies
TTC	Threshold of Toxicological Concern
UF	Ultrafiltration
ULN	Upper limit of normal
USP	United States Pharmacopeia
VCAM	Vascular Cell Adhesion Molecule - 1
VLP	Virus Like Particle
WCB	Working Cell Bank
WFI	Water for Injection
WS	Working Standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 27 October 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Cyltezo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Rheumatoid arthritis
Cyltezo in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Cyltezo can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Adalimumab is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Cyltezo is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Cyltezo is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Cyltezo is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

Cyltezo is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Adalimumab is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Cyltezo is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of agewith an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn's disease

Cyltezo is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Adalimumab is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Cyltezo is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Cyltezo is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Humira; 40 mg; solution for injection in pre-filled syringe, solution for injection in pre-filled pen

- Marketing authorisation holder: Abbvie Ltd
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/03/256/002-005, EU/1/03/256/007-010

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Humira; 40 mg; solution for injection in pre-filled syringe, solution for injection in pre-filled pen
- Marketing authorisation holder: Abbvie Ltd
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/03/256/002-005, EU/1/03/256/007-010

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Humira; 40 mg; solution for injection in pre-filled syringe
- Marketing authorisation holder: Abbvie Ltd
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/03/256/002-005
- Bioavailability study number(s): 1297-0001 and 129-0008

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 14 April 2011, 16 February 2012 and 27 June 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Milena Stain Co-Rapporteur: Jan Mueller-Berghaus

- The application was received by the EMA on 27 October 2016.
- The procedure started on 24 November 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 16 February 2017.
- During the meeting on 23 March 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 June 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 20 July 2017, the CHMP agreed on a List of Outstanding Issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 August 2017.
- During the meeting on 11-14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Cyltezo on 14 September 2017.

2. Scientific discussion

2.1. Problem statement

This centralised marketing authorisation application concerns the Biotech medicinal product Cyltezo, 40 mg solution for injection, developed by Boehringer Ingelheim International GmbH.

The application is submitted under Article 10(4) (similar biological application) of Directive 2001/83/EC, as amended. The reference medicinal product is Humira, originally authorised in the community in 2003.

The active substance is adalimumab, a recombinant human monoclonal antibody.

Cyltezo is presented in 0.8 mL single-dose pre-filled syringes and autoinjector, containing 40 mg adalimumab to be administered via subcutaneous (SC) injection.

2.1.1. Disease or condition

In the EU the reference product Humira is authorised for the treatment of Rheumatoid arthritis (RA), Juvenile idiopathic arthritis (JIA) (polyarticular JIA and enthesitis-related arthritis), Axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), Psoriatic arthritis, Psoriasis, Paediatric plaque psoriasis, Hidradenitis suppurativa (HS), Crohn's disease (CD), Paediatric Crohn's disease, Ulcerative colitis (UC) and Non- infectious Uveitis (UV).

The Applicant intends to claim the same therapeutic indications for the biosimilar Cyltezo as are granted for Humira in the EU.

As Cyltezo is currently only available as a 40 mg prefilled syringe (PFS) presentation, the Applicant intends to claim the paediatric indications only for those patients who can administer the full 40 mg dose. However, a paediatric vial (40 mg/0.8 mL) is being developed for patients who need to administer less than the full 40 mg dose.

2.1.2. About the product

Cyltezo is being developed as a biosimilar candidate to Humira (adalimumab). Adalimumab belongs to the pharmacotherapeutic group "immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors" (ATC code: L04AB04). The mechanism of action of adalimumab is binding specifically to TNF-α and neutralising its biological function by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Please note that BI695501 and Cyltezo are used interchangeably throughout the document.

2.1.3. Type of Application and aspects on development

- Legal basis

  This Marketing Authorisation Application is an abridged application for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

- Accelerated procedure

N/A

- Conditional approval

  N/A

- Exceptional circumstances

  N/A

- Biosimilar application

  Similarity is claimed to Humira (adalimumab) as the reference medicinal product, which has been marketed in the European Union for over 10 years. Humira 40 mg solution for injection in a prefilled syringe was first authorised in the EU on 8 September 2003; the Marketing Authorisation Holder is AbbVie Ltd.

- 1 year data exclusivity

  N/A

- Significance of paediatric studies

  As far as similar biological medicinal products are concerned, there is no requirement for paediatric development (Paediatric Regulation (EC) No 1901/2006).

Scientific Advice

The applicant received Scientific Advice from the CHMP on 14 Apr 2011, 16 Feb 2012 and 27 Jun 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Clinical trials performed by the applicant:

The clinical pharmacology of BI 695501 has been investigated in two phase I trials in healthy male volunteers:

• **Study 1297.1**: comparative PK trial with a trial formulation of BI 695501

• **Study 1297. 8**: 3-way PK similarity trial of the commercial formulation of BI 695501 with US-licensed and EU-approved Humira

The rationale to include the US reference product in the Phase I PK studies was to demonstrate equivalence between EU and US reference, so that the US reference can be used as a “surrogate” for the EU reference in later studies (e.g. study 1297.2).

In addition, supportive PK data was generated in a trial in patients with active RA on stable MTX background therapy (**study 1297.2**). Trough drug concentrations were determined as supportive data for a descriptive pharmacokinetic comparison of BI 695501 and US-licensed Humira and for a population PK analysis.

Two further PK studies were provided to support the development of the autoinjector:

• **Study 1297.6** (phase I) to show similarity between the pre-filled syringe (PFS) and the autoinjector (AI) of BI 695501.

• **Study 1297.11** (phase II) to assess the real life handling experience of PFS and the AI.

TABULAR LISTING OF CLINICAL STUDIES

Type of Study	Study Identifier study no. [doc.no.]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage, Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I PK studies								
PK and safety	1297.1[1] [U13-1096]	PK, safety, and immunogenicity	Open-label, randomized, parallel-group, active-controlled	BI 695501 (TF) PFS, US-licensed Humira, EU-approved Humira; 40 mg single dose; s.c.	Treated: 193 BI 695501 (TF): 67 US Humira: 62 EU Humira: 64	Healthy subjects	Single dose	Complete; Full report
PK and safety	1297.8 [c03070713] VOLTAIRE®-PK	PK, safety, and immunogenicity	Double-blind, randomized, parallel-group, active-controlled	BI 695501 (CF) PFS, US-licensed Humira, EU-approved Humira; 40 mg single dose; s.c.	Treated: 324 BI 695501 (CF): 108 US Humira: 108 EU Humira: 108	Healthy subjects	Single dose	Complete; Full report
Pivotal Phase III study								
Efficacy and safety	1297.2 [c08934295] VOLTAIRE®-RA	Efficacy, safety, and immunogenicity	Double-blind, randomized, parallel-group, multiple-dose, active-controlled	BI 695501 (CF) PFS US-licensed Humira; 40 mg biweekly; s.c.	Treated: 645 BI 695501 (CF): 324 US Humira: 321	Patients with moderately to severely active RA and MTX background therapy	48 weeks	Ongoing; Primary analysis report
Studies supporting the autoinjector								
PK and safety	1297.6 (Phase I) [c09477818] VOLTAIRE®-AI	PK, safety, and immunogenicity	Open-label, randomized, parallel-group, active-controlled	BI 695501 (CF) AI BI 695501 (CF) PFS; 40 mg single dose; s.c.	Treated: 66 BI 695501 PFS (CF): 33 BI 695501 AI (CF): 33	Healthy subjects	Single dose	Ongoing; Final primary analysis report
Real-life handling	1297.11 (Phase II) [c08933683] VOLTAIRE®-RL	Assessment of real-life handling experience	Open-label, single-arm, multiple-dose, uncontrolled	BI 695501 (CF) AI; extension period BI 695501 (CF) PFS; 40 mg biweekly; s.c.	Treated: 77 BI 695501 (CF): AI assessment period: 77	Patients with moderately to severely active RA	50 weeks: 7-week AI assessment, 42-week extension	Ongoing; Primary analysis report

s.c. = subcutaneous, PK = pharmacokinetics, TF = trial formulation, CF = commercial formulation, RA = rheumatoid arthritis, AI = autoinjector, PFS = pre-filled syringe
[1] Study 1297.1 was conducted with a trial formulation (TF) of BI 695501, which was not considered for commercial use. Studies 1297.2, 1297.6, 1297.8, and 1297.11 were conducted using the commercial formulation (CF) that is intended to be marketed after approval.
Source data: [U13-1096, Table 15.1.3: 1], [c03070713, Table 14.1.1], [c08934295, Table 14.1.1.1], [c09477818, Table 14.1.1], [c08933683, Table 14.1.1.1]

TABULAR LISTING OF CLINICAL STUDIES

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage, Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I PK studies								
PK and safety	1297.1[1] [U13-1096]	PK, safety, and immunogenicity	Open-label, randomized, parallel-group, active-controlled	BI 695501 (TF) PFS, US-licensed Humira, EU-approved Humira; 40 mg single dose; s.c.	Treated: 193 BI 695501 (TF): 67 US Humira: 62 EU Humira: 64	Healthy subjects	Single dose	Complete; Full report
PK and safety	1297.8 [c03070713] VOLTAIRE®-PK	PK, safety, and immunogenicity	Double-blind, randomized, parallel-group, active-controlled	BI 695501 (CF) PFS, US-licensed Humira, EU-approved Humira; 40 mg single dose; s.c.	Treated: 324 BI 695501 (CF): 108 US Humira: 108 EU Humira: 108	Healthy subjects	Single dose	Complete; Full report
Pivotal Phase III study								
Efficacy and safety	1297.2 [c08934295] VOLTAIRE®-RA	Efficacy, safety, and immunogenicity	Double-blind, randomized, parallel-group, multiple-dose, active-controlled	BI 695501 (CF) PFS US-licensed Humira; 40 mg biweekly; s.c.	Treated: 645 BI 695501 (CF): 324 US Humira: 321	Patients with moderately to severely active RA and MTX background therapy	48 weeks	Ongoing; Primary analysis report
	[c15074004]							Completed; Final report
Studies supporting the autoinjector								
PK and safety	1297.6 (Phase I) [c09477818] VOLTAIRE®-AI	PK, safety, and immunogenicity	Open-label, randomized, parallel-group, active-controlled	BI 695501 (CF) AI BI 695501 (CF) PFS; 40 mg single dose; s.c.	Treated: 66 BI 695501 PFS (CF): 33 BI 695501 AI (CF): 33	Healthy subjects	Single dose	Ongoing; Final primary analysis report
	[c08933656]							Completed; Final report
Real-life handling	1297.11 (Phase II) [c08933683] VOLTAIRE®-RL	Assessment of real-life handling experience	Open-label, single-arm, multiple-dose, uncontrolled	BI 695501 (CF) AI; extension period BI 695501 (CF) PFS; 40 mg biweekly; s.c.	Treated: 77 BI 695501 (CF): AI assessment period: 77	Patients with moderately to severely active RA	50 weeks: 7-week AI assessment, 42-week PFS extension	Ongoing; Primary analysis report

s.c. = subcutaneous, PK = pharmacokinetics, TF = trial formulation, CF = commercial formulation, RA = rheumatoid arthritis, AI = autoinjector, PFS = pre-filled syringe
[1] Study 1297.1 was conducted with a trial formulation (TF) of BI 695501, which was not considered for commercial use. Studies 1297.2, 1297.6, 1297.8, and 1297.11 were conducted using the commercial formulation (CF) that is intended to be marketed after approval.
Source data: [U13-1096, Table 15.1.3: 1], [c03070713, Table 14.1.1], [c08934295, Table 14.1.1.1], [c09477818, Table 14.1.1], [c08933683, Table 14.1.1.1]

Note that final data of trials 1297.2 and 1297.6, which were ongoing at time of the initial submission, were provided during the procedure.

GMP aspects

Valid GMP certificates are available for the manufacturing and testing sites.

GLP aspects

The preclinical studies submitted and presented in this assessment report were described accordingly and are of adequate quality. The toxicology studies have been conducted in accordance with the OECD Principles of Good Laboratory Practice.

GCP aspects

According to the applicant, all clinical studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and were consistent with International Conference on Harmonisation (ICH) "Guideline for Good Clinical Practice (GCP)" (ICH E6(R1)) and applicable local regulatory requirements and laws. No issues regarding GCP have been identified.

2.2. Quality aspects

2.2.1. Introduction

Cyltezo has been developed as a biosimilar product to the EU authorised reference medicinal product (RMP) Humira (adalimumab). The active substance adalimumab is a recombinant human monoclonal antibody that binds specifically to tumour necrosis factor alpha (TNFα) and neutralizes the biological function of TNF by blocking its interaction with the TNF-receptors TNFR1 and TNFR2.

The finished product is presented as a solution for injection containing 40 mg of adalimumab as active substance for subcutaneous administration.

Other ingredients are: sodium acetate trihydrate, glacial acetic acid, trehalose dihydrate, polysorbate 80 and water for injections as described in section 6.1 of the SmPC.

The product is available in single-use pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and a needle with a needle shield (elastomer containing latex) and in an auto-injector containing a pre-filled syringe as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

Adalimumab (also refered to as BI 695501) is a genetically engineered human monoclonal IgG1 antibody targeted against soluble and membranous tumour necrosis factor alpha (sTNFα/mTNFα) and neutralizes the biological function of TNF by blocking its interaction with the TNF-receptors TNFR1 and TNFR2. Adalimumab is composed of two heterodimers each containing a heavy and a light polypeptide chain. The four polypeptide chains of the antibody molecule are covalently linked together by disulfide bonds. Each heavy chain contains a single N-glycosylation site at asparagine 297. Based on the amino acid sequence, the molecular formula of the disulfide bonded BI 695501 molecule without post - translational modifications like glycosylation is $C_{6448}H_{9964}N_{1732}O_{2020}S_{42}$; the corresponding predicted molecular mass is 145 kDa.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Adalimumab active substance (AS) is manufactured, stability tested, and quality-control tested in accordance with good manufacturing practice (GMP) at Boehringer Ingelheim Fremont, Inc. (BIFI), Fremont, California, USA. The active substance is expressed in a transfected Chinese Hamster Ovary (CHO) cell line. Main steps are thawing of working cell bank vials, cell culture and harvest, and purification. During multiple inoculum steps in shake flasks and wave bioreactors, the cells are repeatedly sub-cultivated to provide sufficient cells to initiate the expansion bioreactors. At the end of the cultivation time of the production bioreactor the cell culture is harvested

The purification process comprises chromatography steps, dedicated orthogonal virus clearance steps, and filtration/concentration steps. Following formulation a final filtration through a 0.2 µm filter is performed. All process steps are performed at ambient temperature. Appropriate containers are used to store DS to provide protection from light and from microbial ingress.

The active substance is harvested, is purified by a series of filtrations and through different chromatographic columns, concentrated and conditioned before being put into storage.

One production bioreactor run results in one batch at the harvest stage, and ultimately in one bulk active substance batch. Unique batch numbers are assigned to assure traceability.Beside the potential re-filtration of the formulated active substance no other reprocessing is foreseen in the manufacturing process of BI 695501. Intermediate hold times which also included extended hold times under exceptional circumstances as well as media and buffer hold times have been appropriately validated taking into account chemical and microbial stability.

Adalimumab (BI 695501) active substance manufacturing process has been adequately described. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance manufacturing process is considered acceptable.

Control of materials

Raw materials are of compendial quality or released against in-house specifications; the respective in-house specifications are provided. Composition and preparation of culture media and buffer solutions are described, and the information on product contact filters and on chromatography resins is provided. A two-tiered cell bank system in overall accordance with ICH Q5A, Q5B, and Q5D guidelines is used. Cell banking procedures are adequately described and characterisation of cell banks is in line with current guidelines. The stability of the cell banks is adequately monitored. Sufficient details are provided on the source and history of the cell substrate, preparation of the expression constructs, and generation of the production clone.

Control of critical steps and intermediates

Critical process parameters and key process parameters impacting critical quality attributes (CQA) or process performance, respectively have been defined. Their normal operating range (NOR) and/or proven acceptable range (PAR) as well as limits/specifications for in-process controls have been derived from process development knowledge, process characterisation studies and large scale process performance qualification.

Process validation

The prospective process validation encompassed consecutive process performance qualification (PPQ) runs which were performed within normal operating ranges at commercial scale at the intended

commercial facility (i.e. BIFI). The validation criteria were based on critical process parameters (CPP) impacting product quality and key process parameters (KPP) impacting performance and critical and key process indicators (CPI/KPI – output parameters) evaluated during process characterisation. All process runs met the acceptance criteria and the resulting AS batches comply with the AS specifications. Removal of impurities was successfully demonstrated. Some discrepancies which occurred during process validation are adequately described and in general, the respective evaluations and conclusions are reasonable. Overall, the results of the PPQ runs demonstrate that the process performs consistently and delivers AS of the desired quality under commercial operating conditions. Chromatography resin lifetime has been established for the different resin types employed during manufacture. A prospective process validation protocol for concurrent validation at large scale has been provided. Overall, the process appears adequately controlled.

Transport validation studies demonstrate that the shipping container and process are suitable to ensure the integrity of the BI 695501 active substance during shipment.

Manufacturing process development

Development of the adalimumab manufacturing process and the control strategy took into account a comprehensive evaluation of critical quality attributes (CQA) of adalimumab, risk assessment (RA) tools, process knowledge including platform knowledge, establishment of qualified scale down models (SDM), and process characterization studies (PCS) performed in these SDMs to identify key and critical in- and output parameters. Detailed information has been provided on evaluation of the CQA, RA, SDM, and PCS. The results of the PCS are adequately reflected in the control strategy. Additionally, prediction profiling analyses have been provided. Overall, the variation of parameters (univariate and/or multivariate) during PCS is considered adequate.

The manufacturing process development was rather straightforward; after production for non-clinical studies, the process was scaled up for supply of clinical material. Upon process improvements the process was transferred to BIFI and scaled up to commercial scale. Comparability of AS from the different scales and production sites was demonstrated in accordance with ICH Q5E. The presented data including stability data support the conclusion that material from the different processes is comparable.

Characterisation

Orthogonal standard and state-of-the-art methods were applied to determine physicochemical and immunological properties, biological activity, purity, impurities and quantity of BI 695501. Primary and higher order structure, heterogeneity with respect to size, charge, glycosylation, and hydrophobicity, oxidation as well as biological activity and binding to TNFα and CD16a were analysed. A much more comprehensive characterisation of BI 695501 is provided in the biosimilarity assessment.

Removal of both, aggregates and fragments, has been adequately addressed.

Process-related impurities encompass those derived from or introduced during the active substance manufacturing process. Included are impurities from the host cell line and raw materials used during cell culture and downstream processing. Removal of these impurities to predefined acceptance criteria was demonstrated during challenge studies performed at small-scale during process characterisation and confirmed during process validation.

Specification

The AS specification is in line with ICH Q6B and includes tests and limits for general attributes, identity, purity/impurity, charge heterogeneity and glycosylation pattern, potency, quantity, and microbiological attributes. Stability is evaluated against the same specifications except peptide and oligosaccharide mapping as well as endotoxin and bioburden testing which are not assessed during stability testing.

The AS specification limits were derived from batch analysis data, analytical variability, and stability data. For those parameters that were not statistically evaluated, manufacturing experience, industry standard, pharmacopoeial requirements and relevant guidelines were considered.

Removal of process related impurities has been adequately demonstrated and hence it is acceptable that these are not part of the specification. Polysorbate 80 is controlled at finished product release.

The analytical methods are sufficiently described and, if applicable, a reference to the pharmacopoeia is provided.

The non-compendial analytical procedures are adequately validated; suitability of compendial methods addressing safety aspects (endotoxin and bioburden) has been verified. The results indicate that the analytical methods for AS release are suitable for their intended use.

The origin and history as well as qualification data of all development and reference standards which were produced from BI 695501 AS lots representative for the respective development stage is presented. The standards have been sufficiently qualified using release testing and additional characterisation tests.

Batch release data for batches used in non-clinical, clinical, and stability studies as well as process performance qualification are presented. The results demonstrate that the manufacturing process delivers AS with consistent quality.

Stability

Based on stability data collected to date, an expiry period is supported for BI 699501 active substance stored at the recommended storage temperature. Stability studies were conducted at the recommended storage temperature to support the expiry period. The long-term stability studies were performed according to ICH Q5C guideline.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Cyltezo is supplied as a sterile solution for injection at a concentration of 50 mg/mL for subcutaneous administration. It is a clear to slightly opalescent solution, presented in a 1 mL Type I glass syringe with a nominal fill volume of 0.8 mL. Cyltezo finished product is available in two presentations:

- Pre-filled syringe
- Auto-injector containing the pre-filled syringe

Cyltezo is formulated with sodium acetate trihydrate, glacial acetic acid, trehalose dihydrate, polysorbate 80 and water for injections as described in section 6.1 of the SmPC.

Pharmaceutical Development

The quality target product profile (QTPP) which summarizes all finished product quality attributes that are needed to ensure quality, safety and efficacy of the finished product for the patient was presented. Based on the QTPP, the quality attributes of the finished product were identified and used to guide finished product development. Critical quality attributes (CQAs) which could potentially be impacted by the finished product manufacturing process and are critical to the finished product safety and efficacy have been identified.

The formulation development consisted of pH and buffer selection as well as selection of an agent for tonicity adjustment. Based on several experiments, the pH which was identified as the most stable pH for the adalimumab molecule was selected. The buffer was selected considering the route of administration. Finally the tonifying agent was chosen considering the selected buffer.

For the initial non-clinical studies and the initial clinical trial 1297.1, BI 695501 finished product was manufactured using the trial formulation. During development, the formulation composition was changed to commercial formulation. Batch data from these early finished product batches has been provided and do not indicate any significant differences in quality attributes between batches formulated in “trial formulation” and in “commercial formulation”.

Manufacturing Process Development

The selection and optimisation of the manufacturing process which consists of thawing, pooling (optional), bioburden reduction (optional), sterile filtration, and the final filling - stoppering - assembling to the pre-filled syringe, has been adequately described and justified. Process parameters which may have an impact on the critical quality attributes were identified on the basis of a failure mode and effect analysis (FMEA). A panel of characterisation studies to evaluate the robustness of the finished product manufacturing has been performed.

It should be mentioned that for the majority of the clinical finished product batches, active substance derived from the intended commercial active substance manufacturing process has been used. Comparative flow charts as well as a more detailed comparison of the clinical and commercial finished product manufacturing processes have been provided. The comparability assessment does not indicate any differences between finished products.

The suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product as well as the microbiological attributes of the dosage form has been appropriately discussed. The suitability of the final pre-filled syringe for storage, transportation and use of the BI 695501 finished product is supported by design verification test data. Specifications were established and verified by design verification testing.

Potential leachables and extractables of the manufacturing process equipment coming into contact with the finished product process stream as well as of the primary container closure components have been evaluated.

A sufficient description of the auto-injector and its assembly process has been provided. The manufacture of the BI 695501 auto-injector consists of inserting the pre-filled syringe directly into the auto-injector. To ensure a consistent and reliable production of each auto-injector, assembly equipment with various controls that ensure proper positioning of each component is utilized. Functionality testing verifies the safety, performance and functionality of the BI 695501 auto-injector.

Manufacture of the product and process controls

Description of Manufacturing Process

The manufacturing steps at the finished product manufacturing sites include thawing, pooling and bioburden reduction filtration (optional), sterile filtration of the active substance, followed by filling of the syringes, stoppering and visual inspection. The pre-filled syringes are finally assembled or inserted into the AI. Differences in the process between the manufacturing sites have been discussed and supported by data. Afterwards secondary packaging is conducted and BI 695501 finished product is stored at 2-8°C. Reprocessing and reworking are not performed.

Control of Critical Steps and Intermediates

Critical process parameters with their respective Normal Operating Ranges and Proven Acceptable Ranges as well as in-process controls with either process specifications or process limits have been established for critical steps in finished product manufacture. These controls seem to be appropriate for monitoring process consistency and to ensure that the process delivers a product with consistent high quality.

Process validation

A prospective validation of the manufacturing process was performed to demonstrate that the manufacturing process is controlled and reproducible, consistently yielding finished product with the required product quality. The manufacturing steps have been successfully validated.

Batch consistency of the aseptic filling process was evaluated. All results of lot consistency of the aseptic filling were successfully validated.

Functional testing criteria were analysed for the auto-injector. The data from functionality testing have shown that no significant differences were observed. All results were well within the predefined ranges and therefore successfully validated. Product quality testing was performed to demonstrate that the assembly process has no influence on the product quality and to demonstrate a consistent robust process. Product quality has been successfully demonstrated. The assembly process has no influence on product quality.

Further validation studies included filter validation, media fills and transport validation, covering the transport of the bare pre-filled syringe as well as the transport of the assembled pre-filled syringe and the auto-injector.

Product specification

The finished product specification includes test methods and limits for general characteristics, identity, biological activity, purity and product-related impurities, quantity, content of Polysorbate 80, performance characteristics of the syringe and the auto-injector, and safety.
The panel of analytical methods established for finished product batch release control is considered adequate and ensures that only product with a sufficient high quality will enter the market.

Brief method descriptions have been provided; validation results and summaries of the validation exercises are provided for non-compendial methods. For the majority of the acceptance limits for release and stability testing are identical, in a few cases more liberate limits have been established for stability testing, however this widening of limits has been appropriately justified.

A considerable amount of finished product batches for a biosimilar candidate have been manufactured. The provided batch release data support the conclusion that the finished product manufacturing process performs effectively and reproducibly to produce final product meeting its predetermined

specifications and quality attributes. Concerning the auto-injector, batch analyses data have been presented and do not raise any concern. Finally, impurities present or potentially present at finished product level have also appropriately addressed. No new impurities are introduced in the finished product manufacture.

Stability of the product

For the pre-filled syringe presentation, the stability program is comprised of long-term stability testing at 5 °C for up to 48 months and testing at an accelerated temperature of 25 °C for up to 12 months. A number of additional studies (such as temperature cycling) for simulation of temperature deviations that may arise during transport have been conducted as well as certain stress studies to investigate the impact of stress factors on the finished product quality.

Concerning the auto-injector the strategy to consider results from the product in pre-filled syringe, as these data form part of the basis for the shelf-life claim of the product in the auto-injector, is reasonable. Stability data do not indicate any significant trends or out-of-specification results and indicate that the auto-injector functionality is not impacted by the proposed long-term storage condition at 5°C ± 3°C. Taking all these results into account it is not expected that any issues arise with the functionality of the auto-injector during the remaining long-term storage up to 24 months at 5°C ± 3°C. Thus, a shell-life of 24 months for the auto-injector presentation when stored at (5°C ± 3°C) is acceptable.

The presence of foreign particles has been detected in some pre-filled syringe lots. In addition, visible white, translucent particles have been observed during stability testing of product lots. Initially this observation raised serious concerns on the safety profile of the product. Upon request from the CHMP a thorough discussion on the presence of visible foreign particles as well as on the visible, product-related particles was provided. Detailed information about characterisation and further investigations, identity/obvious root causes for the occurrence of these particles, a toxicological and a clinical assessment including a risk assessment as well as corrective actions which have been implemented, were presented. The provided information allowed a conclusive and an in-depth assessment, and potential safety issues arising from the presence of particles could be ruled out. In addition the product specification for the visible particles has been revised and the instructions for use (label section 7) include the statement: “Do not use if: Medication is cloudy, discolored, frozen, or contains flakes or particles”.
Taking all these arguments and information together, it can be concluded that the visible particles identified in a very few Cyltezo syringes do not pose a risk to patients´ safety and the issue related to the presence of visible particles is considered by the CHMP to be resolved.

Based on overall available stability data, the shelf-life of 2 years, for both the pre-filled syringe and the pre-filled pen, as well as the storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Biosimilarity exercise

An extensive analytical and *in vitro* pharmacological evaluation of similarity of the proposed biosimilar Cyltezo to the EU authorised reference medicinal product (RMP) Humira has been conducted. The similarity exercise included also a demonstration of similarity of US-licensed Humira which was used in the non-clinical and clinical development programme to EU-sourced Humira (and of Cyltezo to US-Humira). Overall, the chosen approach for demonstration of biosimilarity is deemed acceptable and in line with biosimilar guidelines CHMP/437/04 Rev 1 and CHMP/BWP/247713/2012.

The evaluated physicochemical properties comprise primary sequence, secondary and higher order structure, in-depth analysis of post-translational modifications (e.g. glycosylation, oxidation, deamidation and truncation), other modifications, as well as charge, size, and hydrophobicity heterogeneity. Functional activity was compared by a large panel of cell-based biological assays and binding assays covering the main mode of action for the various targeted indications. In addition, attributes related to antibody clearance were considered as well. Method validation or qualification data, chromatograms etc. and structure-function relationship studies, support the conclusion that the analytical methods are suitable and sensitive to detect even minor differences in molecular structure and function.

A large number of EU-sourced Humira and US-Humira lots have been analysed without pre-selection of lots. Hence, it is likely that the actual variability of the RMP will be reflected. Even if not all lots were tested in every assay the number of tested lots is deemed sufficient to draw valid conclusions on similarity.

Lots covering an appropriate range of ages are included for both Cyltezo and Humira.

In general, the applied similarity ranges are acceptable, although in some instances rather wide ranges were obtained due to individual lots showing a strongly divergent result. However, this has been adequately addressed and justified.

Overall, adequate data and/or justifications taking into account structure function relationship data, criticality of the respective attribute, data distribution, number of tested lots, and results for US Humira are provided to conclude that the impact of the observed differences on efficacy/potency, immunogenicity and/or safety is low or negligible. The results of the forced degradation studies indicate similar degradation pathways for Cyltezo and Humira.

To demonstrate that US Humira, which was used in certain non-clinical and clinical studies, is representative for EU Humira the same approach as for the similarity evaluation between Cyltezo and EU Humira was followed. Differences which are observed between results for EU Humira and US Humira have been adequately justified.

In summary, despite minor differences which are not expected to have an impact on clinical performance, similarity of Cyltezo and EU-Humira on the quality level was demonstrated. In addition, the analytical data sufficiently demonstrate that US-Humira is representative for EU-Humira.

Adventitious agents

For early cell line development different media containing animal and human derived components have been used. Non-viral and viral adventitious agents in these media and reagents are deemed to be sufficiently discussed. Master/working cell bank generation and manufacture include two animal derived components. For both, TSE and viral safety are discussed and deemed acceptable.

The virus validation studies have been performed in accordance with CPMP/BWP/268/95 guideline and the choice of model viruses is considered appropriate. A comparison of process parameters from manufacture and down-scale was provided. Interference and cytotoxicity studies have been performed and taken into account.
Overall the inactivation/removal of different types of viruses is considered to be sufficient.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance manufacturing process has been described in sufficient detail; all raw and starting materials including the cell banks used in the manufacture of adalimumab are listed identifying where each material is used in the process. Information on the quality and control of these materials has been provided. Also all excipients used for finished product formulation comply with the Ph. Eur. Overall, an adequate process control system, consisting of process input and process output parameters, is in place which ensures a consistent routine manufacture of Cyltezo. Process validation supports the conclusion that the manufacturing process for active substance as well as for finished product reliably produces active substance and finished product meeting predetermined specifications and quality attributes. The provided active substance and finished product batch analyses data support this conclusion. Comparability of adalimumab throughout the development has been demonstrated. An appropriate control strategy ensures that material of sufficiently high quality will enter the market.

Concerning the demonstration of biosimilarity, a sound and comprehensive biosimilarity exercise has been performed and presented. In general, analytical results of multiple Cyltezo lots were evaluated against min-max similarity ranges established by extensive characterisation of a large number of EU Humira lots, ensuring that the variability of the reference product is adequately reflected. For some parameters, fewer lots have been analysed and thus the variability may not be fully reflected. However, overall the number of tested lots is deemed sufficient to draw valid conclusions on similarity.

The relevant quality attributes of the adalimumab molecule were assessed using a quite exhaustive panel of orthogonal standard and state-of-the art techniques. Analysis covered primary sequence, secondary and higher order structure, in-depth analysis of post-translational modifications, and other modifications, as well as charge, size, and hydrophobicity heterogeneity. Functional activity was compared by a large panel of cell-based biological assays and binding assays covering the main mode of action and other relevant and potential mechanisms for the targeted indications. In addition, attributes related to antibody clearance were also sufficiently considered. The presented data demonstrate that the analytical methods are suitable and sensitive to detect even minor differences in molecular structure and function.

The biosimilarity assessment is complemented by exemplary side-by-side analysis of Cyltezo, EU Humira, and US Humira, forced degradation studies, detailed characterisation of molecule variants and structure function relationship studies. These complementary studies are adequately designed to support the conclusions drawn. Differences observed for various attributes are adequately justified.

In summary, the presented data support the conclusion that Cyltezo is similar to the reference product EU Humira. In addition, the submitted data demonstrate that US Humira is highly similar to EU Humira.

The presence of foreign particles detected in some pre-filled syringe lots has been satisfactorily addressed. The provided detailed information allowed a conclusive and an in-depth assessment, and potential safety issues arising from the presence of particles could be ruled out. The product specification for the visible particles has been revised and the instructions for use (label section 7) include appropriate statement. Taking all these arguments and information together, it can be concluded that the visible particles identified in a very few Cyltezo syringes do not pose a risk to patients´ safety and the issue related to the presence of visible particles is considered by the CHMP to be resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.
No quality aspects impacting on the Benefit-Risk balance have been identified for Cyltezo.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Pharmacology

An extensive panel of in vitro assays was performed to assess the reported mode of action as well as biosimilarity of BI 695501 and the reference product Humira. These assays evaluated target- and Fc-binding as well as biological activity.

The in vitro assays were classified in TNFα neutralization and binding functions, reverse signalling and Fc-mediated effector functions.

Neutralization of sTNFα and binding to mTNFα, the mechanism reported to be key for the action of adalimumab, were addressed by two separate comparative assays.

There is some published evidence for reverse signalling activity of adalimumab being an important immunomodulatory mode of action for some indications, such as IBD. This was adequately addressed by assessing induction of apoptosis.

Fc-related functions of BI 695501 in comparison to EU- and US-licensed Humira were evaluated by a comprehensive panel of assays: Antibody dependent cytotoxicity (ADCC) was quantified to detect any differences. The cell-based ADCC assay was complemented by two independent CD16a-binding assays. Further comparative Fc-receptor binding assays () were performed to support the biosimilarity exercise. Complement dependent cytotoxicity (CDC) was addressed by cell-based CDC assay and an ELISA-based C1q binding assay.

In vitro studies are considered paramount for the non-clinical assessment of biological similarity between BI 695501 and Humira. A broad panel of orthologous/ heterogeneous comparative in vitro studies with a different level of relevance for safety and efficacy of adalimumab were applied; comparability is sufficiently shown as the results are comparable and relevant batches were tested head to head against the reference product. These data generally provide more sensitive measures to assure comparability/biosimilarity than in vivo studies. As such, the absence of comparative in vivo studies is well justified.

In summary, the pharmacology studies conducted within the frame of the biological comparability exercise demonstrate the functional similarity of BI 695501 and the reference product Humira. The in vitro studies were appropriately qualified or validated for their intended purpose.

2.3.2. Pharmacokinetics

For the assessment of the pharmacokinetic profile of and the immunogenicity response to BI 695501 in comparison to the reference medicinal product Humira three separate studies using three different formulations for BI 695501 and EU- or US-licensed Humira were performed in cynomolgus monkeys. In addition, a toxicokinetic study was included into a GLP-compliant repeat-dose toxicity study in cynomolgus monkeys.

The study results are based on sufficiently validated ELISA and electro-chemiluminescence methods to detect drug levels and ADAs, respectively.

The pharmacokinetic data after a single subcutaneous administration of 0.8 mg/kg of the respective formulation of BI 695501 or EU- or US-licensed Humira showed that the products can be considered as biosimilar. The administered dose level is comparable to the human dose of 40 mg in human based on body weight normalization. A deviation from the nominal protein content of the commercial formulation of BI 695501 was identified and data were dose-corrected for the definite analysis of data.

A slight, albeit not statistically significant, overexposure of animals treated with BI 695501 was noted throughout all formulations as compared to Humira. With respect to interpretation of PK results a number of factors influencing the PK of the drug, such as high interindividual variability (higher in the BI 695501-treated group), use of male and female animals, variable bioavailability due to subcutaneous administration, different formulations as well as the administration of human antibodies to primates, have to be taken into account.

ADA were detectable starting from day 7 in all animals and, thus, an influence of ADA from the time point of their emergence on the PK parameters analysed is likely given.

Toxicokinetic evaluation after weekly intravenous administration of 157 mg/kg BI 695501 (trial formulation), EU-licensed Humira or vehicle control (BI 695501 diluent) for 5 consecutive weeks to male and female cynomolgus monkeys revealed comparable exposures to both products with no gender-specific differences. Nevertheless, a slightly, but statistically insignificant higher exposure was observed in BI 695501-treated animals in comparison to Humira. The evaluation of immunogenicity in the toxicokinetic study was hampered by the presence of excess drug which inhibited the detection of ADA. Thus, no animal was screened positive for ADA at any time of the study.

From a nonclinical PK perspective it can be concluded that the PK of BI 695501 and Humira can be considered similar. However, it is noted that the PK evaluation in a NHP setting can only be of supportive value for the overall assessment of biosimilarity: this is due to the low number of animals together with high interindividual variability and higher overall immunogenicity in NHPs as compared to humans.

The absence of studies of distribution, metabolism, excretion and drug-drug interactions is consistent with CHMP guidance (EMA/CHMP/BMWP/403543/2010, Guideline on similar biological medicinal products containing monoclonal antibodies).

2.3.3. Toxicology

In a comparative GLP-compliant 5-week repeat-dose toxicity study in cynomolgus monkeys intravenous administration of 157 mg/kg of BI 695501 or EU-licensed Humira similar toxicological profiles were established for BI 695501 and Humira. The comparison of toxicokinetic parameters was included into the study.

Both products were well tolerated and no BI 695501- or Humira-related effects on mortality, clinical signs, food consumption, body weight, physical examination parameters, ophthalmology, electrocardiology, blood pressure, haematology, coagulation, urinalysis, peripheral blood mononuclear cell subsets as evaluated via flow cytometry or gross findings.

Mild reversible increases in globulin levels, mild reversible decreases in albumin/globulin rations, reduction in number and size of germinal centers in the spleens persisting throughout the recovery period and reversible reduced activation of lymphoid follicles in lymph nodes were found to comparable degrees in BI 695501- and Humira-treated animals and considered as non-adverse.

Evaluation of toxicokinetic parameters (Cmax, AUC and biosimilar ratios based on AUC0-168 values) resulted in comparable profiles for BI 695501 and Humira in male and female animals after single and repeated administration. Immunogenicity assessment was hampered by the inability to detect anti-drug antibodies at any evaluated time point most probably due to the presence of excess amounts of drug.

The comparative repeat-dose toxicity study in cynomolgus monkeys did not indicate differences between BI 695501 and Humira, thus simply confirmed the expected outcome. However, due to exaggerated dose levels far above the pharmacological need and/ clinical usage it is also considered insensitive for biosimilarity testing purposes. Neither the composition of the final drug product formulation nor the differences observed on the in vitro level justify a comparative toxicology study.

The absence of developmental and reproductive toxicity studies is justified by the nature of the product and the type of application.

No BI 695501/product related clinical observations or local irritations other than slight procedure-related erythema were noticed. Also, assessment of body weights, gross pathology and histopathology did not point towards an irritating potential of BI 695501 in either formulation.

In support of the toxicology program studies on potential cross reactivity of anti-TNFα antibodies with cryosections of a panel of human tissues and on the potential of various cytokines to bind to was performed. In addition, the potential of BI 695501 to induce cytokine release and complement activation in human blood cells and serum, respectively, was tested. These rather exploratory assays are considered of limited significance for the overall assessment of biosimilarity; no findings resulting in any safety concern were reported.

The detection of ADA was hampered by drug interference caused by an excess of adalimumab present in the plasma of treated animals. However, a sound assessment of the antigenicity of adalimumab cannot be expected anyway, as even in cynomolgus the formation of antibodies against a drug substance consisting of human protein has to be anticipated.

No signs for immunotoxic effects of BI 695501 or Humira could be detected.

The Applicant performed a toxicological risk assessment on process related impurities, leachables and extractables as well as excipients. No safety concerns were reported.

Taken all together, the submitted non-clinical in vivo and in vitro data support the biosimilar exercise of BI 695501 and the human use thereof.

2.3.4. Ecotoxicity/environmental risk assessment

According to the CHMP Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2) for products containing vitamins, electrolytes,

amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies.

According to Directive 2001/83/EC, applicants are required to submit an ERA also for applications under Art 10(4) similar biological applications. However, the ERA dossier may consist of an adequate justification for the absence of specific study data. The justification of the absence of significant increase of the environmental exposure, based on a description of the molecule and its intended use, can be accepted as a justification for the absence of a complete ERA.

The Applicant provided sufficient documentation to justify that specific studies on environmental exposure were not required. Therefore, the Applicant's approach is agreed.

2.3.5. Discussion on non-clinical aspects

The Applicant provided a comprehensive panel of in vitro pharmacology studies in order to demonstrate comparability of BI 695501 to the reference product Humira. The in vitro studies are considered suitable to investigate the reported main mechanism of action, i.e. neutralization of and binding to soluble and membrane-bound TNFα, respectively. Additional assays reverse signalling and Fc-related functions were performed. In summary, the panel of in vitro assays conducted within the scope of the biosimilarity exercise is regarded suitable to cover all reported mechanisms of action for adalimumab.

The absence of in vivo pharmacology studies for the purpose of demonstrating biosimilarity is acknowledged due to the limited sensitivity of in vivo studies and the lack of appropriate models in this regard.

The pharmacokinetic profile of BI 695501 in comparison to EU- and US-licensed Humira was assessed for three different formulations. A slight, however, not statistically significant overexposure was observed throughout all studies. In this regard, a number of factors influencing the PK of the drug, such as high interindividual variability of the subcutaneous administration, potential gender related effects, different formulations as well as the formation of ADAs, have to be taken into account.

In a GLP-compliant, 5-week repeat-dose toxicity study no compound-related effects on mortality, clinical signs, food consumption, body weight, physical examination parameters, ophthalmology, electrocardiology, blood pressure, haematology, coagulation, urinalysis and peripheral blood mononuclear cells of BI 695501 in comparison to Humira were observed.

Studies regarding reproduction toxicology are not required for non-clinical testing of biosimilars. The nature of the product and the type of application justifies the absence of developmental and reproductive toxicity studies.

The Applicant did not submit ERA studies but provided an adequate justification which is in line with EMA Guideline on the Environmental Risk assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr. 2).

2.3.6. Conclusion on the non-clinical aspects

The applicable regulatory guidelines were taken into consideration. Comparative in vitro studies together with in vivo pharmacokinetic and toxicology data demonstrated biosimilarity. Thus, the application for Cyltezo is considered approvable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

TABULAR LISTING OF CLINICAL STUDIES

Type of Study	Study Identifier study no. [doc.no.]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage, Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I PK studies								
PK and safety	1297.1[1] [U13-1096]	PK, safety, and immunogenicity	Open-label, randomized, parallel-group, active-controlled	BI 695501 (TF) PFS, US-licensed Humira, EU-approved Humira; 40 mg single dose; s.c.	Treated: 193 BI 695501 (TF): 67 US Humira: 62 EU Humira: 64	Healthy subjects	Single dose	Complete; Full report
PK and safety	1297.8 [c03070713] VOLTAIRE®-PK	PK, safety, and immunogenicity	Double-blind, randomized, parallel-group, active-controlled	BI 695501 (CF) PFS, US-licensed Humira, EU-approved Humira; 40 mg single dose; s.c.	Treated: 324 BI 695501 (CF): 108 US Humira: 108 EU Humira: 108	Healthy subjects	Single dose	Complete; Full report
Pivotal Phase III study								
Efficacy and safety	1297.2 [c08934295] VOLTAIRE®-RA	Efficacy, safety, and immunogenicity	Double-blind, randomized, parallel-group, multiple-dose, active-controlled	BI 695501 (CF) PFS US-licensed Humira; 40 mg biweekly; s.c.	Treated: 645 BI 695501 (CF): 324 US Humira: 321	Patients with moderately to severely active RA and MTX background therapy	48 weeks	Ongoing; Primary analysis report
Studies supporting the autoinjector								
PK and safety	1297.6 (Phase I) [c09477818] VOLTAIRE®-AI	PK, safety, and immunogenicity	Open-label, randomized, parallel-group, active-controlled	BI 695501 (CF) AI BI 695501 (CF) PFS; 40 mg single dose; s.c.	Treated: 66 BI 695501 PFS (CF): 33 BI 695501 AI (CF): 33	Healthy subjects	Single dose	Ongoing; Final primary analysis report
Real-life handling	1297.11 (Phase II) [c08933683] VOLTAIRE®-RL	Assessment of real-life handling experience	Open-label, single-arm, multiple-dose, uncontrolled	BI 695501 (CF) AI; extension period BI 695501 (CF) PFS; 40 mg biweekly; s.c.	Treated: 77 BI 695501 (CF): AI assessment period: 77	Patients with moderately to severely active RA	50 weeks: 7-week AI assessment, 42-week extension	Ongoing; Primary analysis report

s.c. = subcutaneous, PK = pharmacokinetics, TF = trial formulation, CF = commercial formulation, RA = rheumatoid arthritis, AI = autoinjector, PFS = pre-filled syringe

[1] Study 1297.1 was conducted with a trial formulation (TF) of BI 695501, which was not considered for commercial use. Studies 1297.2, 1297.6, 1297.8, and 1297.11 were conducted using the commercial formulation (CF) that is intended to be marketed after approval.

Source data: [U13-1096, Table 15.1.3: 1], [c03070713, Table 14.1.1], [c08934295, Table 14.1.1.1], [c09477818, Table 14.1.1], [c08933683, Table 14.1.1.1]

TABULAR LISTING OF CLINICAL STUDIES

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage, Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I PK studies								
PK and safety	1297.1[1] [U13-1096]	PK, safety, and immunogenicity	Open-label, randomized, parallel-group, active-controlled	BI 695501 (TF) PFS, US-licensed Humira, EU-approved Humira; 40 mg single dose; s.c.	Treated: 193 BI 695501 (TF): 67 US Humira: 62 EU Humira: 64	Healthy subjects	Single dose	Complete; Full report
PK and safety	1297.8 [c03070713] VOLTAIRE®-PK	PK, safety, and immunogenicity	Double-blind, randomized, parallel-group, active-controlled	BI 695501 (CF) PFS, US-licensed Humira, EU-approved Humira; 40 mg single dose; s.c.	Treated: 324 BI 695501 (CF): 108 US Humira: 108 EU Humira: 108	Healthy subjects	Single dose	Complete; Full report
Pivotal Phase III study								
Efficacy and safety	1297.2 [c08934295] VOLTAIRE®-RA	Efficacy, safety, and immunogenicity	Double-blind, randomized, parallel-group, multiple-dose, active-controlled	BI 695501 (CF) PFS US-licensed Humira; 40 mg biweekly; s.c.	Treated: 645 BI 695501 (CF): 324 US Humira: 321	Patients with moderately to severely active RA and MTX background therapy	48 weeks	Ongoing; Primary analysis report
	[c15074004]							Completed; Final report
Studies supporting the autoinjector								
PK and safety	1297.6 (Phase I) [c09477818] VOLTAIRE®-AI	PK, safety, and immunogenicity	Open-label, randomized, parallel-group, active-controlled	BI 695501 (CF) AI BI 695501 (CF) PFS; 40 mg single dose; s.c.	Treated: 66 BI 695501 PFS (CF): 33 BI 695501 AI (CF): 33	Healthy subjects	Single dose	Ongoing; Final primary analysis report
	[c08933656]							Completed; Final report
Real-life handling	1297.11 (Phase II) [c08933683] VOLTAIRE®-RL	Assessment of real-life handling experience	Open-label, single-arm, multiple-dose, uncontrolled	BI 695501 (CF) AI; extension period BI 695501 (CF) PFS; 40 mg biweekly; s.c.	Treated: 77 BI 695501 (CF): AI assessment period: 77	Patients with moderately to severely active RA	50 weeks: 7-week AI assessment, 42-week PFS extension	Ongoing; Primary analysis report

s.c. = subcutaneous, PK = pharmacokinetics, TF = trial formulation, CF = commercial formulation, RA = rheumatoid arthritis, AI = autoinjector, PFS = pre-filled syringe

[1] Study 1297.1 was conducted with a trial formulation (TF) of BI 695501, which was not considered for commercial use. Studies 1297.2, 1297.6, 1297.8, and 1297.11 were conducted using the commercial formulation (CF) that is intended to be marketed after approval.

Source data: [U13-1096, Table 15.1.3: 1], [c03070713, Table 14.1.1], [c08934295, Table 14.1.1.1], [c09477818, Table 14.1.1], [c08933683, Table 14.1.1.1]

During the procedure, final data for trials 1297.2 and 1297.6 were provided.

2.4.2. Pharmacokinetics

PK biosimilarity between Humira and Cyltezo was investigated in the following studies

- Study **1297.1**: comparative PK trial with a trial formulation of BI 695501
- Study **1297.8**: 3-way PK similarity of the commercial formulation of BI 695501 with US-licensed and EU-approved Humira
- Study **1297.2**: efficacy/safety study in patients with with moderate to severely active RA: PK data was analysed as supportive data for a descriptive pharmacokinetic comparison of BI 695501 and US-licensed Humira and for a population PK analysis

A further PK study was provided in support of the development of the autoinjector:

• Study **1297.6** to show similarity between the pre-filled syringe (PFS) and the autoinjector (AI)

Analytical methods

PK assays

The Company developed an indirect ELISA for determination of EU and US-sourced Humira in human K_2EDTA plasma, which was subsequently cross-validated for determination of BI 695501. Cross-

validation included determination of intra- and inter-assay precision and accuracy, and comparison of calibration curves prepared from BI 6995501 and Humira, which were run on the same plate.

The method was largely appropriately validated and appears suitable for its intended purpose. The lower and upper limit of quantification is 25 and 2,000 ng/mL, respectively. Notably, quite frequent over-recoveries (i.e. recoveries >125%) were observed in the conducted studies. The Company explained the failures by the applied dilution scheme which was subsequently corrected. The Company´s justification can be accepted.

Immunogenicity testing

The Company developed an ADA assay for screening, confirmation and titration based on a homogeneous ECL bridging assay applied in a single assay approach. Neutralizing capacity of confirmed ADA positive samples was tested by inhibition of an in vitro functional activity in a cell-based assay format (TNFα -dependent antibody-dependent cell-mediated cytotoxicity [ADCC]).

The assays were validated and seem generally acceptable for testing immunogenicity in trial subjects and patients.

Study 1297.1 (conducted with pre-commercial "trial" formulation)

Trial title:

Pharmacokinetics and safety of BI 695501 in healthy subjects: a randomized, open-label, single-dose, parallel-arm, active-comparator clinical Phase I trial

Primary objective:

To investigate the PK, safety, and tolerability of a trial formulation of BI 695501 and to establish the PK similarity of BI 695501 to adalimumab (US-licensed Humira and EU-approved Humira).

Methods:

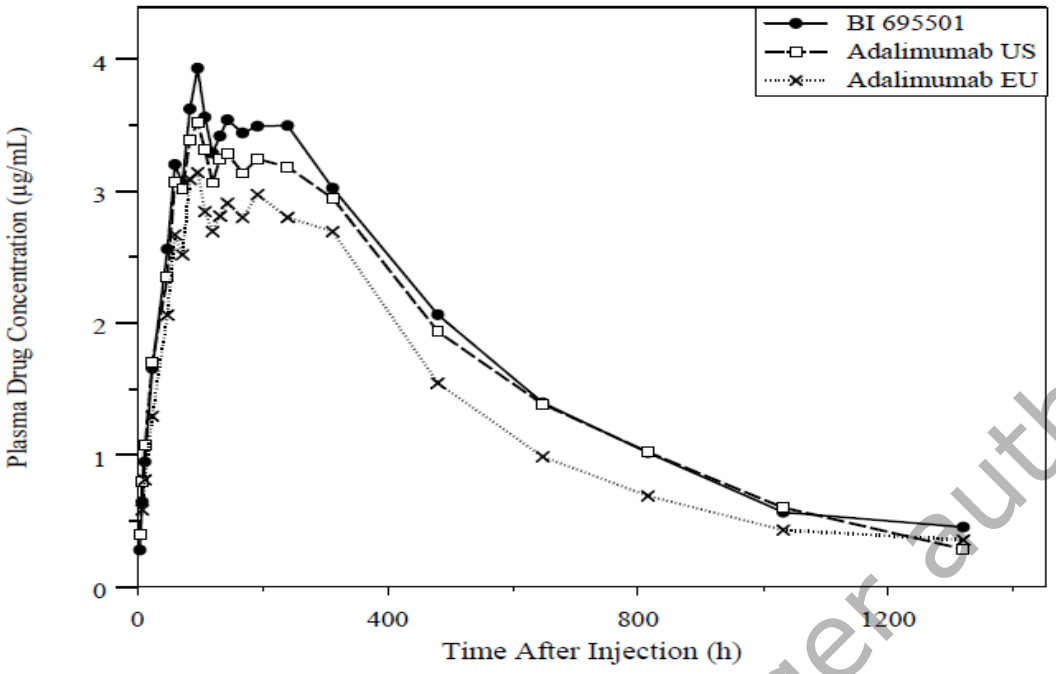
This was an open-label, randomized, parallel-arm, single-dose, active comparator trial in healthy subjects (2 sites in New Zealand). Three parallel treatment groups were investigated: BI 695501, US-licensed Humira, and EU-approved Humira.

Primary PK parameters

The primary endpoints were AUC_{0-inf}, AUC_{0-tz}, and C_{max}.

Results

Geometric mean plasma concentration-time curves after single SC administration of 40 mg BI 695501 or adalimumab from US source or EU source to healthy volunteers (linear scale):



Adjusted geometric means, T/R ratios, and 90% CIs of primary PK parameters after single SC injection of 40 mg BI 695501 (trial formulation) or Humira (US-licensed or EU-approved) - PK analysis set:

Parameter	Comparison (Test/Ref.)	Treatment	N	Adjusted[2] gMean	Adjusted[2] gCV	Adjusted[2] gMean Ratio (Test/Ref.)	Two-sided 90% CI	
							Lower Limit	Upper Limit
					[%]	[%]	[%]	[%]
$AUC_{0-\infty}$[1] [ug*h/mL]	BI 695501 vs. Humira US	BI 695501	60	2708.710	47.3	113.22	98.752	129.812
		Humira US	61	2392.390				
	BI 695501 vs. Humira EU	BI 695501	60	2707.768	51.8	132.24	113.984	153.412
		Humira EU	59	2047.672				
	Humira EU vs. Humira US	Humira EU	59	2057.551	48.9	86.51	74.974	99.830
		Humira US	61	2378.298				
AUC_{0-tz} [ug*h/mL]	BI 695501 vs. Humira US	BI 695501	60	2460.805	39.8	109.42	97.384	122.935
		Humira US	61	2249.030				
	BI 695501 vs. Humira EU	BI 695501	60	2446.849	43.6	128.88	113.492	146.365
		Humira EU	59	1898.483				
	Humira EU vs. Humira US	Humira EU	59	1917.588	41.5	86.24	76.238	97.564
		Humira US	61	2223.430				
C_{max} [ug/mL]	BI 695501 vs. Humira US	BI 695501	61	4.468	34.5	110.30	99.687	122.035
		Humira US	62	4.051				
	BI 695501 vs. Humira EU	BI 695501	61	4.419	37.1	117.53	105.638	130.757
		Humira EU	64	3.760				
	Humira EU vs. Humira US	Humira EU	64	3.831	35.3	96.53	87.064	107.017
		Humira US	62	3.969				

[1] $AUC_{0-\infty,\ predicted}$, [2] Adjusted for treatment and age as fixed effects
N: number of observations considered for the inferential statistics (observations from safety run in not included)

The relevant geometric mean ratios [and 90% CIs] for the primary endpoints were:

BI 695501 / US-Humira:

$AUC_{0\text{-}inf}$: 113.22% [98.752; 129.812]

$AUC_{0\text{-}tz}$: 109.42% [97.384; 122.935]

C_{max}: 110.30% [99.678; 122.035]

The 90% CIs of the ratio of the adjusted gMeans for $AUC_{0\text{-}tz}$ and C_{max} fell within the standard acceptance limits for bioequivalence (80 to 125%). For $AUC_{0\text{-}inf}$ the upper limit of the 90% CI was 129.81%, i.e. above the acceptance range.

BI 695501 / EU-Humira:

$AUC_{0\text{-}inf}$: 132.24% [113.984; 153.412]

$AUC_{0\text{-}tz}$: 128.88% [113.492; 146.365]

C_{max}: 117.53% [105.638; 130.757]

BI 695501 vs. EU-Humira: The 90% CIs for the ratios of the adjusted gMeans were outside the (80 to 125%) standard acceptance limits for all primary PK parameters.

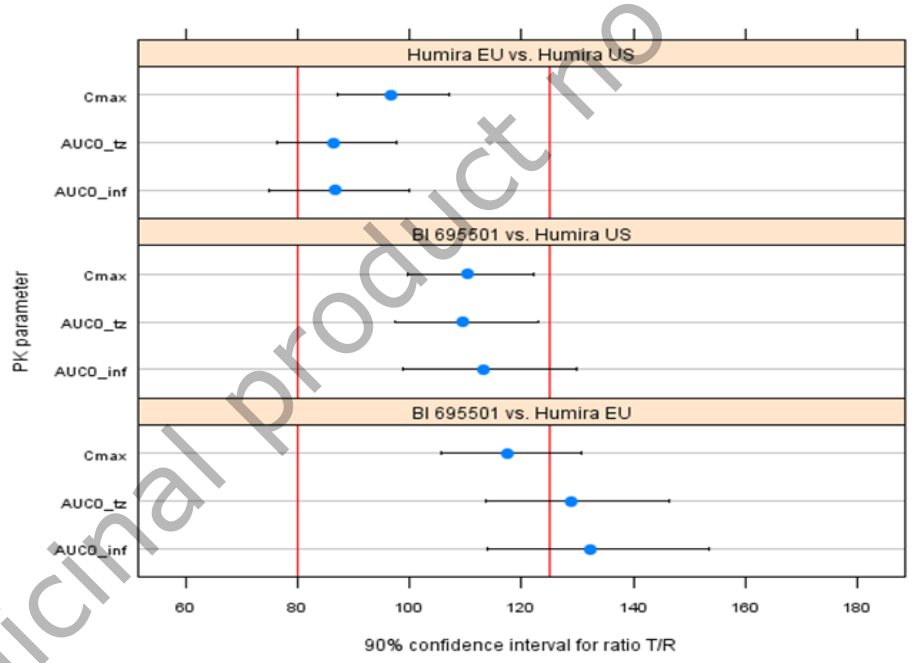
EU-Humira / US-Humira:

$AUC_{0\text{-}inf}$: 86.51% [74.974; 99.830]

$AUC_{0\text{-}tz}$: 86.24% [76.238; 97.564]

C_{max}: 96.53% [87.064; 107.017]

US- Humira vs. EU-Humira: The lower bound of the 90% CI for the ratios of the adjusted gMeans for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}tz}$ fell below the standard acceptance limits; for C_{max} it was contained within.



The study failed to demonstrate similarity of (the trial formulation of) Cyltezo and EU-Humira within the predefined standard acceptance limits of 80.00-125.00%. Moreover, the study did not support similarity of PK parameters of EU and US-Humira.

The company performed post hoc analyses in order to identify a root cause for the observed dissimilarity. These analyses revealed several factors that either contributed to the overall variability (e.g. body weight, ADA formation) or affected the adjusted GM ratio (e.g. protein content of the drug products) of the PK of BI 695501 and US-Humira and EU-Humira. Accounting for these factors (sample

size estimate based on higher gCV: N = 100; adjustment for body weight, age and protein content) revealed that nearly all comparisons would show PK similarity.One factor that could not be explained was the exposure of the EU-licensed reference product in 1297.1, which was lower than the US-approved reference product with the same protein concentration. This was not observed in trial 1297.8.

Pivotal PK-study 1297.8, EudraCT Number: 2013-003722-84

Study title:

Pharmacokinetics and safety of BI 695501 in healthy subjects: a randomized, double-blind, single-dose, parallel-arm, active-comparator clinical Phase I study

Study design:

This was a 10-week, randomised, double-blind, single-dose, parallel, 3-arm, clinical Phase I study, comparing PK, safety and tolerability of single doses of 40 mg/0.8 mL BI 695501 (commercial formulation) vs US-Humira and EU-Humira (all as PFS) in 324 healthy male subjects.

Subjects were randomized in a 1:1:1 ratio to receive BI 695501, US-Humira, or EU-approved Humira.

Study population

324 subjects (108 per treatment arm) were planned to be entered to achieve 300 completers. Included were healthy male subjects aged 18 to 55 years, with a body mass index from 18.5 to 29.9 kg/m^2.

Subjects were kept under close medical surveillance until 24 hours following the trial medication administration. Standardized meals were served during the residential period. Day 3 through Day 56 and the end of trial visit were conducted as ambulatory visits.

The inclusion of male healthy volunteers is considered acceptable for a biosimilar trial aiming to compare two products in a sensitive and homogenous setting.

Sample size

Assumptions on the total variability of the primary endpoints were based on a previous trial (BI 1297.1). For AUC_{0-inf}, the gCV was estimated to be approximately 45% and was observed higher than for AUC_{0-tz} and C_{max}. Sample size estimation was performed by simulations in order to account for multiple comparisons.

Based on these simulations results, a sample size of 3 x 100 = 300 yielded a power of approximately 89% (assuming ratios of 1:1:1 and 45% total variability). According to the high variability of AUC_{0-inf} in the failed PK study 1297.1, the sample size calculations were done more conservatively.

The sample size calculation, including the rationale of the assumptions made, could be followed. The planned sample size was considered sufficiently large to demonstrate similarity using the conventional bioequivalence criteria for all three PK parameters simultaneously.

Data sets included:

Treated: n= 324 (108 BI695501, 108 US-Humira, 108 EU-Humira)

Completed: n= 320 (106 BI695501, 107 US-Humira, 107 EU-Humira)

Used in PK Analysis: n= 322 (107 BI695501, 108 US-Humira, 107 EU-Humira)

It is deemed acceptable, that a subject that withdraws after $1/10^{th}$ of the study duration and does not provide enough data is excluded from PK analysis set; also the exclusion of the subject with the high pre-dose concentration is deemed acceptable.

Pre dose concentration:

Predose-concentrations were noted across treatment groups:

N= 3 for BI 695501: 0.034 µg/mL (subject), 0.048 µg/mL (subject), 0.035 µg/mL (subject)

N= 4 for US-Humira: 0.04 µg/mL (subject), 0.034 µg/mL (subject), 0.117 µg/mL (subject), 0.029 µg/mL (subject)

N= 6 for EU-Humira: 0.514 µg/mL (subject *), 0.029 µg/mL (subject), 0.056 µg/mL (subject), 0.034 µg/mL (subject), 0.037 µg/mL (subject), 0.039 µg/mL (subject)

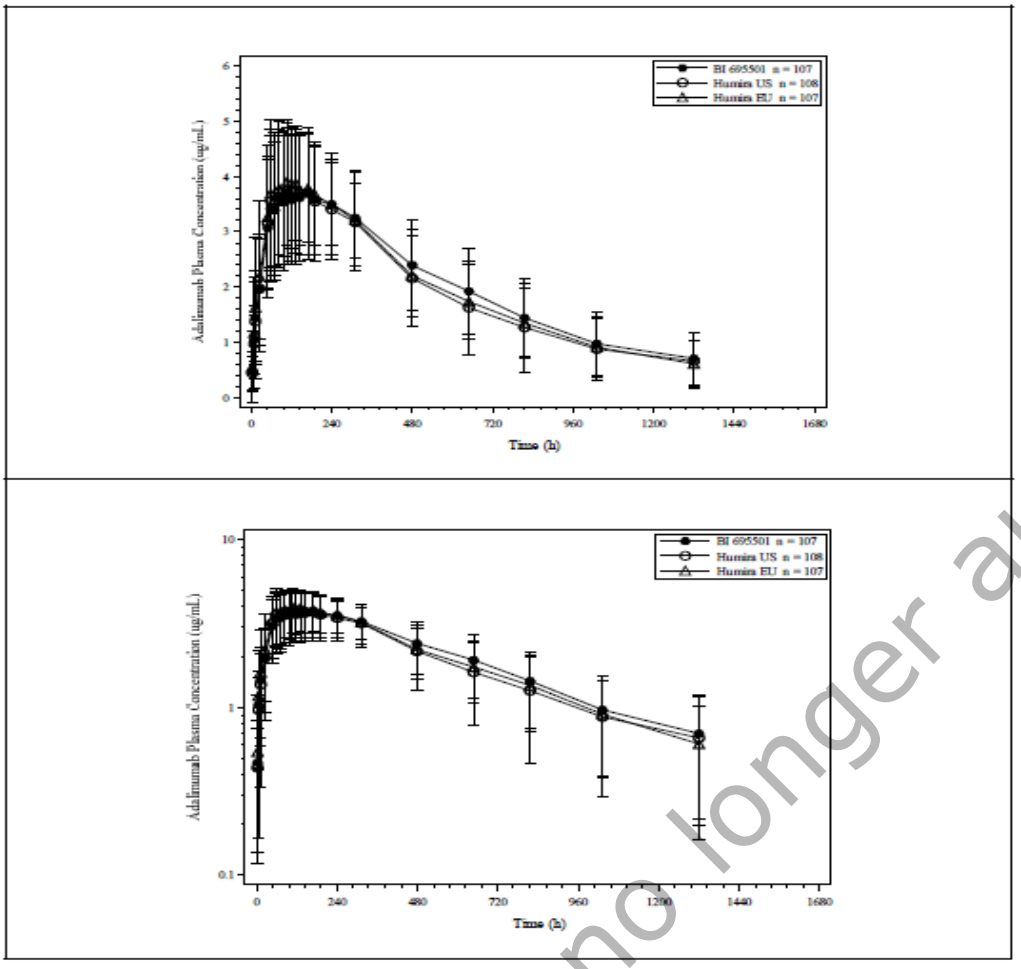
Subjects excluded from the PK analysis set and from the summary statistics are indicated with an *.

The observed pre-dose concentrations were altogether low, apart from subject whose pre-dose value was larger than 20 times the LLOQ. Since adalimumab concentrations are not to be expected in this trial population of healthy volunteers and because the 1h measurements are consistent with the pre-dose values, an obvious explanation may be the high sensitivity of the assay.

Subject was excluded from the PK analysis set (and thus primary analysis), since his pre-dose concentration was greater than 5% of Cmax. Although the exclusion was decided post-hoc and it may not be an obvious “violation thought to significantly affect the PK” (or, likewise also leads to the exclusion of all subjects with pre-dose concentration above the LLOQ), it appears plausible and the in/exclusion of this single patient should not impact the similarity conclusion. Therefore, no concern is raised.

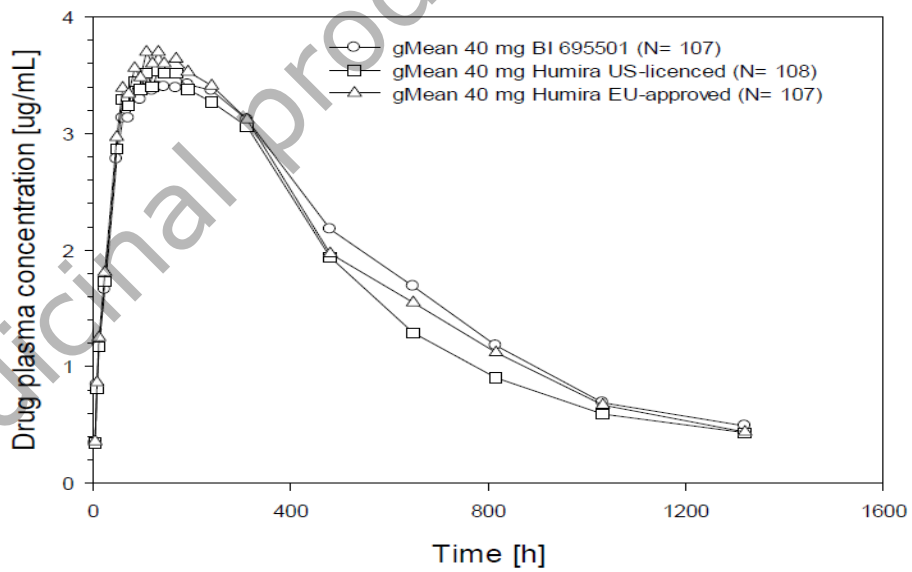
According to the Trial Statistical Analysis Plan (TSAP), the last considered measurements (for the descriptive statistics) was the one at 1320 hrs after study medication administration, referring to a so called “2/3 rule” meaning that descriptive statistics of concentrations at specific time points were calculated only when at least 2/3 of the individuals had concentrations within the validated concentration range of the assay. At 1680 hrs (last sampling time point) less than 2/3 of the subjects had values above the limit of quantification and descriptive comparisons between treatments were not provided. However no further concern has been raised, since single concentration values for 1680h have been reported and the calculation of PK parameters is not affected by this rule.

Arithmetic Mean (±SD) Plasma Concentration-time Profiles for all Treatments on Linear and Semi-logarithmic Scales:



Source: Table 14.2.1

Geometric mean plasma concentration-time profiles after single SC injection of 40 mg BI 695501 or Humira (US-licensed or EU-approved)-linear scale:



Last time point (1680 h) is not displayed, as no gMeans were calculated due to 2/3 rule.
N represents highest number of observations considered for desc. stats in treatment group (N at individual time points can be lower).

Primary pharmacokinetic parameters (unadjusted GM, gCV%) after single SC injection of 40 mg BI 695501 or Humira (US-licensed or EU-approved):

Parameter Geometric mean (% gCV)	N	BI 695501 40 mg	N	Humira US-licensed 40 mg	N	Humira EU-approved 40 mg
$AUC_{0-\infty}$[1] [ug*h/mL]	106	2630 (52.4)	105	2470 (51.2)	105	2650 (38.5)
AUC_{0-tz} [ug*h/mL]	106	2440 (47.8)	107	2300 (45.1)	106	2480 (33.5)
C_{max} [ug/mL]	107	3.907 (34.1)	108	3.900 (34.5)	107	4.140 (30.4)

[1] $AUC_{0-\infty, predicted}$

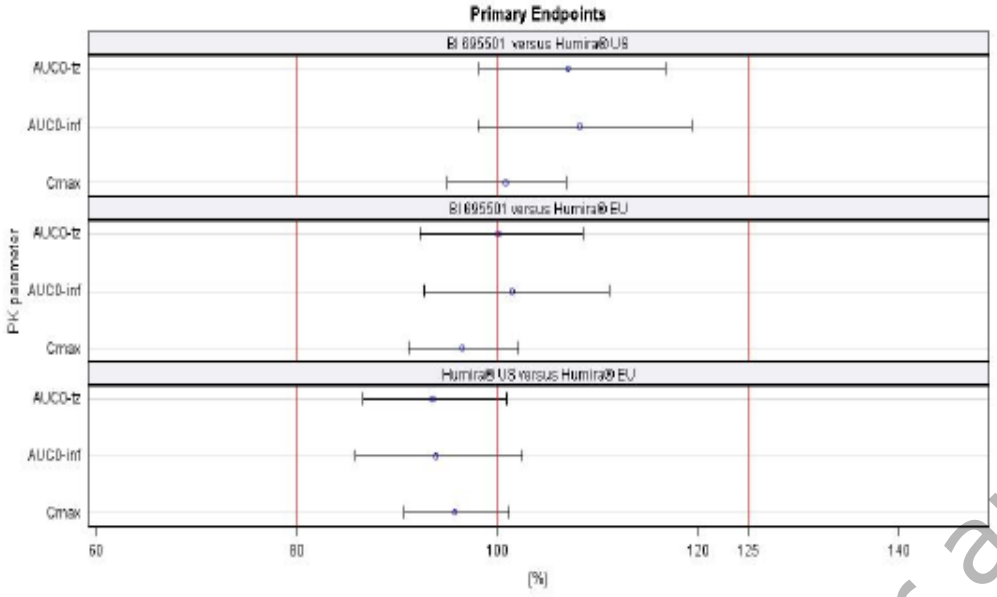
N: number of observations considered for the descriptive statistics

Source data: Study No. 1297. 8 [c03070713, Table 14.2.2]

PK similarity results - Primary analysis - PK analysis set

PK Parameter	Comparison [a]	Treatment	n (missing)	Adjusted Geometric Mean	Adjusted Geometric CV%	Comparison Ratio (%)	Comparison Geom SE	Comparison 90% CI
AUC(0-inf) (µg*h/mL)	BI 695501 versus Humira® US					108.62	1.061	(98.50,119.79)
		BI 695501	106 (2)	2649	46.0			
		Humira US	105 (3)	2438	43.8			
	BI 695501 versus Humira® EU					101.27	1.057	(92.45,110.94)
		BI 695501	106 (2)	2654	46.5			
		Humira EU	105 (3)	2620	36.3			
	Humira® US versus Humira® EU					94.02	1.055	(86.01,102.78)
		Humira US	105 (3)	2478	44.3			
		Humira EU	105 (3)	2635	36.3			
AUC(0-tz) (µg*h/mL)	BI 695501 versus Humira® US					107.32	1.053	(98.49,116.94)
		BI 695501	106 (2)	2449	41.1			
		Humira US	107 (1)	2282	37.4			
	BI 695501 versus Humira® EU					99.93	1.050	(92.15,108.37)
		BI 695501	106 (2)	2458	41.0			
		Humira EU	106 (2)	2460	31.3			
	Humira® US versus Humira® EU					93.66	1.047	(86.76,101.11)
		Humira US	107 (1)	2308	37.9			
		Humira EU	106 (2)	2464	31.2			
Cmax (ug/mL)	BI 695501 versus Humira® US					100.85	1.036	(95.15,106.88)
		BI 695501	107 (1)	3.9202	27.2			
		Humira US	108 (0)	3.8872	25.1			
	BI 695501 versus Humira® EU					96.39	1.035	(91.06,102.03)
		BI 695501	107 (1)	3.9485	27.5			
		Humira EU	107 (1)	4.0965	23.3			
	Humira® US versus Humira® EU					95.93	1.034	(90.83,101.33)
		Humira US	108 (0)	3.9363	25.6			
		Humira EU	107 (1)	4.1032	23.5			

CI = Confidence interval; PK = pharmacokinetic; SE = standard error; CV% = coefficient of variation; Geom = geometric;
AUC(0-inf) is based on the concentration predicted by regression for the time tz.
Results based on an ANCOVA model with treatment and site as fixed effects, age and weight as continuous covariates. Body weight at baseline is a statistically significant predictor of Cmax and AUC (p<0.0001 for all pairwise analyses). Subject age is a statistically significant predictor of Cmax (p<0.026 for all pairwise analyses) but not for AUC (p>0.149 for all pairwise analyses).
[a] BI 695501 - BI 695501 (Test);



90% Confidence interval for the ratio test/reference (T/R)
Point estimate for the ratio of adjusted geometric mean in % and associated 90% confidence interval are presented for each endpoint. 80% and 125% are acceptance borders for PK similarity

Source: Table 14.2.3 and Figure 14.2.7

The relevant gMean ratios [and 90% CI] for the primary endpoints were:

BI 695501 / US-Humira:

AUC_{0-inf}: 108.62% [98.50; 119.79]

AUC_{0-tz}: 107.32% [98.49; 116.94]

C_{max}: 100.85% [95.15; 106.88]

BI 695501 / EU-Humira:

AUC_{0-inf}: 101.27% [92.45; 110.94]

AUC_{0-tz}: 99.93% [92.15; 108.37]

C_{max}: 96.39% [91.06; 102.03]

US-Humira / EU-Humira:

AUC_{0-inf}: 94.02% [86.01; 102.78]

AUC_{0-tz}: 93.66% [86.76; 101.11]

C_{max}: 95.93% [90.83; 101.33]

The primary PK parameters AUC_{0-inf}, AUC_{0-tz} and C_{max} of BI 695501, US-Humira and EU-Humira were similar: The ratios of the geometric mean (GM) parameters were close to unity. The 90% CIs of the gMeans ratios of AUC_{0-inf}, AUC_{0-tz} and C_{max} were well within the pre-defined equivalence margin 0.8 to 1.25.

PK study 1297.8 demonstrated biosimilarity in its primary measures between Cyltezo and EU Humira; also the demonstration of PK similarity for both originator products, which substantiates the bridging undergone on the quality level and the use of US-sourced Humira in the pivotal efficacy trial 1297.2.

The secondary endpoints (truncated AUCs) fell within the 80-125% limits of the 90%CIs.

Referring to the "further endpoints" t_{max}, $t_{1/2}$, V_z/F and CL/F, the measured t_{max} values were in line with what was expected from Humira. Mean estimated $t_{½}$ was between 12.8 and 13.6 days; this is in line with the approximately 2 weeks provided in the SmPC of the reference product. Furthermore, estimates seem quite similar between the groups. Clearance and volume of distribution showed comparable results between the three products concerning median values; however, high variability is noted for each of these measures, rendering a confirmatory assessment of equivalence difficult.

Treatments (dose, regiment, route, device)	Drug Product [Batch Number]	Subj. treated /analysed for PK	Results – PK parameters [unit] Geometric mean (% gCV)						
			AUC [ug*h/mL]		C_{max} [ug/mL]	t_{max}[1] [h]	CL/F [mL/min]	Vz/F [L]	Other
40 mg BI 695501, single dose, s.c. injection, PFS	BI 695501 solution for single dose s.c. injection, 40 mg /0.8 mL [306795]	108/ 107	$AUC_{0-\infty, pred}$	2630 (52.4)	3.907 (34.1)	132.22 (48.0-649.0)	0.253 (52.4)	5.13 (51.8)	t1/2 [h] 234 (95.7)
			$AUC_{0-\infty, obs}$	2630 (52.6)					
			AUC_{0-tz}	2440 (47.8)					
			AUC_{0-168}	480 (41.1)					
			AUC_{0-312}	957 (36.5)					
			AUC_{0-480}	1400 (35.8)					
			AUC_{0-648}	1730 (37.0)					
			AUC_{0-1032}	2190 (41.4)					
40 mg Humira (US-licensed), single dose, s.c. injection, PFS	Humira (US-licensed) solution for single dose s.c. injection, 40 mg /0.8 mL [241182E]	108/108	$AUC_{0-\infty, pred}$	2470 (51.2)	3.900 (34.5)	109.09 (58.9-480.0)	0.27 (51.2)	5.680 (46.1)	t1/2 [h] 243 (83.4)
			$AUC_{0-\infty, obs}$	2470 (51.3)					
			AUC_{0-tz}	2300 (45.1)					
			AUC_{0-168}	493 (40.7)					
			AUC_{0-312}	967 (34.9)					
			AUC_{0-480}	1390 (32.2)					
			AUC_{0-648}	1680 (33.2)					
			AUC_{0-1032}	2080 (38.5)					
40 mg Humira (EU-approved), single dose, s.c. injection, PFS	Humira (EU-approved) solution for single dose s.c. injection, 40 mg /0.8 mL [24356XH10]	108/107	$AUC_{0-\infty, pred}$	2650 (38.5)	4.140 (30.4)	120.02 (12.0-648.0)	0.252 (38.5)	5.630 (56.6)	t1/2 [h] 258 (82.9)
			$AUC_{0-\infty, obs}$	2640 (38.5)					
			AUC_{0-tz}	2480 (33.5)					
			AUC_{0-168}	513 (39.9)					
			AUC_{0-312}	1010 (31.6)					
			AUC_{0-480}	1440 (28.0)					
			AUC_{0-648}	1760 (27.2)					
			AUC_{0-1032}	2210 (29.1)					

[1]median (range); Source data: Study No. 1297.8 [c03070713, Table 14.2.2], Source data for drug product batch number: P210 document [q00232921]

Trial 1297.2, PK Analysis in patients with RA

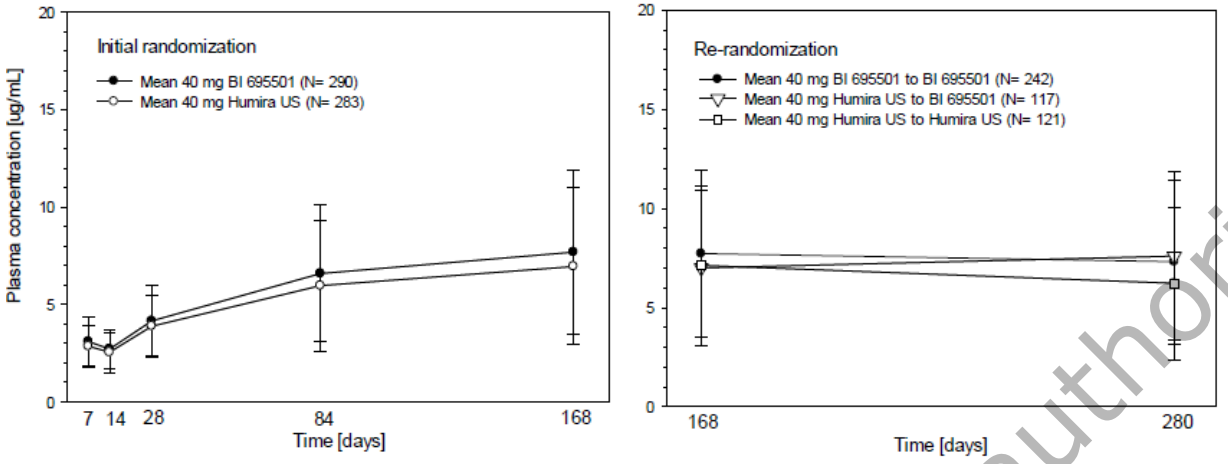
Title:

Efficacy, safety and immunogenicity of BI 695501 versus adalimumab in patients with active rheumatoid arthritis: a randomized, double-blind, parallel-group multiple dose, active comparator trial (For a thorough assessment of study 1297.2, please refer to "clinical efficacy" and "clinical safety"; this section assesses the analysed PK Set)

Objective:

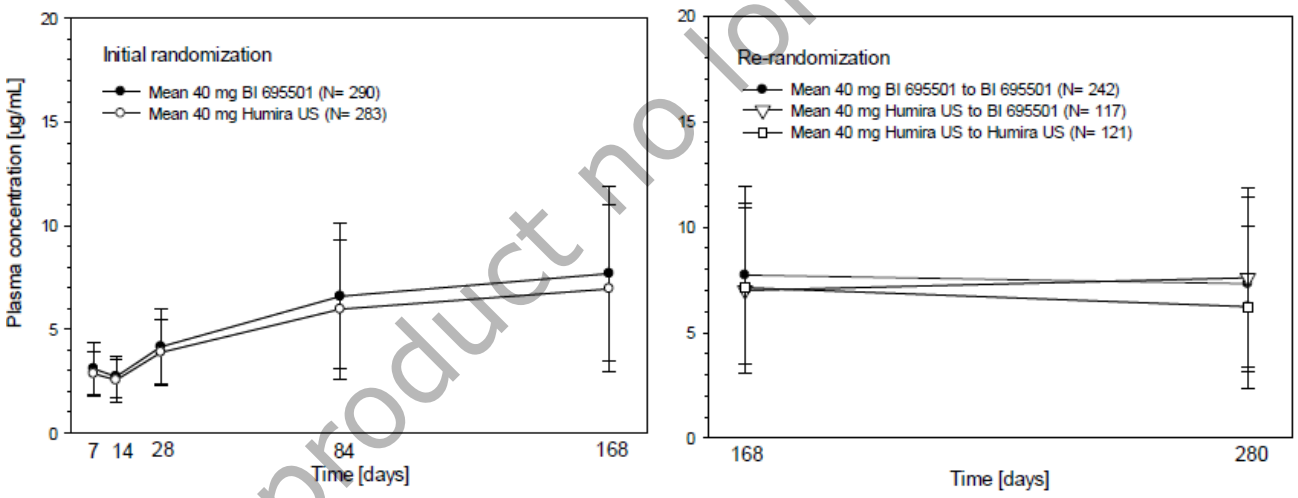
Exploratory PK data was generated from this pivotal efficacy trial to assess the impact of ADA formation on adalimumab plasma concentrations (see clinical safety) and to investigate PopPK.

The comparison of mean C_{trough} levels of Cyltezo to US-Humira (PK Full Analysis Set = all patients with at least one valid post-dose PK data point, 323 BI/321 Hu) in patients with rheumatoid arthritis in the efficacy and safety study provides supportive evidence for PK similarity. Patients were scarcely sampled in period one until Week 24 (Baseline, days 7,14,28,84, and 168) and after re-randomisation (Period 2) until Week 58 (days 280, 336, and 406).



Day (pre-dose), Day 1 (6h), Day 336 and Day 406 are not displayed, as no Means were calculated due to 2/3 rule.
All measurements except Day 7 represent trough values.
N represents highest number of observations considered for desc. stats in treatment group (N at individual time points can be lower).
Source data: Study No.1297.2 [c08934295, Table 14.3.5.10]

Figure 4 Arithmetic mean plasma concentration-time profiles (± SD) of BI 695501 and US-licensed Humira following multiple s.c. injections of 40 mg BI 695501 or US-licensed Humira to RA patients (left panel: initial randomization, right panel: after re-randomization; both linear scale).



Day (pre-dose), Day 1 (6h), Day 336 and Day 406 are not displayed, as no Means were calculated due to 2/3 rule.
All measurements except Day 7 represent trough values.
N represents highest number of observations considered for desc. stats in treatment group (N at individual time points can be lower).
Source data: Study No.1297.2 [c08934295, Table 14.3.5.10]

Figure 4 Arithmetic mean plasma concentration-time profiles (± SD) of BI 695501 and US-licensed Humira following multiple s.c. injections of 40 mg BI 695501 or US-licensed Humira to RA patients (left panel: initial randomization, right panel: after re-randomization; both linear scale).

Table 9 Arithmetic mean plasma concentrations (± SD) of BI 695501 and US-licensed Humira following multiple s.c. injections of 40 mg BI 695501 or US-licensed Humira to RA patients.

Treatment group	Arithmetic mean plasma concentrations (SD) [ug/mL]							
	Day 1 (predose)	Day 1 (6 hours)	Day 7	Day 14	Day 28	Day 84	Day 168	Day 280
BI 695501, initial randomization	N = -	N= -	N =282	N =287	N =290	N =265	N =243	N =213
	-	-	3.10 (1.25)	2.72 (0.995)	4.16 (1.80)	6.59 (3.51)	7.69 (4.23)	7.31 (4.14)
Humira US , initial randomization	N = -	N = -	N =283	N =274	N =273	N =260	N =242	N =193
	-	-	2.86 (1.09)	2.55 (1.03)	3.89 (1.58)	5.97 (3.37)	6.96 (4.02)	6.87 (4.12)
BI 695501, re-randomized to BI 695501	N = -	N = -	N =264	N =267	N =270	N =251	N =242	N =213
	-	-	3.08 (1.23)	2.73 (0.992)	4.12 (1.79)	6.53 (3.48)	7.72 (4.22)	7.31 (4.14)
Humira US , re-randomized to Humira US	N = -	N = -	N =131	N =129	N =123	N =123	N =121	N =96
	-	-	2.96 (1.16)	2.64 (1.01)	4.06 (1.65)	6.09 (3.15)	7.12 (4.04)	6.22 (3.85)
Humira US , re-randomized to BI 695501	N = -	N = -	N =129	N =127	N =132	N =125	N =117	N =96
	-	-	2.83 (1.03)	2.52 (1.08)	3.79 (1.58)	6.09 (3.59)	7.00 (3.91)	7.59 (4.25)

N: number of observations considered for the descriptive statistics
Source data: Study No. 1297.2 [c08934295, Table 14.3.5.10]

Demographic factors potentially influencing PK (e.g. BMI) were equally distributed between treatment groups (see clinical efficacy).

Achievement of steady state seems to have been reached between Week 12 and 24, however due to the scarcity of sampling points, this is hard to determine and impossible to compare. More intense plasma sampling, namely every other week, would have been preferable to describe the ascending part of the mean concentration-time curve. Nonetheless, when looking at the results, major deviations in the ascending part do not seem likely and arithmetic means and SDs seem roughly comparable between treatments across Period 1.

The applicant has not incorporated baseline values into its main concentration time graphs and tables referring to the "2/3 rule" explained above. The narrative explains that high pre-first-dose adalimumab plasma concentrations were identified in both the BI 695501 and the US licensed Humira treatment group [c08934295, Table 22]. The company performed two sensitivity analyses to evaluate the influence of excluding patients from the data set who had pre-first dose adalimumab concentrations greater than 0.025 µg/mL (= the lower limit of quantification (LLOQ)), and of subjects who had pre-first-dose concentrations greater than 0.195 g/mL (i.e. > 5% of GM C_{max} after single dose as determined in study 1297.8). These analyses were conducted as part of the PPK analysis and the resulting PK parameter estimates were similar to the estimates which were based on the full PK data set.

For an assessment of the impact on ADA on PK in trial 1297.2 please refer to clinical safety.

Conclusion:

Similar adalimumab plasma concentrations were observed in the BI 695501 and the US-licensed Humira group during the initial randomization period and after re-randomization. BI 695501 and Humira plasma concentrations declined with increasing ADA titer. The effect was similar across all

treatment groups. The conclusions drawn at the time of the final primary analysis were confirmed by the follow-up analysis, which was provided during the procedure.

Population Pharmacokinetic Analysis

Population pharmacokinetic analysis has been performed to develop a population pharmacokinetic model for BI 695501 and Humira across healthy subjects and patients with active RA, to estimate the effect of covariates (gender, body size, age, C-reactive protein (CRP), rheumatoid factor (RF), albumin (ALB), anti-drug antibodies (ADA), and neutralizing anti-drug antibodies (nAb)) on the pharmacokinetics (PK) of BI 695501 and Humira and to assess if relevant differences exist between BI 695501 and Humira in relation to PK, and the influence of ADA on PK.

The PK of adalimumab was best described by a two-compartment model with sequential zero- and first-order absorption and linear elimination in both healthy subjects and RA subjects. Based on the final Phase I PPK model, adalimumab apparent clearance (CL/F) increased with the increasing body weight and ADA titre value in the healthy subjects. The final Phase III PPK model indicated adalimumab CL/F elevated with higher body weight, ADA titre value, CRP, and BRF, and lower ALB in patients with RA. Effects of ALB and BRF can be judged not clinically relevant in patients with RA. Adalimumab CL/F was lower without ADA in both healthy subjects and patients with RA.

As regards PK differences between BI 695501 and Humira and the influence of ADA on PK, it is concluded that PK as well as the ADA effect on PK is similar between BI 695501 and Humira. However, the usefulness of the proposed population PK analysis to evaluate biosimilarity is questioned, because the analysis did not allow different model parameters between treatment arms and is prone to over-fitting affecting effect estimates (point- and interval estimates of difference in relevant PK parameters). The added value (beyond the results of the individual concentration measures in healthy volunteers and patients with RA) of the presented population PK analysis is questioned, but the consideration of the phase I studies in HVs and plasma levels in the phase III study 1297.2 are deemed sufficient to assess PK biosimilarity.

Study 1297.6, Comparison of PK between AI and PFS

This was a 14-week, randomized, single-dose, parallel-arm, open-label, Phase I trial to investigate and compare the PK, safety and tolerability of BI 695501 (a single dose of 40 mg/0.8 mL) administered subcutaneously via pre-filled syringe (PFS) or autoinjector (AI) in healthy, male Caucasian subjects.

Plasma samples for the analysis of adalimumab were taken before drug administration and over a time period of 6 weeks (43±1 days) after the injection (at 1h, 4h, 8h, 12h, 24h, 48h, 60h, 72h, 84h, 96h, 108h, 120h, 132h, 144h, 168h, 216h, 336h, 504h, 672h, 840h, and 1032h after the injection). Plasma samples to determine ADA were taken on Day 1 before drug administration and on Day 22 and 43.

It was planned to include 66 healthy, male, Caucasian subjects aged 18 to 65 years to ensure at least 60 subjects with evaluable PK data. Each treatment arm was originally planned to consist of 33 subjects (11 subjects in each BMI group). During the trial, due to difficulties recruiting subjects with low BMI, the protocol was amended to increase the number of subjects in the medium and high BMI groups and maintain the required sample size as planned for primary analysis. Each treatment arm (PFS and AI) in the primary analysis report was to consist of up to 15 subjects in the medium and the high BMI groups and at least 3 subjects in the low BMI group, in order to ensure a broad range of BMI values for the assessment of PK profiles, safety, and immunogenicity.

Subjects were randomly assigned to receive BI 695501 40 mg/0.8 mL either via PFS or AI by SC injection.

Subjects were kept under close medical surveillance until 24 hours following trial medication administration.

The trial consisted of a screening period of up to a maximum of 28 days, a 43-day observation period where each subject received one dose of trial medication, and a safety follow-up period (up to 70 days after the trial medication administration).

Trial medication	Formulation (concentration)	Manufacturer	Batch number	Expiry Date
BI 695501	Solution for injection in autoinjector (40 mg/0.8 mL)	BI Pharma GmbH & Co. KG, Germany	B151002680	Jan-2017
BI 695501	Solution for injection in pre-filled syringe (40 mg/0.8 mL)	BI Pharma GmbH & Co. KG, Germany	B151002450	Jul-2017

Study objectives:

The primary objective of this trial was to characterise and compare the PK of 40 mg BI 695501 (commercial formulation) administered subcutaneously using a pre-filled syringe (PFS) or an autoinjector (AI).

The secondary objective of this trial was to evaluate the safety of BI 695501 (see clinical safety).

Additional objectives of this trial included evaluation and comparison of selected further PK parameters of interest between the two different delivery devices (PFS and AI), as well as the assessment of other safety and immunogenicity parameters.

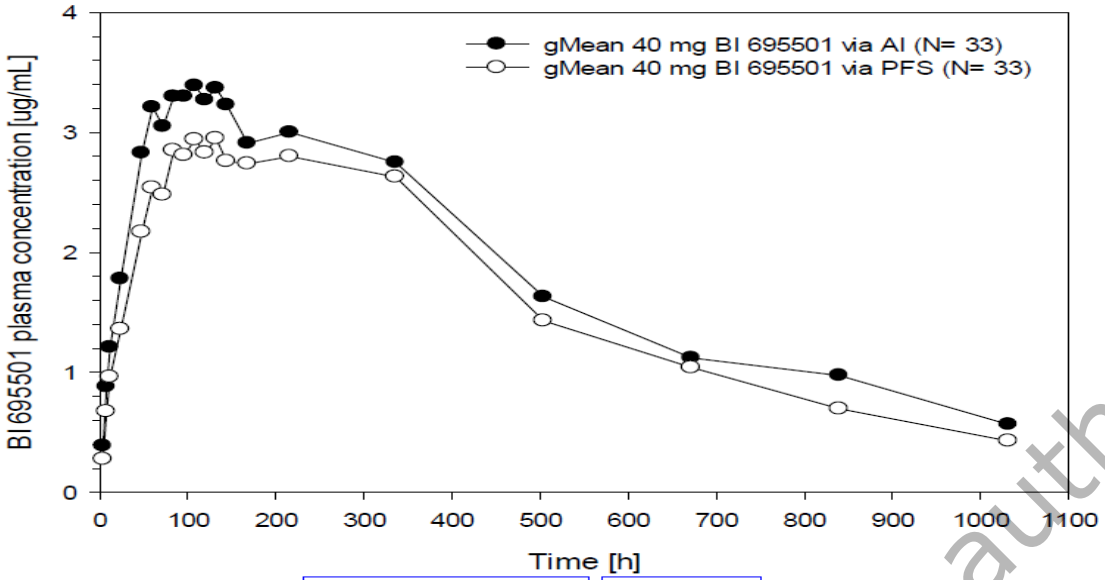
Endpoints:

The primary endpoints were AUC_{0-1032}, C_{max} and AUC_{0-inf}.

The *secondary endpoint* was defined as the number (proportion) of subjects with drug-related AEs occurring from Day 1 through Day 70.

Results:

Geometric mean plasma concentration-time profiles of BI 695501 after single SC injection of 40 mg BI 695501 via autoinjector or via PFS over all BMI groups (linear scale):



Source data: Study No.1297.6 [c09477818, Table 14.2.1.1: 5, Table 14.2.1.1:6]
N represents highest number of observations considered for desc. stats in treatment group (N at individual time points can be lower).

Table 5 *Adjusted geometric means, T/R ratios and 90% confidence intervals of primary PK parameters after single SC injection of 40 mg BI 695501 via autoinjector or via prefilled syringe to healthy volunteers over entire BMI range - results of primary model – PK analysis set*

Parameter	Treatment	N	Adjusted[2] gMean	Adjusted[2] gCV	Adj.[2] gMean Ratio (AI/PFS.)	Two-sided 90% CI	
						Lower Limit	Upper Limit
				[%]	[%]	[%]	[%]
AUC_{0-1032} [ug*h/mL]	BI 695501 (AI)	33	1964.620	42.832	104.09	87.81	123.39
	BI 695501 (PFS)	32	1887.367				
$AUC_{0-\infty}$[1] [ug*h/mL]	BI 695501 (AI)	33	2317.971	53.164	106.17	86.34	130.56
	BI 695501 (PFS)	32	2183.263				
C_{max} [ug/mL]	BI 695501 (AI)	33	4.066	32.373	114.83	100.86	130.75
	BI 695501 (PFS)	33	3.541				

[1]$AUC_{0-\infty, observed}$, [2]Adjusted for treatment and BMI group as fixed effects,
N: number of observations considered for the inferential statistics
Source data: Study No.1297.6 [c09477818, Table 14.2.4.2]

Summary of results for the AI vs. PFS comparison, primary endpoints:

AUC_{0-1032}:

Adjusted GM ratio: 104.09%

90%CI: [87.81-123.39]

AUC_{0-inf}:

Ratio: 106.17%

90%CI: [86.34%-130.56%]

C_{max}:

Ratio: 114.83%

90% CI: [100.86%-130.75%]

The ratio of the gMeans and the 90% CI for AUC_{0-1032} [87.81-123.39] fell within the acceptance range of 80.00 to 125.00%; the upper bounds of the 90% CIs of AUC_{0-inf} [86.34%-130.56%] and C_{max} [100.86%-130.75%] crossed the 125% limit.

The applicant explained this with higher variability of AUC_{0-inf}, assumed to be caused by a considerable number of subjects with >20% extrapolated portion of the area under the curve during the elimination phase (AI: 9/33; PFS: 6/32, 27% vs 19%). Further, the applicant considers AUC_{0-inf} less relevant than AUC_{0-1032}, since the terminal elimination phase might not be affected by the device used. This can be followed since the exact same formulations in the exact same amount were used.

The results of the primary analysis actually demonstrate an effective difference in C_{max} between the AI and the PFS, although it was not powered to do so [90% CI (100.86%, 130.75%)]. The applicant argued that this is not considered clinically relevant as no safety concern is associated with a high peak exposure and efficacy is expected to be primarily driven by total exposure. Specifically, no dose-limiting toxicities were observed for adalimumab (US PI and the EU SmPC). This is agreed in principle.

The applicant further explained that the concentrations of one subject from the PFS group exhibited very low BI 695501 plasma concentrations (the values over the planned time points differ by 50- 60% from the "next higher" subject) and the exclusion of this extremely low C_{max} value in a post hoc sensitivity analysis resulted in a clear decrease in inter-individual variability (44.9% to 33.9%) and a 90% CI included in the 80.00% to 125.00% range (98.60%, 122.53%). While the sensitivity analysis is appreciated, no rationale was given, why exclusion of this subject should not be regarded as data driven. It also highlights the uncertainty of any PK conclusions based on this small data set, considering also the relatively high variability of the PK parameters.

The study was still ongoing at the time of the primary analysis aiming for inclusion of further subjects into the low BMI group. Additional 5 subjects could be recruited in the low BMI group after the cut-off for the final primary analysis; thus a total of 71 subjects were randomized to either BI 695501 PFS (36 subjects) or BI 695501 AI (35 subjects) and included in the PKS of the follow-up analysis. The point estimates for the adjusted gMean ratios for AUC_{0-inf}, AUC_{0-1032}, and C_{max} were closer to 100% (100.22, 100.14, and 110.19, respectively) as compared to the final primary analysis. Furthermore, 90% CIs were within 80.00-125.00% for both AUC_{0-inf}, and AUC_{0-1032}, and the 90% CI for C_{max} ranged from 96.80 to 125.44%. Thus, the result of the follow-up analysis did no longer support an effective difference in C_{max} between the AI and the PFS.

Conclusion:

Further insight on potential consequences of using different devices for the PK could be gained from *in vitro* models (investigating whether the same amount of drug is delivered into the same depth of derma) or from *in vivo* studies. The applicant chose to investigate comparability of PK after delivery of BI 695501 per PFS or AI in a small, relative bioavailability study. In principle, it is agreed that formal bioequivalence would not have to be shown, in line with the Guideline on the Investigation of Bioequivalence (CHMP/EWP/QWP/1401/98 Rev. 1), where it is stated that "*a bioequivalence study is not required for an aqueous parenteral solution with comparable excipients in similar amounts, if it can be demonstrated that the excipients have no impact on the viscosity"* (APPENDIX II Parental solutions).

The composition of the drug substance in the PFS and AI is identical. The applicant demonstrated that extractable volumes of autoinjector and PFS are the same (0.8mL) by ejecting the AI and determining dose accuracy gravimetrically by weighing.

C_{max} seems to differ following application of BI 695501 via PFS or AI, but it is not seen as a critical parameter for the efficacy of adalimumab nor would slightly higher C_{max} levels compromise its safety. The extent of exposure - based on AUC_{0-1032} values, which appear more reliable than AUC_{0-inf} in this study - seems comparable (GM ratios are even within conventional BE limits). Elimination is not expected to differ.

2.4.3. Pharmacodynamics

No clinical comparative PD study was submitted by the applicant. No accepted specific pharmacodynamic (PD) markers exist, being predictive of efficacy of adalimumab in patients.

PD similarity of Cyltezo and Humira in terms of TNF-α inhibition has been investigated in non-clinical in-vitro and in-vivo similarity studies and is supported by demonstration of efficacy equivalence of Cyltezo and Humira in the clinical Phase III study.

The applicant has been asked to justify the lack of data analysis on inflammation markers (RF, anti-CCP, ESR, and CRP) measured in comparative clinical studies. The results for the PD markers determined in the pivotal study 1297.2 updated by the final data set were presented. No treatment group differences were noted in the median change from baseline for CRP or ESR over the entire trial duration.

2.4.4. Discussion on clinical pharmacology

Healthy volunteers, failed vs. successful trial

The applicant performed two single dose PK studies (1297.1 and 1297.8) in healthy male volunteers to establish comparability between Cyltezo and Humira EU and as well to allow bridging between US and EU comparator.

In study 1297.1, which was performed with a trial formulation exhibiting differences in the buffering system compared to the commercialised formulation, the applicant failed to demonstrate equivalence of the trial formulation of Cyltezo and Humira EU within the predefined standard acceptance limits of 80.00-125.00% for all primary measures (AUC_{0-inf}: 132.24% [113.984; 153.412] AUC_{0-t}: 128.88% [113.492; 146.365] C_{max}: 117.53% [105.638; 130.757])

The applicant stated that the results obtained from the initial trial 1297.1 were not taken into account for the PK similarity assessment as the study was conducted with a trial formulation of BI 695501. This cannot be endorsed, because the PK exposure difference between EU- and US-Humira is considered the crucial finding which is not affected by the BI 695501 formulation used.

Post hoc and mainly data driven analyses, correcting e.g. for body weight and protein content as covariates, were performed but were unable to provide a satisfactory rationale for the observed differences.

In the EMA Scientific advice in 2013 (EMA/CHMP/SAWP/352889/2013) the following was stated: As was also noted by the Applicant it could not be demonstrated through the primary analysis that EU Humira had equivalent PK to BI 695501. Hence, trial 1297.1 must be regarded as a failed study. However, the possibility to repeat the study, as soon as the final, to be commercialized product is established, remains. Reference to study 1297 .1 would be expected, including a thorough discussion explaining the impact of the reformulation on the PK of BI 695501, which would ideally support that the reformulation could minimize the differences.

The applicant followed CHMP's advice and performed another larger study using the to be commercialised formulation of BI 695501, taking the insights gained from this failed study into an improved study planning process (e.g. a larger sample size due to the unexpectedly high CV, a harmonised injection site, double blind conduction of the trial, body weight and age primarily included as covariates). PK similarity was demonstrated for all comparisons (BI 695501 versus US-licensed Humira® and EU-approved Humira®, and US-licensed Humira® versus EU-approved Humira®) for all primary PK parameters based on the predefined hypothesis test. Point estimates for the geometric mean ratios were close to 1.

Secondary PK parameters supported PK similarity as all 90% CIs were also contained in the standard acceptance range.

The Applicant provided a comparison between adjusted GM primary PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}tz}$ and C_{max}) of study 1297.1 and 1297.8, revealing that the adjusted GM for BI 695501 and US-licensed Humira were highly comparable across both studies, while the GM observed for EU-approved Humira were approximately 25% lower in 1297.1 compared to 1297.8.

A discussion on the comparative study designs regarding their sensitivity to detect differences in biosimilarity, including a tabulated comparison of all the differences in methodology between study 1297.1 and 1297.8, were requested together with a discussion on the impact of the reformulation. The applicant discussed the differences in design of both healthy volunteer PK studies (1297.1 and 1297.8) regarding their potential sensitivity. It was made clear that some observations that probably confounded sensitivity in trial 1297.1 - such as a slight imbalance in body weight, differences in protein concentrations and variable injection sites - were better controlled in trial 1297.8. Furthermore an increase in sample size was incorporated into the design of 1297.8 to account for the observation of unexpectedly high variability in trial 1297.1. While all of these factors do not seem to have been the main root cause for dissimilarity of the PK in trial 1297.1 (rather, most likely the unexpected performance of EU Humira), it is plausible that study 1297.8 is the more relevant and sensitive model to detect true, product related differences. Furthermore, the company convincingly argued that the potential clinical impact of the reformulation of the biosimilar candidate, which was instituted between the two PK trials, is low or non-existent. It was further concluded that due to an unknown reason, EU-Humira showed an unexpectedly low exposure in trial 1297.1, which persisted even after correction for protein concentration. Shelf-life, shipment and storage conditions for EU Humira were analysed and found to be comparable between studies 1297.1 and 1297.8, as well as molecular and pharmacological properties of the used Humira lots.

Overall, it is agreed that trial 1297.8, which clearly demonstrated similarity between treatment, is the more sensitive and relevant trial. The main driver for the observed dissimilarity in PK between BI 695501 and Humira observed in trial 1297.1 was an unexpected (and probably unexplainable) low exposure of EU Humira that was not observed in the second PK trial. In conclusion, the biosimilar candidate can therefore be considered biosimilar to Humira in terms of PK.

PK by ADA status

Since 80-95% of the subjects in both healthy volunteers' studies were detected to be ADA positive and ADAs strongly decrease free adalimumab concentrations, the combined PK comparison of ADA negative and positive subjects can mask possible other differences in PK between the drug substances. Therefore, re-evaluation of the PK equivalence results of both healthy volunteers' studies stratified by ADA status was requested of the applicant. The company did not provide re-analysis stratified by ADA status justifying this by several scientific reasons which is acceptable. They instead provided a descriptive graphical comparison of individual ADA titres and PK concentrations observed. This analysis indicates that adalimumab plasma concentrations decrease with increasing ADA titre in the majority of

PK samples in trial 1297.8, and that the impact of ADA on the PK was similar for the 3 treatments tested. Furthermore, graphical displays of weighted residuals over ADA titre values generated by the PopPK modelling approach for studies 1297.8 and 1297.2 show smooth curves close to zero without systematic trends and were similar in the BI 695501 and Humira groups. In conclusion, the possibility that differences in the PK of the 3 treatments in trial 1297.8 could have been masked by ADA has been ruled out.

For trial 1297.1, the correlation plot between ADA titre and adalimumab plasma concentrations shows a different trend for the EU-approved Humira treatment group at a few high ADA values. However, it is agreed that both the time course and the distribution of ADA titres were comparable between the groups. Thus, the conclusion that the reason for the low exposure of EU approved Humira in 1297.1 appears to be a generally lower bioavailability, rather than a different immunogenic profile, is endorsed.

Patients with RA and pop PK

PK similarity between BI695501 and US-Humira in patients with RA on stable MTX background therapy was supported by the results of the pivotal Phase III study 1297.2. The mean trough plasma concentration-time profiles were similar during the initial randomization period from Day 1 to Day 168 and no relevant changes in arithmetic mean trough concentrations were observed after re-randomization at Week 24 (Day 168) in none of the three treatment groups (BI 695501 to BI 695501, US-licensed Humira to US-licensed Humira, and US-licensed Humira to BI 695501, respectively. The high variability of trough concentrations in both groups was mainly due to a strong decrease in exposure of free adalimumab in about half the patients due to ADA development (42.8 vs. 50.3%). Nevertheless, subgroup and population PK analysis support the conclusion that the similar ADA response across the two treatment groups had a similar impact on drug plasma concentration.

A Population PK analysis was based on one Phase I study (1297.8) and the Phase III study (1297.2). Plasma concentration observations, dosing histories, event times, and covariates (gender, body size, age, CRP, RF, ALB, ADA, and nAb) were assembled and formatted for analysis. The combined adalimumab PK data from BI 695501 and Humira study arms was described by a two-compartment model with sequential zero- and first-order absorption and linear elimination. Population PK analysis is generally endorsed and considered important to understand the effect of patient characteristics and other covariates, in particular antibody formation, on the PK of Humira and BI695501.

From a biosimilarity assessment perspective only the third objective was of interest: the evaluation of differences between BI695501 and Humira in relation to PK, and the influence of ADA on PK. While results of the analysis are generally supporting biosimilarity, this study is rather considered as supportive evidence since the value of comparing PK across two very different populations and studies is unknown.

PK data with the autoinjector

The applicant performed an open-label, randomized, single-dose, parallel-group trial in healthy male volunteers. The primary objective was to characterize and compare the PK of BI 695501 (commercial formulation) after subcutaneous injection using either a PFS or an AI. This study was not powered for formal equivalence testing and evaluated adjusted GM ratios and their 90%CIs for $AUC_{0\ 1032}$, $AUC_{0\text{-}inf}$ and C_{max}.

The ratios of the GMs for the primary endpoints and the 90%CI of $AUC_{0\ 1032}$ [87.81 123.39] fell within the “classical” BE range of 80.00 to 125.00% range; the upper bounds of the 90% CIs of $AUC_{0\text{-}inf}$ [86.34% 130.56%] and C_{max} [100.86% 130.75%] crossed the 125% limit.

The applicant explains this with higher variability of AUC_{0-inf} caused by a considerable number of subjects with an extrapolated portion of the area under the curve >20% during the elimination phase. Further, they consider AUC_{0-inf} less relevant than AUC_{0-1032}, since the terminal elimination phase might not be affected by the device used. This can be followed since the exact same formulations in the exact same amount were used.

The study actually demonstrates an effective difference in C_{max} between the AI and the PFS [90% CI (100.86%, 130.75%)], although it was not powered to do so. The applicant argues that no safety concern is associated with a high peak exposure and efficacy is expected to be primarily driven by total exposure. Specifically, no dose-limiting toxicities were observed for adalimumab (US PI and the EU SmPC). This is agreed in principle.

The study was still ongoing at the time of the primary analysis. Additional 5 subjects could be recruited in the low BMI group after the cut-off for the final primary analysis. The point estimates obtained in the follow-up analysis for the adjusted gMean ratios for AUC_{0-inf}, AUC_{0-1032}, and C_{max} were closer to 100% (100.22, 100.14, and 110.19, respectively) as compared to the final primary analysis. The 90% CIs were within 80.00-125.00% for both AUC_{0-inf}, and AUC_{0-1032}, and the 90% CI for C_{max} ranged from 96.80 to 125.44%. Thus, the result of the follow-up analysis did no longer support an effective difference in C_{max} between the AI and the PFS.

The composition of the drug substance in the PFS and AI is identical. The applicant demonstrated that extractable volumes of autoinjector and PFS are the same (0.8mL) by ejecting the AI and determining dose accuracy gravimetrically by weighing.

The small sample size and high variability of PK parameters need to be considered in interpreting the results. C_{max} seems to differ following application of BI 695501 via PFS or AI, but it is not seen as a critical parameter for the efficacy of adalimumab nor would slightly higher C_{max} levels compromise its safety. The extent of exposure - based on AUC_{0-1032} values, which appear more reliable than AUC_{0-inf} in this study - seems comparable (GM ratios are even within conventional BE limits). Elimination is not expected to differ.

t is agreed that the advantages outweighs the risks and that finally, patients can decide whether to change to the PFS device in case of adverse outcome or not.

2.4.5. Conclusions on clinical pharmacology

The applicant established PK biosimilarity between Cyltezo and EU Humira as well as successful bridging between EU and US originator in the single-dose healthy volunteer PK study (1297.8). Biosimilarity at the PK level is supported by evaluation of Ctrough levels in the pivotal efficacy study (1297.2).

2.5. Clinical efficacy

A clinical efficacy and safety study (1297.2) was conducted to demonstrate similarity in terms of clinical efficacy in a representative study population. This study was designed to be sufficiently sensitive to detect potential differences between Cyltezo and US licensed Humira in efficacy in accordance with EMA “Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues” (EMEA/CHMP/BMWP/42832/2005 Rev. 1) and “Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues” (EMA/CHMP/BMWP/403543/2010).

Among the approved therapeutic indications of Humira, RA has been most thoroughly studied and validated, and reasonably sensitive methods to determine disease activity are available, which qualifies RA as an appropriate model for demonstrating similarity in efficacy.

Table 1 Trial included in the analysis of efficacy

Trial number Report	Trial description	Trial design	Phase	Patients, N
Pivotal Phase III trial				
1297.2 (VOLTAIRE®-RA) Primary analysis CTR [c08934295]	Efficacy, safety and immunogenicity of BI 695501 versus US-licensed Humira in patients with moderately to severely active RA with stable MTX background	Double-blind, randomized, parallel group, multiple dose, active comparator	III	Treated: 645 BI 695501: 324 Humira US: 321 Ongoing [1]: 261

[1] Randomized patients who had not yet completed the trial or prematurely discontinued the trial at the primary analysis cut-off (29 April 2016) were counted as ongoing in the trial at the cut-off

Study design

The primary objective of the pivotal trial 1297.2 was to evaluate equivalence in efficacy between Cyltezo and US-licensed Humira in patients with active RA with stable MTX background, based on a statistical comparison of the proportion of patients meeting the ACR20 response criteria at Week 12 and at Week 24. The secondary objectives of trial 1297.2 were to compare the efficacy, safety, and immunogenicity of BI 695501 and US licensed Humira in patients with active RA, including those undergoing the transition from US-licensed Humira to BI 695501 after 24 weeks.

A total of 645 patients with moderately to severely active RA and stable MTX background were randomized (1:1) to double-blind treatment with either BI 695501 or US-licensed Humira according to the stratification factors region and prior exposure to a biologic agent.
Each patient was to receive 40 mg of trial drug every 2 weeks by SC injection (Figure 1 below). Patients were to continue to take their regular MTX therapy (15 to 25 mg/week at a stable dose) and a stable weekly dose of adequate folic acid (at least 5 mg per week or as per local practice) or folinic acid (at least 1 mg per week or as per local practice) from their usual source.

The trial consisted of a screening period of ≤28 days, a pre-randomization phase of ≤10 days, and a 48-week treatment period (Figure 1 below). At Week 24, all patients were re-randomized in a blinded fashion. Patients who were originally randomized to US-licensed Humira were re-randomized (1:1) to either continue on US-licensed Humira or to transition to BI 695501. Patients who originally received BI 695501 were dummy re-randomized to BI 695501 in order to maintain the blind for all patients.

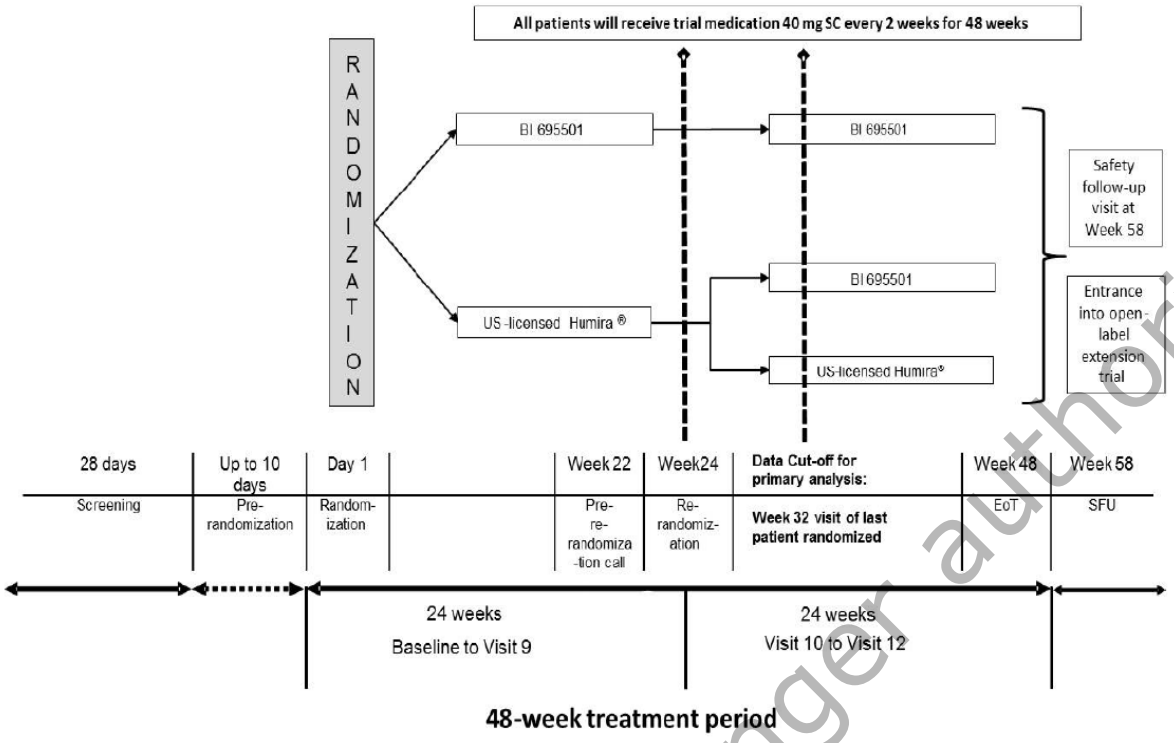


Figure 1 Trial design of 1297.2

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

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		
1297.2 (VOLTAIRE-RA), 2012-002945-40 (EudraCT number)		
This was a randomized, double-blind, parallel group, multicentre clinical study of BI 695501 and US-licensed Humira with a 48-week treatment period, in patients with active RA receiving background methotrexate (MTX) treatment. The trial was designed to establish that the proposed biosimilar (BI 695501) has an equivalent efficacy and similar risk profile to US-licensed Humira. A PPK analysis with sparse sampling was carried out in addition to measurement of plasma concentration at specific visits in order to assess the PK of BI 695501 and US-licensed Humira in this trial. The trial consisted of a Screening period of up to a maximum of 28 days, a pre-randomization phase of up to ten days, and a 48 week treatment period. At Week 24, all patients were to be re-randomized. Patients who were originally randomized to US-licensed Humira were re-randomized to either continue on US-licensed Humira or transition to BI 695501 at Week 24 in a blinded fashion in a 1:1 ratio. Patients who originally received BI 695501 were dummy re-randomized to BI 695501 in order to maintain the blind for all patients.		
Duration of main phase:	24 weeks (primary endpoint), 48 weeks (end of active treatment)	
Duration of Run-in phase:	4 weeks	
Equivalence; equivalence margin for the difference in ARC20 response rate at week 12 [-12%, 15%] and 24: [-15%, 15%]		
BI 695501	BI 695501 40 mg, SC, every other week, From Day 1 up to Week 24, Randomized (at Day 1): n=324	
Humira	Humira US 40 mg, SC, every other week, From Day 1 up to Week 24, Randomized (at Day 1): n=321	
Humira/Humira	Humira US 40 mg, SC, every other week, From Day 1 up to Week 24, Humira US 40 mg, SC, every other week, from Week 0 up to Week 48, re-randomized (at Week 24): n=148	
Humira/BI 695501	Humira US 40 mg, SC, every other week, From Day 1 up to Week 24, BI 695501 40 mg, SC, every other week, from Week 24 up to Week 48, re-randomized (at Week 24): n=147	
All subjects received 15-25 mg/week of oral or parenteral MTX		
Co-Primary efficacy endpoints	ACR20	ACR20 response rate at Week 12 and 24
Further efficacy endpoint	ACR20	ACR20 response rate at Week 48
Further efficacy endpoint	ACR50	ACR50 response rate at Week 12,24 and Week 48
Further efficacy endpoint	ARC70	ACR70 response rate at Week 12,24, and Week 48
Further efficacy endpoint	Individual components of ACR	Change in individual ACR parameters at Week 12 and Week 24
Secondary efficacy endpoint	DAS28-ESR	Change in DAS28 score from baseline at Week 12,24 and 48
Further efficacy endpoint	EULAR Response	EULAR response at Week 12, 24 and Week 48
Secondary Safety endpoints	AEs	Proportion of patients with Investigator-assessed drug-related AEs

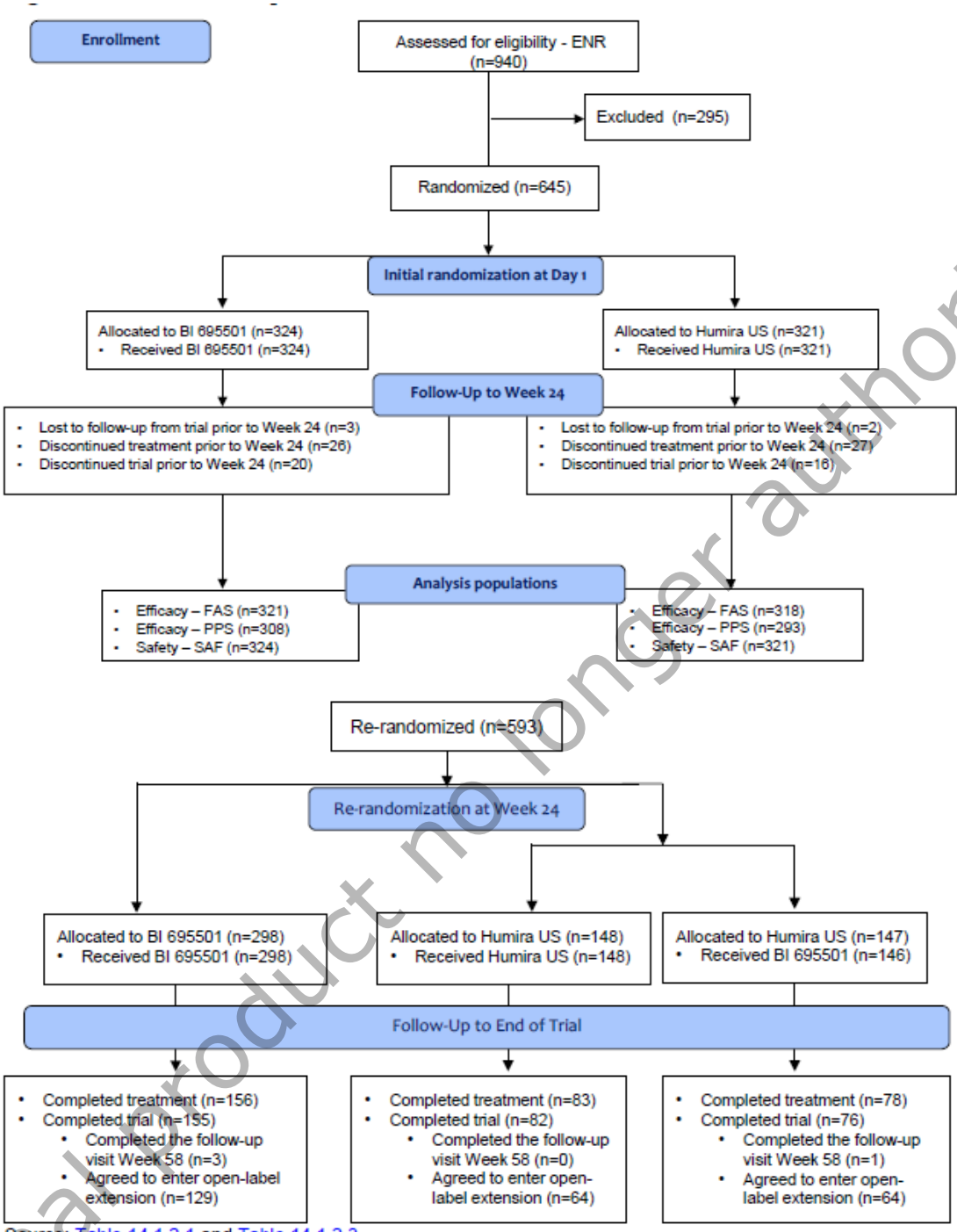
Further Safety endpoints	SAEs	Incidence of serious adverse events (SAEs).
	AEs	Incidence of adverse events (AEs, graded as mild, moderate and severe).
	Clinical abnormality	Incidence of clinical laboratory abnormalities. Vital signs abnormalities.
	Immunogenicity	Incidence of anti-drug antibodies (ADA). Incidence of neutralising antibodies. Serum concentration were taken at baseline (prior to dosing), 6 hours after dosing and at Days 7, 14, 28, 84, 168, 280, 336, and 406
PK Endpoints		

Main Results and Analyses

Analyses description	**Primary/Secondary Analyses**		
Effect estimate per comparison	**Primary endpoint ACR20 at w12 FAS, primary analysis**	Comparison groups	**BI 695501 vs. Humira**
		Treatment difference	**5.9%**
		90% CI	**[−0.9%, 12.7%]**
		Test	**-0.12 < CI < 0.15**
	Primary endpoint ACR20 at w12 PPS, secondary analysis	Comparison groups	**BI 695501 vs. Humira**
		Treatment difference	**4.2%**
		95% CI	**[−4.2%, 12.6%]**
		Test	**-0.12 < CI < 0.15**
	Primary endpoint ACR20 at w24 FAS, primary analysis	Comparison groups	**BI 695501 vs. Humira**
		Treatment difference	**4.5%**
		95% CI	**[−3.5%, 12.4%]**
		Test	**-0.15 < CI < 0.15**
	Primary endpoint ACR20 at w24 PPS, secondary analysis	Comparison groups	**BI 695501 vs. Humira**
		Treatment difference	**1.6%**
		95% CI	**[−6.6%, 9.8%]**
		Test	**-0.15 < CI < 0.15**
	Secondary endpoint DAS28-ESR at w12 FAS	Comparison groups	BI 695501 vs. Humira
		Treatment difference	-0.1
		95% CI	[-0.28, 0.08]
		Test	None
	Secondary endpoint DAS28-ESR at w24	Comparison groups	BI 695501 vs. Humira
		Treatment difference	0%
		95% CI	[−0.16%, 0.23%]

	FAS	Test	None
	Further endpoint ACR50 at w12 FAS	Comparison groups	BI 695501 vs. Humira
		Treatment difference	-1.75%
		95% CI	Not provided
		Test	None
	Further endpoint ACR50 at w24 FAS	Comparison groups	BI 695501 vs. Humira
		Treatment difference	0.21%
		95% CI	Not provided
		Test	None
	Further endpoint ACR70 at w12 FAS	Comparison groups	BI 695501 vs. Humira
		Treatment difference	-0.93
		95% CI	Not provided
		Test	None
	Further endpoint ACR 70	Comparison groups	BI 695501 vs. Humira
		Treatment difference	-4.31%
		95% CI	Not provided
		Test	None
	Further endpoint ACR70 at w12 FAS	Comparison groups	BI 695501 vs. Humira
		Treatment difference	-0.93
		95% CI	Not provided
		Test	None
Notes	For Week 12, the 95%CI of is considered more relevant by CHMP. The results were also within the equivalence margins (95%CI: -2.2, 14.0). Equivalence was demonstrated Further sensitivity analysis (unadjusted for covariates) confirmed the results. No hypotheses were defined for the secondary endpoints regarding DAS28-ESR.		

Recruitment and Participant Flow:



Source: Table 14.1.2.1 and Table 14.1.2.3.

FAS = full analysis set; PPS = per-protocol set; SAF = safety set; ENR = all patients enrolled set.

940 patients were screened at 137 trial centres and 645 patients were initially randomized 1:1 to receive either BI 695501 or US Humira: 324 in the BI 695501 group and 321 patients in the US-Humira group. Six subjects (three in each study arm) who were randomised and treated with study drug were excluded from the FAS.

At Week 24, a total of 593 (91.9%) patients were re-randomized; 298 patients from BI 695501 to BI 695501, 148 patients from US-Humira to US-Humira, and 147 patients from US-Humira to BI 695501.

A total of 70 (10.9%) patients had discontinued the trial prematurely. The most common reasons for trial discontinuation prior to Week 12 were withdrawal by patient (31.3% total [5/16 patients]) and AE

(non-fatal), lost to follow-up and other (all 18.8% total [3/16 patients]). The most common reason for trial discontinuation prior to Week 24 was withdrawal by patient (38.9% total [14/36 patients]). There was no notable difference in the rate of treatment or trial discontinuation between the BI 695501 and US-Humira treatment groups or between any of the re-randomization treatment groups.

Protocol Deviations:

Important protocol deviations and their consequences for the allocation of patients to analysis datasets were assessed before unblinding and locking of data for the primary analyses. Overall, 38 patients (5.9% of patients in the FAS) had at least one important protocol deviation leading to exclusion from the PPS. Fewer patients with protocol deviations leading to exclusion from the PPS were noted in the BI 695501 group (4.0%) as opposed to the US-licensed Humira group (7.9%). This difference is derived from an imbalance in the most common deviation: “severe deviation to the restricted DMARD therapy prior to primary endpoint assessment at Week 24” (25 patients, 3.9% total).

All other protocol deviations leading to exclusion from the PPS were very rare (≤ 9 patients in total). One patient in the US-Humira to BI 695501 group (Patient 39090014) received incorrect medication (not as randomized) prior to the Week 24 assessment. The patient was initially randomized to US-Humira and received the correct medication up to Week 20; on Day 154 (Week 22) the patient was administered BI 695501 in error. The patient was re-randomized to BI 695501 at Week 24 and continued to receive BI 695501 from Week 24 to the end of the trial.

In summary, severe protocol deviations were rare, and equally distributed with the exception of deviations concerning restricted DMARD therapy, which was slightly more frequent in the US-Humira treated group.

Baseline Characteristics

Demographic characteristics were sufficiently balanced between treatment groups, regarding age, ethnicity, gender, BMI, and prior exposure to biologics. Baseline disease characteristics in terms of duration and severity of RA were well balanced at initial and at re-randomisation.

Table 12 Demographic characteristics at baseline (SAF)

Characteristic (unit)	Initial Randomization		Re-randomization			Overall	Total
	BI 695501 (N=324)	Humira US (N=321)	BI 695501 to BI 695501 (N=298)	Humira US to Humira US (N=148)	Humira US to BI 695501 (N=146)	Humira US continuously (N=175)	(N=645)
Age (years)							
Mean	53.7	53.6	53.5	52.9	53.8	53.4	53.6
SD	12.04	11.32	12.12	12.31	10.41	12.06	11.68
Age category (n [%])							
< 65	264 (81.5)	275 (85.7)	243 (81.5)	124 (83.8)	128 (87.7)	147 (84.0)	539 (83.6)
≥ 65 to < 76	52 (16.0)	44 (13.7)	49 (16.4)	22 (14.9)	18 (12.3)	26 (14.9)	96 (14.9)
≥ 76 to < 85	8 (2.5)	2 (0.6)	6 (2.0)	2 (1.4)	0	2 (1.1)	10 (1.6)
≥ 85	0	0	0	0	0	0	0
Gender (n [%])							
Male	57 (17.6)	52 (16.2)	50 (16.8)	19 (12.8)	26 (17.8)	26 (14.9)	109 (16.9)
Female	267 (82.4)	269 (83.8)	248 (83.2)	129 (87.2)	120 (82.2)	149 (85.1)	536 (83.1)
Race (n [%])							
American Indian or Alaska Native	0	0	0	0	0	0	0
Asian	8 (2.5)	6 (1.9)	8 (2.7)	3 (2.0)	2 (1.4)	4 (2.3)	14 (2.2)
Black or African American	6 (1.9)	7 (2.2)	5 (1.7)	1 (0.7)	3 (2.1)	4 (2.3)	13 (2.0)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
White	309 (95.4)	304 (94.7)	285 (95.6)	141 (95.3)	140 (95.9)	164 (93.7)	613 (95.0)
Other	1 (0.3)	4 (1.2)	0	3 (2.0)	1 (0.7)	3 (1.7)	5 (0.8)
Ethnicity (n [%])							
Hispanic or Latino	45 (13.9)	44 (13.7)	38 (12.8)	21 (14.2)	19 (13.0)	25 (14.3)	89 (13.8)
Not Hispanic or Latino	273 (84.3)	276 (86.0)	255 (85.6)	126 (85.1)	127 (87.0)	149 (85.1)	549 (85.1)
Not reported	6 (1.9)	1 (0.3)	5 (1.7)	1 (0.7)	0	1 (0.6)	7 (1.1)
Geographic region (n [%])							
Asia	6 (1.9)	6 (1.9)	6 (2.0)	3 (2.0)	2 (1.4)	4 (2.3)	12 (1.9)
Europe	231 (71.3)	228 (71.0)	219 (73.5)	108 (73.0)	107 (73.3)	121 (69.1)	459 (71.2)
Latin America	25 (7.7)	26 (8.1)	22 (7.4)	13 (8.8)	10 (6.8)	16 (9.1)	51 (7.9)
USA	62 (19.1)	61 (19.0)	51 (17.1)	24 (16.2)	27 (18.5)	34 (19.4)	123 (19.1)
Weight (kg)							
Mean	73.1	75.1	72.9	72.6	76.6	73.9	74.1
SD	16.87	17.07	16.71	15.87	17.24	16.87	16.99
Weight category (n [%])							
< 50 kg	14 (4.3)	11 (3.4)	14 (4.7)	8 (5.4)	3 (2.1)	8 (4.6)	25 (3.9)
≥ 50 to < 100 kg	289 (89.2)	275 (85.7)	265 (88.9)	128 (86.5)	125 (85.6)	150 (85.7)	564 (87.4)
≥ 100 kg	21 (6.5)	35 (10.9)	19 (6.4)	12 (8.1)	18 (12.3)	17 (9.7)	56 (8.7)
BMI (kg/m^2)							
Mean	27.04	27.86	26.97	27.1	28.21	27.58	27.45

Characteristic (unit)	Initial Randomization		Re-randomization			Overall	Total
	BI 695501 (N=324)	Humira US (N=321)	BI 695501 to BI 695501 (N=298)	Humira US to Humira US (N=148)	Humira US to BI 695501 (N=146)	Humira US continuously (N=175)	(N=645)
SD	5.422	6.309	5.405	5.806	6.385	6.25	5.888
BMI category (n [%])							
< 20 kg/m^2	23 (7.1)	23 (7.2)	22 (7.4)	8 (5.4)	14 (9.6)	9 (5.1)	46 (7.1)
≥ 20 to < 25 kg/m^2	106 (32.7)	90 (28.0)	98 (32.9)	56 (37.8)	28 (19.2)	62 (35.4)	196 (30.4)
≥ 25 kg/m^2	195 (60.2)	205 (63.9)	178 (59.7)	83 (56.1)	102 (69.9)	103 (58.9)	400 (62.0)
Missing	0	3 (0.9)	0	1 (0.7)	2 (1.4)	1 (0.6)	3 (0.5)
Prior exposure to a biological agent (n [%])							
Yes	85 (26.2)	86 (26.8)	77 (25.8)	40 (27.0)	42 (28.8)	44 (25.1)	171 (26.5)
No	239 (73.8)	235 (73.2)	221 (74.2)	108 (73.0)	104 (71.2)	131 (74.9)	474 (73.5)

Source: Table 14.1.3.1.

BMI = body mass index; n = number of patients; N = number of patients in analysis set; SAF = safety set; SD = standard deviation.

All the data collected are presented, split by :

Initial randomization and treatment administered:

- BI 695501: all patients initially randomized and treated with BI 695501
- Humira US: all patients initially randomized and treated with US-licensed Humira

Re-randomization and treatment administered after re-randomization:

- BI 695501 to BI 695501: all patients initially randomized and treated with BI 695501 and re-randomized and treated after re-randomization.
- Humira US to Humira US: all patients initially randomized and treated with US-licensed Humira and re-randomized and treated after re-randomization to US-licensed Humira
- Humira US to BI695501: all patients initially randomized and treated with US-licensed Humira and re-randomized and treated after re-randomization to BI 695501

Overall:

- Humira US continuously: all patients initially randomized and treated with US-licensed Humira and re-randomized to US-licensed Humira or (not Re-randomized or not treated after re-randomization).

Total: all patients assigned to the population set.

% = percentage of patients calculated relative to the total number of patients in the analysis set (per group), percentage of patients with childbearing potential

Characteristic (unit)	Initial Randomization		Re-randomization			Overall	Total
	BI 695501 (N=324)	Humira US (N=321)	BI 695501 to BI 695501 (N=298)	Humira US to Humira US (N=148)	Humira US to BI 695501 (N=149)	Humira US continuously (N=175)	(N=645)
Previous DMARD therapies							
Mean	2.2	2.4	2.2	2.4	2.4	2.4	2.3
SD	1.37	1.51	1.38	1.5	1.6	1.44	1.44
Methotrexate dosage (mg/week)							
Mean	16.30	16.79	16.23	17.01	16.64	16.91	16.55
SD	3.619	3.911	3.531	4.079	3.765	4.036	3.772
Patients with positive ADA (n [%])	11 (3.4)	21 (6.5)	11 (3.7)	12 (8.1)	8 (5.5)	13 (7.4)	32 (5.0)
Patients with positive nAb (n [%])	9 (2.8)	16 (5.0)	9 (3.0)	9 (6.1)	6 (4.1)	10 (5.7)	25 (3.9)
RF and anti CCP antibodies (n [%])							
Total	324 (100.0)	321 (100.0)	298 (100.0)	148 (100.0)	146 (100.0)	175 (100.0)	645 (100.0)
Both negative	0	1 (0.3)	0	0	1 (0.7)	0	1 (0.2)
RF positive or indeterminate or anti-CCP positive	324 (100.0)	320 (99.7)	298 (100.0)	148 (100.0)	145 (99.3)	175 (100.0)	644 (99.8)

Source: Table 14.1.5.1 and Table 14.1.6.1.

ADA = anti-drug antibody; CCP = cyclic citrullinated peptide; CRP = c-reactive protein; DAS28 = disease activity score 28; DMARD = disease modifying anti-rheumatic drugs; ESR = erythrocyte sedimentation rate; n = number of patients; N = number of patients in analysis set; nAb = neutralizing anti-drug antibodies; RA = rheumatoid arthritis; RF = rheumatoid factor; SAF = safety set; FAS = full analysis set.

Percentage of patients was calculated relative to the total number of patients in the FAS. The total column represents all patients assigned to the population set.

Table 13 Baseline disease and other baseline characteristics (SAF)

Characteristic (unit)	Initial Randomization		Re-randomization			Overall	
	BI 695501 (N=324)	Humira US (N=321)	BI 695501 to BI 695501 (N=298)	Humira US to Humira US (N=148)	Humira US to BI 695501 (N=149)	Humira US continuously (N=175)	Total (N=645)
Duration of RA (years)							
Mean	7.36	7.06	7.31	7.23	7.18	6.96	7.21
SD	7.27	6.765	7.195	6.043	7.531	6.084	7.02
Duration of RA category (n [%])							
< 2 years	86 (26.5)	73 (22.7)	80 (26.8)	30 (20.3)	34 (23.3)	39 (22.3)	159 (24.7)
≥ 2 years	229 (70.7)	237 (73.8)	209 (70.1)	117 (79.1)	106 (72.6)	131 (74.9)	466 (72.2)
Missing	9 (2.8)	11 (3.4)	9 (3.0)	1 (0.7)	6 (4.1)	5 (2.9)	20 (3.1)
ESR (mm/hour)							
Mean	45.5	43.2	45.1	43.6	42.9	43.5	44.4
SD	19.16	17.99	19.28	19.04	15.94	19.58	18.61
DAS28-ESR							
Mean	6.59	6.56	6.57	6.55	6.59	6.53	6.57
SD	0.812	0.815	0.812	0.844	0.779	0.846	0.813
DAS28-ESR category (n [%])							
≤ 3.2	0	0	0	0	0	0	0
> 3.2	324 (100.0)	321 (100.0)	298 (100.0)	148 (100.0)	149 (100.0)	175 (100.0)	645 (100.0)
DAS28-CRP							
Mean	5.68	5.68	5.67	5.67	5.70	5.66	5.68
SD	0.843	0.873	0.837	0.893	0.866	0.881	0.858

Results

Primary endpoints

The co-primary efficacy analysis was carried out on the FAS; supportive efficacy analyses of the co-primary endpoints were performed on the FAS and the PPS.

BI 695501 was similar to Humira in the proportion of patients achieving ACR20 after 12 weeks, 67.0% in the BI 695501 and 61.1% in the US Humira group (FAS). The treatment difference in ACR20 response rate at Week 12 was 5.9% and the 90% CI of the adjusted treatment difference was [-0.9; 12.4], which was completely contained within the pre-defined equivalence margin [−12%, 15%]. In addition, the 95% CI of the adjusted treatment difference, which is considered of more importance by the CHMP, was [-2.2; 14.0], which was also completely contained within the pre-defined equivalence margin [−12%, 15%].

At week 24, 69.0% of subjects in the BI 695501 and 64.6% in the US-Humira group in the FAS reached ACR20. The treatment difference in ACR20 response rate was 4.5%, with a 95% CI [-3.5; 12.4] completely contained within the pre-defined equivalence margin [−15%, 15%].

Table 14 Primary efficacy: estimate and CIs for differences in ACR20 response rate at Week 12 and 24 (NRI and MI) (FAS)

				Difference in proportion (BI 695501 – Humira US,%)		
		N	Proportion (%)	Estimate	90% CI	95% CI
Week 12	BI 695501	321	67.0			
	Humira US	318	61.1	5.9	**(-0.9;12.7)**	(-2.2;14.0)
Week 24	BI 695501	321	69.0			
	Humira US	318	64.6	4.5	(-2.2;11.2)	**(-3.5;12.4)**

Source: Table 14.2.1.2.

CI = confidence interval; FAS = full analysis set; N = number of patients in the FAS population with non-missing ACR20 results; NRI = non-responder imputation; MI = multiple imputation.

Missing data were imputed according to NRI and/or MI. The results were from two separate logistic regression models. The proportion was the least squares mean per treatment group back transformed using inverse logit function. The estimate was the difference in ACR20 response rate (BI 695501 – Humira US,%). The CIs for the difference in proportion in the original scale were calculated using the cumulative distribution function method of Reeve.

Table 15 Primary efficacy sensitivity analysis: estimate and CIs for differences in ACR20 response rate at Week 12 and 24 (NRI and MI) (PPS)

				Difference in proportion (BI 695501 – Humira US,%)		
		N	Proportion (%)	Estimate	90% CI	95% CI
Week 12	BI 695501	308	67.1			
	Humira US	293	62.9	4.2	(-2.9;11.2)	(-4.2;12.6)
Week 24	BI 695501	308	70.3			
	Humira US	293	68.8	1.6	(-5.3;8.4)	(-6.6;9.8)

Source: Table 14.2.1.5.

CI = confidence interval; N = number of patients in the PPS with ACR20 results non-missing; PPS = per-protocol set;
NRI = non-responder imputation; MI = multiple imputation.

Missing data were imputed according to NRI and/or MI. The results were from two separate logistic regression models. The proportion was the least squares mean per treatment group back transformed using inverse logit function. The estimate was the difference in ACR20 response rate (BI 695501 – Humira US,%). The CI for the difference in proportion in the original scale was calculated using the method of Reeve.

The results indicate similarity, however with a trend for higher response in BI 695501 treated patients. Furthermore it is noted that a plateau in ACR20 response is already reached at week 12. However, the applicant also submitted comparative data for the steep part of the dose response curve, which are also suggestive of similarity. While arguably, the clinical relevance of a difference in a proportion of patients improving beyond a predefined threshold (ACR20) is hard to evaluate, the results for both, week 12 and week 24, point towards similarity profile in these measures supporting comparable efficacy of Cyltezo and US-Humira.

Similarity seems more pronounced in the sensitivity analysis on the PPS, the difference between both products in ACR20 at week 12 and 24 ranges from 4.2% (12 weeks) to 1.6% (24 weeks). At both time points the adjusted treatment difference was completely contained within the pre-defined equivalence margins.

An additional exploratory analysis of the co-primary efficacy variables evaluated the correlation between the Week 12 and Week 24 ACR20 responses. The proportion of patients who met ACR20 response at Week 12 and continued to meet the criteria at Week 24 was similar between the BI

695501 (82.1%) and US-licensed Humira (83.6%) groups. However subjects not meeting ACR20 at week 12 in the BI 695501 had a higher chance to reach ACR 20 at 24 four weeks (42.3%) as compared to US Humira treated patients (34.8%).

Although the dataset for both primary endpoints was presented as complete and was already assessed earlier in the evaluation procedure, the applicant repeated the primary analysis "*due to a few corrected component ACR data in 4 patients"* with partially updated data for the final report. Minor numerical changes in the data were observed; however the results were close to identical with the previous analysis. No change was noted in the repeated analysis for the 90% CI (-0.9, 12.7) for the difference in proportions (%) (BI 695501 – US-licensed Humira) of patients achieving an ACR20 response at Week 12 in the FAS. The 95% CI, which is considered by CHMP the primary analysis for this matter,was also unchanged (-2.2, 14.0). A marginal change was noted for the 95% CI for the difference in the proportions of patients achieving an ACR20 response at Week 24 in the FAS compared with the primary analysis report (95% CI changed from [-3.5; 12.4] to [-3.4, 12.5]), this difference is however not considered meaningful.

Secondary and Further Endpoints

The secondary and further endpoints of this trial included both efficacy and safety endpoints. This section presents the results of the efficacy analyses.

DAS28

Data on DAS28-ESR were presented for weeks 12 and 24. Mean baseline DAS28-ESR scores were 6.59 in the BI 695501 group and 6.56 in the US-licensed Humira group. The mean change from baseline in DAS28-ESR was similar between the two treatment groups at Week 12 and Week 24. The LS mean for treatment difference was close or equal to zero and the 90% and 95% CIs include zero.

Table 17 Secondary efficacy endpoints: ANCOVA models for DAS28-ESR at Week 12 and Week 24 (FAS)

			Mean change from Baseline		Treatment difference (BI 695501 – Humira US)		
		N	LS Mean	95% CI	LS Mean	90% CI	95% CI
Week 12	BI 695501	319.6	-2.1	(-2.28, -2.00)			
	Humira US	317.1	-2.0	(-2.18, -1.91)	-0.1	(-0.25, 0.06)	(-0.28, 0.08)
Week 24	BI 695501	314.3	-2.4	(-2.51, -2.21)			
	Humira US	314.9	-2.4	(-2.54, -2.25)	0	(-0.13, 0.20)	(-0.16, 0.23)

Source: Table 14.2.2.2.

MI = multiple imputation; CI = confidence interval; FAS = full analysis set; LS = least squares; N = mean number of patients in the FAS with DAS28-ESR results computable across the multiply imputed datasets.

Missing data were imputed according to MI.

Results based on DAS28-ESR mean changes from baseline after 12 or 24 weeks of treatment = overall mean + treatment group + baseline DAS28-ESR + prior exposure to a biologic agent + random error.

These findings are supportive of the analysis of the co-primary endpoints in showing that the two treatments result in similar efficacy. Mean change from baseline in this continuous measure is almost identical between both treatment groups at both time points. Although no formal equivalence testing has been applied, these finding are considered of importance due to the sensitivity of the DAS (continuous rather than dichotomous as ACR20) and support the claim of similarity since the observation for a potential superiority of BI 695501 (see: non-significant trend in primary measures) is not substantiated by this finding. Similarity remains unchanged with or without data imputation.

ACR 50 and ACR 70

Efficacy data over time were provided for ACR20 and also for ACR 50 and ACR70 (see long term efficacy and table 2 below). Overall, similarity between the Cyltezo and US Humira is seen across different measures and timepoints, but a few uncertainties are noticed: The primary endpoints (ACR20 at week 12 and 24) display a trend for higher efficacy of Cyltezo. This trend seems similarly pronounced at week 4, which is considered a very sensitive timepoint since it is in the steep part of the dose response curve. 6.9% more patients in the biosimilar arm reach ACR20 at week 4 as compared to US Humira (no confidence intervals provided). The differences are much smaller when looking at ACR50 (1.02%) and ACR 70 (-0.65%) and do not persist over time. In summary, the data is suggestive of similarity.

Table 2 ACR20, ACR50, and ACR70 response rate over time for re-randomised patients – FAS (NRI + MI)

Visit	Category	BI 695501 to BI 695501 (N=298) n (%)	Humira US to Humira US (N=148) n (%)	Humira US to BI 695501 (N=147) n (%)
	ACR20 response rate			
Week 4	Mean number of responders	136.8 (45.91)	55.8 (37.68)	59.0 (40.14)
	Number of patients with MI having an impact on ACR response	7 (2.3)	3 (2.0)	0
	Number of patients with NRI	0	0	2 (1.4)
Week 12	Mean number of responders	206.1 (69.17)	95.5 (64.54)	95.0 (64.61)
	Number of patients with MI having an impact on ACR response	6 (2.0)	4 (2.7)	1 (0.7)
	Number of patients with NRI	2 (0.7)	1 (0.7)	2 (1.4)
Week 24	Mean number of responders	221.4 (74.28)	98.8 (66.79)	106.3 (72.30)
	Number of patients with MI having an impact on ACR response	9 (3.0)	3 (2.0)	1 (0.7)
	Number of patients with NRI	4 (1.3)	3 (2.0)	5 (3.4)
Week 40	Mean number of responders	210.0 (70.46)	105.0 (70.93)	103.0 (70.07)
	Number of patients with MI having an impact on ACR response	2 (0.7)	3 (2.0)	0
	Number of patients with NRI	17 (5.7)	9 (6.1)	11 (7.5)
Week 48	Mean number of responders	202.2 (67.85)	103.9 (70.23)	94.0 (63.95)
	Number of patients with MI having an impact on ACR response	2 (0.7)	2 (1.4)	0
	Number of patients with NRI	28 (9.4)	14 (9.5)	20 (13.6)
	ACR50 response rate			
Week 4	Mean number of responders	34.0 (11.41)	13.1 (8.83)	16.3 (11.12)
	Number of patients with MI having an impact on ACR response	0	2 (1.4)	2 (1.4)
	Number of patients with NRI	0	0	2 (1.4)
Week 12	Mean number of responders	89.9 (30.17)	42.3 (28.57)	53.0 (36.05)
	Number of patients with MI having an impact on ACR response	3 (1.0)	3 (2.0)	0
	Number of patients with NRI	2 (0.7)	1 (0.7)	2 (1.4)
Week 24	Mean number of responders	118.0 (39.59)	55.9 (37.74)	61.0 (41.50)
	Number of patients with MI having an impact on ACR response	8 (2.7)	3 (2.0)	0
	Number of patients with NRI	4 (1.3)	3 (2.0)	5 (3.4)
Week 40	Mean number of responders	132.9 (44.61)	63.3 (42.77)	65.6 (44.62)
	Number of patients with MI having an impact on ACR response	2 (0.7)	3 (2.0)	1 (0.7)
	Number of patients with NRI	17 (5.7)	9 (6.1)	11 (7.5)
Week 48	Mean number of responders	129.2 (43.37)	65.2 (44.06)	60.0 (40.82)
	Number of patients with MI having an impact on ACR response	5 (1.7)	2 (1.4)	0
	Number of patients with NRI	28 (9.4)	14 (9.5)	20 (13.6)

To be continued on the next page

Table 2 (cont'd) ACR20, ACR50, and ACR70 response rate over time for re-randomised patients – FAS

Visit	Category	BI 695501 to BI 695501 (N=298) n (%)	Humira US to Humira US (N=148) n (%)	Humira US to BI 695501 (N=147) n (%)
	ACR70 response rate			
Week 4	Mean number of responders	7.0 (2.35)	5.0 (3.37)	4.0 (2.72)
	Number of patients with MI having an impact on ACR response	0	1 (0.7)	0
	Number of patients with NRI	0	0	2 (1.4)
Week 12	Mean number of responders	31.5 (10.56)	16.0 (10.81)	18.0 (12.24)
	Number of patients with MI having an impact on ACR response	3 (1.0)	2 (1.4)	0
	Number of patients with NRI	2 (0.7)	1 (0.7)	2 (1.4)
Week 24	Mean number of responders	43.8 (14.69)	31.1 (20.99)	26.7 (18.14)
	Number of patients with MI having an impact on ACR response	8 (2.7)	4 (2.7)	1 (0.7)
	Number of patients with NRI	4 (1.3)	3 (2.0)	5 (3.4)
Week 40	Mean number of responders	68.5 (22.99)	33.1 (22.36)	34.0 (23.13)
	Number of patients with MI having an impact on ACR response	3 (1.0)	3 (2.0)	0
	Number of patients with NRI	17 (5.7)	9 (6.1)	11 (7.5)
Week 48	Mean number of responders	75.1 (25.22)	32.1 (21.69)	28.9 (19.66)
	Number of patients with MI having an impact on ACR response	2 (0.7)	1 (0.7)	1 (0.7)
	Number of patients with NRI	28 (9.4)	14 (9.5)	20 (13.6)

NRI, non-responder imputation; MI, multiple imputations

Source data: [Appendix to Question 82, Tables 14.2.3.34.1 to 3]

At week 24, while similarity is observed in ACR 50, a trend for higher response rate was noted for US Humira (18.16%) compared with BI 695501 (13.75%) for ACR 70. This was further discussed in context of the 48 week data and comparing patients with major clinical response (ACR70 ≥6 months). At end of study, 11.54% of patients in the Cyltezo group and 15.60% in the US originator group showed major clinical response.

Table 1 Relationship of ACR70 response rate between Week 24 and Week 48 (NRI + MI) – FAS

	BI 695501 to BI 695501 (N=298) Mean, n (%)	Humira US to Humira US (N=148) Mean, n (%)	Humira US to BI 695501 (N=147) Mean, n (%)
Patients with ACR70 response at Week 24	43.8 (100.0)	31.1 (100.0)	26.7 (100.0)
With ACR70 response at Week 48	34.4 (78.5)	23.1 (74.3)	16.7 (62.5)
Patients without ACR70 response at Week 24	254.2 (100.0)	116.9 (100.0)	120.3 (100.0)
Without ACR70 response at Week 48	213.5 (84.0)	107.9 (92.3)	108.1 (89.8)

Mean is the mean number of patients after applying NRI+MI. The non-integer patient numbers represented mean values after implementation of MI.

Source data: [Appendix to Question 90, Table 14.2.1.12]

It seems like patients, who reached ACR70 at week 24, mostly remained positive till end of study (BI: 78.5%, US Humira: 74.3%). The same pattern emerges when looking at non-responders where again a majority of ACR70 negative patients at w24 remain so till end of study (BI: 84%, US Humira: 92%). The difference between Cyltezo and US-Humira observed at week 24 is still visible, but seems to be smaller, since slightly more patients in the biosimilar arm stay ACR70 positive, once they reach the measure, and slightly more previously ACR70 negative patients become responders. Taking all the findings together, there is no relevant difference between treatments in patients with a particularly good response (see also “long term efficacy”).

Individual parameters of the ACR improvement criteria

The individual parameters of the ACR improvement criteria at Week 12 and Week 24 included: swollen joint count; tender joint count; patient's assessment of pain; patient's global assessment of disease activity; physician's global assessments of disease activity; HAQ-DI; and CRP.

The individual parameters of the ACR improved in both treatment groups at Week 12 and Week 24. In most cases, the median percentage of improvement was similar in both treatment groups for each each time-point, however a general tendency for slightliy higher improvement in the BI 695501 is noted. These trends are not perceived to be of clinically meaningful magnitude.

Table 19 Median (IQR) improvement at Week 12 and at Week 24 in individual parameters of the ACR improvement criteria (with MI) (FAS)

Parameter (Median [IQR])	Visit	BI 695501 (N=321)	Humira US (N=318)
Swollen joint count (66 joints)	Baseline	14.00 (11.000)	14.00 (10.000)
	Week 12	4.00 (7.000)	4.00 (7.000)
	Week 24	2.06 (6.000)	3.00 (7.000)
Improvement (%) from Baseline in swollen joint count	Week 12	70.00 (49.158)	70.98 (45.936)
	Week 24	81.82 (37.500)	81.25 (41.250)
Tender joint count (68 Joints)	Baseline	23.00 (17.000)	22.00 (17.000)
	Week 12	7.10 (11.000)	8.00 (11.955)
	Week 24	6.00 (9.939)	6.00 (12.000)
Improvement (%) from Baseline in tender joint count	Week 12	62.50 (43.825)	60.87 (44.737)
	Week 24	71.05 (38.235)	68.75 (45.411)
Patient's assessment of pain[a]	Baseline	67.00 (28.000)	67.00 (26.000)
	Week 12	35.00 (36.000)	39.00 (34.000)
	Week 24	34.00 (35.000)	34.00 (39.094)
Improvement (%) from Baseline in patient's assessment of pain[a]	Week 12	38.33 (57.484)	38.10 (52.063)
	Week 24	44.29 (51.162)	43.28 (54.336)
Patient's global assessment of disease activity	Baseline	67.00 (23.000)	66.00 (23.000)
	Week 12	38.00 (32.000)	41.00 (32.000)
	Week 24	36.00 (33.000)	37.00 (35.000)
Improvement (%) from Baseline in patient's global assessment of disease activity	Week 12	35.71 (50.212)	32.26 (47.459)
	Week 24	42.86 (49.612)	37.50 (52.724)
Physician's global assessment of disease activity	Baseline	63.00 (19.000)	65.00 (21.000)
	Week 12	29.00 (25.000)	28.00 (25.000)
	Week 24	23.00 (25.000)	20.87 (24.000)
Improvement (%) from Baseline in physician's global assessment of disease activity	Week 12	54.12 (40.831)	54.76 (38.882)
	Week 24	59.38 (35.425)	66.23 (38.681)
HAQ-DI[b]	Baseline	1.50 (0.750)	1.50 (0.875)
	Week 12	1.00 (0.875)	1.00 (0.875)
	Week 24	1.00 (1.000)	1.00 (0.875)

Parameter (Median [IQR])	Visit	BI 695501 (N=321)	Humira US (N=318)
Improvement (%) from Baseline in HAQ-DI[(b)]	Week 12	25.00 (50.000)	22.22 (49.595)
	Week 24	28.57 (55.556)	27.78 (50.811)
CRP	Baseline	6.00 (11.000)	6.00 (12.000)
	Week 12	2.00 (5.000)	2.52 (5.179)
	Week 24	3.00 (6.000)	3.00 (5.719)
Improvement (%) from Baseline in CRP	Week 12	50.00 (76.471)	50.00 (75.000)
	Week 24	50.00 (75.000)	50.00 (75.000)

Source: Table 14.2.3.5 through Table 14.2.3.11.
FAS = full analysis set; IQR = inter quartile range; CRP = C-reactive protein; HAQ-DI = Health Assessment Questionnaire – Disability Index; VAS = visual analogue scale.
(a) The VAS for pain ranged from 0 (no pain) to 100 (severe pain).
(b) The HAQ-DI scale ranged from 0 (no difficulty) to 3 (unable to perform activity).
Improvement (%) = (100 x [Baseline – post-baseline]/Baseline).

EULAR response criteria

Table 20 Proportion of patients with EULAR response at Week 12 and Week 24 (FAS)

Visit	Category	BI 695501 (N=321) n (%)	Humira US (N=318) n (%)
Day 84 (Week 12)	Good response	53 (16.5)	54 (17.0)
	Moderate response	210 (65.4)	182 (57.2)
	No response	51 (15.9)	69 (21.7)
Day 168 (Week 24)	Good response	66 (20.6)	83 (26.1)
	Moderate response	194 (60.4)	176 (55.3)
	No response	36 (11.2)	42 (13.2)

Source: Table 14.2.3.14
% = percentage of patients calculated relative to the total number of patients in the analysis set.

The proportion of patients who met the ACR/EULAR definition of remission was low at both Week 12 and Week 24. Six patients (1.9%) in the BI 695501 group and 1 patient (0.3%) in the US-licensed Humira group met the definition for remission at Week 12 and 6 patients (1.9%) and 3 patients (0.9%), respectively, at Week 24.

While a similar percentage of patients displays “good response” at week 12 (16.5% BI 695501/17.0% US Humira), a lower proportion of patients had a good response in the BI 695501 group compared with the US-licensed Humira group (20.6% versus 26.1%) at week 24.

On the other hand the percentage of patients displaying “moderate response” remains consistently higher in the BI 695501 group, while the number of “non responders “ is higher in the US Humira group at week 12 and almost equal at week 24.

Long term efficacy

When looking at long term data presented in the finals study report it appears that the numerical imbalance for ACR20 in favor of Cyltezo observed at week 12 and 24 does not persist. The mean

proportion of patients meeting the ACR20 response criteria at Week 48 is 67.85% in the BI 695501 to BI 695501 group, 70.23% in the US-licensed Humira to US-licensed Humira group and 63.95% in the US-licensed Humira to BI 695501 group.

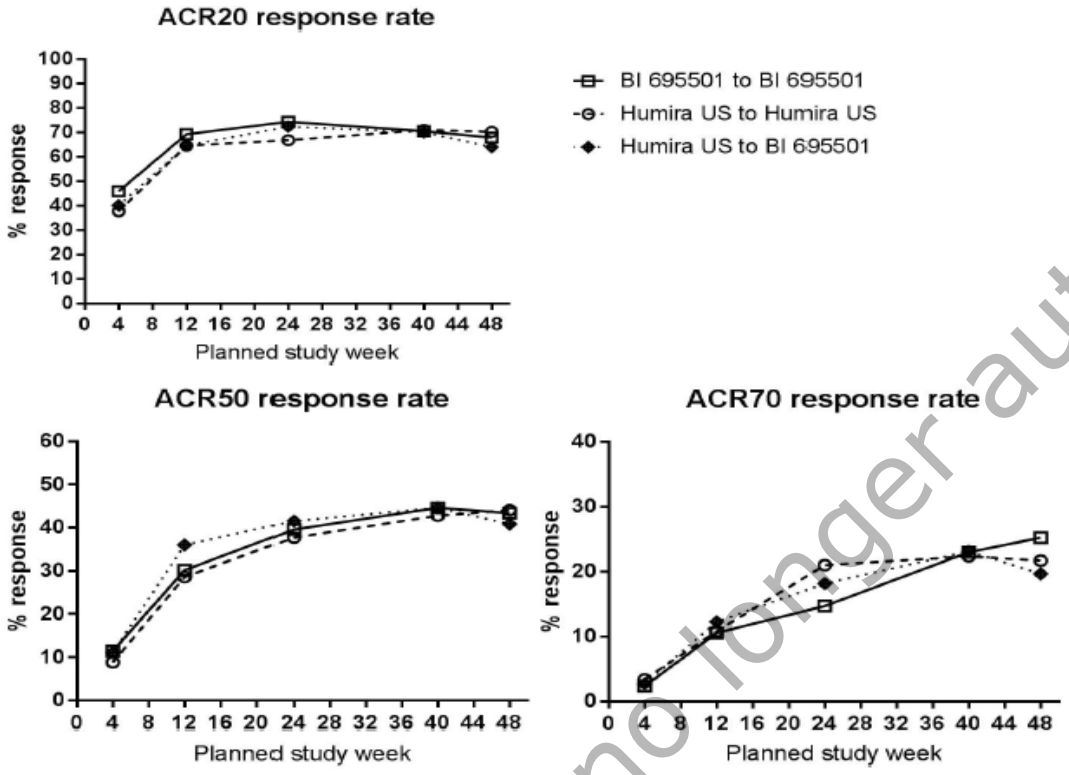


Figure 1 ACR20, ACR50, and ACR70 response rate over time for re-randomised patients – FAS

Source data: [Appendix to Question 82, Tables 14.2.3.34.1 to 3]

As to durability of the effect of BI695501 on ACR20, it is noted that 74.3% of patients reached ACR20 at week 24, but only 67.9% of patients reach this measure at week 48. While a slow increase of effect over time is noted for US Humira (66.8% w24 to 70.2% w48), a decrease is noted for patients who switched from US Humira to BI 695501 (72.3% at w24 to 64% at w48). This finding is however not confirmed by other efficacy measures like DAS-ESR, EULAR response, ACR 50 and ACR 70 and is, also due to its small magnitude, considered most likely a chance finding.

Table 4 Selected long-term efficacy results of trial 1297.2 – FAS

	Final report (completed trial)		
	BI 695501 to BI 695501	Humira US to Humira US	Humira US to BI 695501
Total number of patients, N (%)	298 (100.0)	148 (100.0)	147 (100.0)
Patients meeting ACR20 response criteria at Week 24			
Mean number of responders, N (%)	221.4 (74.3)	98.8 (66.8)	106.3 (72.3)
Patients meeting ACR20 response criteria at Week 48			
Mean number of responders, N (%)	202.2 (67.9)	103.9 (70.2)	94.0 (64.0)
Patients meeting ACR50 response criteria at Week 24			
Mean number of responders, N (%)	118.0 (39.6)	55.9 (37.7)	61. 0(41.5)
Patients meeting ACR50 response criteria at Week 48			
Mean number of responders, N (%)	129.2 (43.4)	65.2 (44.1)	60.0 (40.8)
Patients meeting ACR70 response criteria at Week 24			
Mean number of responders, N (%)	43.8 (14.7)	31.1 (21.0)	26.7 (18.1)
Patients meeting ACR70 response criteria at Week 48			
Mean number of responders, N (%)	75.1 (25.2)	32.1 (21.7)	28.9 (19.7)
Change from baseline in DAS28-ESR at Week 24			
Mean change from baseline (SD)	-2.1 (1.2)	-2.1 (1.2)	-2.2 (1.2)
Change from baseline in DAS28-ESR at Week 48			
Mean change from baseline (SD)	-2.4 (1.2)	-2.3 (1.2)	-2.4 (1.2)
Patients with EULAR response at Week 24			
Good response, N (%)	66 (22.1)	42 (28.4)	37 (25.2)
Moderate response, N (%)	193 (64.8)	84 (56.8)	90 (61.2)
No response, N (%)	35 (11.7)	21 (14.2)	20 (13.6)
Patients with EULAR response at Week 48			
Good response, N (%)	92 (30.9)	52 (35.1)	46 (31.3)
Moderate response, N (%)	164 (55.0)	70 (47.3)	77 (52.4)
No response, N (%)	27 (9.1)	18 (12.2)	15 (10.2)

Missing data were imputed according to NRI and/or MI.

Source data: [c15074004, Tables 14.2.3.1, 14.2.3.4, 14.2.3.5, 14.2.3.7, 14.2.3.8, 14.2.3.21, 14.2.3.27]

Efficacy Assessment by ADA Status

The applicant provided a thorough review concerning ADA status and its correlation with ACR20 response at Week 24. One could argue that despite the numerically slightly higher impact of ADA positivity on ACR20 responses on Cyltezo versus US Humira treated patients a disadvantage for ADA positive patients treated with Cyltezo is not recognisable.

ACR20 responses:

- ADA positive patients: Cyltezo 69.3% versus US Humira 64.6%; numerical difference 4.7%
- ADA negative patients: Cyltezo 78.4% - versus US Humira 71.3%; numerical difference 7.1%

Table 21 ACR20 response at Week 24 by ADA and nAb measurement at Week 24, LOCF + NRI (FAS/SAF)

Subgroup variable	N		Week 24 ACR20 response rate (%)	
Subgroup category	BI 695501	Humira US	BI 695501	Humira US
Overall trial population (FAS)	321	318	69.0	64.6
ADA positive at Week 24 (SAF)	127	144	69.3	64.6
Titer: low (Q1)	32	39	75.0	66.7
Titer: medium (Q2-Q3)	59	69	72.9	66.7
Titer: high (Q4)	36	36	58.3	58.3
ADA negative at Week 24 (SAF)	167	157	78.4	71.3
nAb positive at Week 24 (SAF)	48	61	60.4	55.7
nAb negative at Week 24 (SAF)	246	240	77.2	71.3

For ADA: the "not reportable" category is not shown in the table (a total of 12 patients); see source outputs for results.
For nAb: the "not reportable" category is not shown in the table (a total of 12 patients); see source outputs for results.
ADA titer: Q1, Q2 to Q3, Q4 were quartiles for ADA titer at Week 24 for patients initially randomized to US-licensed Humira

When looking at titres, it becomes evident that the percentage of ACR 20 responders is higher in the BI 695501 for patients with low [75% vs. 66.7%] and medium titres [72.9% vs. 66.7%], compared to patients treated with US licensed Humira. Interestingly this difference is non existent in patients with high ADA titres. [58.3% vs 58.3%]

Neutralising antibodies seem to dramatically reduce the percentage of ACR20 responders [-16.8% vs -15.6%], however they do so in equal magnitude in both treatments.

While ADA status and quality at week 24 do not cause major differences in similarity of ACR20 at week 24, it was initially unclear whether the same would hold true for high responders (ACR 50 and ACR70). This concern could be resolved in the course of the procedure, where no major differences in ADA status were noted in high responders.

Clinical studies in special populations

Patients enrolled ranged from 21 to 81 years of age. No children or adolescents were included. No studies were made in patients with severe hepatic or renal impairment.

Supportive study(ies)

Trial 1297.11

Trial 1297.11 was a 7-week, open-label, single-arm, uncontrolled, multiple dose trial in patients with moderately to severely active RA using the BI 695501 AI (AI assessment period), followed by an optional 42-week extension phase with BI 695501 PFS (extension phase).

The main objective was to assess the real-life patient handling experience of self-injecting BI 695501 with an AI, in patients with RA and no prior experience in using an AI or pen. This objective aiming to assess the patient´s handling with the device is acknowledged.

The dose of 40 mg BI 695501 was self-injected using an AI by 77 patients (100.0%) on Day 1, 72 patients (93.5%) on Day 15, 73 patients (94.8%) on Day 29, and 73 patients (94.8%) on Day 43. In the AI assessment period, the mean duration of treatment was 41.2 (SD 8.34) days. Overall, the mean duration of treatment was 66.6 (SD 30.71) days.

Endpoints and results:

The **primary endpoint** was the percentage of successful self-injections as reported in the questionnaires completed by both the trial site personnel and the patient. During the period of the trial, patients performed a total of 4 SC injections of trial medication using an AI at the trial site under supervision by the investigator or the qualified trial site personnel. The first injection was considered a training injection and did therefore not contribute to the primary endpoint.

Overall, 216 (99.1%) out of 218 attempted initial self-injections with the AI, performed by 77 patients treated in the AI assessment period, were reported to be successful. In both cases of unsuccessful initial attempts, the patients were able to successfully perform a self-injection with a second autoinjector immediately after the first injection attempt.

The **secondary endpoint** of the AI assessment period was the frequency of any AI handling event (e.g. problems when removing the cap) during the self-injection process as reported in the questionnaires completed by both the qualified trial site personnel and the patient. If an AI handling event was reported in at least one questionnaire, it was counted as an AI handling event. For 2 out of 77 patients treated in the AI assessment period, AI handling events, and thus an unsuccessful self-injection with the AI, were reported. Both patients were able to perform a successful self-injection with a second AI immediately after the first injection attempt. Both AIs were returned to the sponsor for visual inspection. None of the returned AIs and complaints could be confirmed as a technical complaint. The returned complaints are hence attributed to potential use errors.

A further endpoint was AI robustness, assessed for the first approximately 100 AIs received by the Sponsor that were functioning normally. Autoinjector robustness was evaluated through visual inspection by the BI device engineer, who inspected the AIs for any signs of damage, malfunctioning, or injection incompleteness. All 109 AIs passed all 5 inspection criteria for damage, malfunctioning, or injection incompleteness. Thus, the AIs were found to be robust after real-life usage.

As a conclusion, results show that patients could successfully inject the full dosage using the AI, with only single occurrences of handling events. Furthermore, no damage, malfunctioning or injection incompleteness of the device could be seen.

Extrapolation of indications

Quality

From a quality perspective (including the *in-vitro* assays) the applicant performed a sound and comprehensive biosimilarity exercise. A large number of EU Humira (and US Humira) lots were extensively characterised to establish min-max similarity ranges. More than 100 relevant quality attributes of the adalimumab molecule were investigated using an exhaustive panel of orthogonal standard and state-of-the art techniques. An extensive analysis of the N-glycosylation variants including those known to impact Fc-mediated effects was part of the similarity assessment. Beside physicochemical features the biological profile of adalimumab was covered by a broad panel of cell-based biological assays and binding assays. These covered the main mode of action (binding/neutralisation of sTNFα/mTNFα) and other relevant (ADCC, CDC, reverse signalling) and potential mechanisms (e.g. Fcγ-receptor binding triggering regulatory macrophages, ADCP) for adalimumab in the various indications.

Some minor quantitative differences were observed between BI 695501 and Humira which included also reverse signalling activity, CDC, ADCP, and binding to Fcγ-receptors. These differences were

adequately justified and do not preclude a similarity conclusion. Overall, the analytical and *in vitro* pharmacological results support extrapolation to all targeted indications.

It is generally believed that neutralisation of sTNFα/mTNFα is of key relevance for the efficacy of adalimumab in the rheumatology or psoriasis indications by preventing TNF from inducing TNFR-mediated pro-inflammatory effects; involvement of this mode of action is also likely for IBD, HS and UV.

For its effects in IBD it is currently considered that additional mechanisms (ADCC, CDC, reverse signalling upon binding to mTNFα) are likely involved. These mechanisms may also contribute in case of HS and UV. Involvement of other functions like ADCP or regulatory macrophages is under scientific debate and far less clear. The relevance of these mechanisms in IBD, HS, and UV is mainly deducted from the differential pattern of authorised indications of other TNFα antagonists, and this is in principle agreeable. However, it needs to be emphasized that the relative contribution of these various effects is currently unknown.

Non Clinical

A comparative assessment of the pharmacokinetic and toxicokinetic parameters of BI 695501 in comparison to Humira in cynomolgus monkeys with three different formulations (TF, AF, CF) did not indicate significant differences with respect to PK. However, these animal studies are of limited relevance with respect to clinical extrapolation due to limited group size, high interindividual variability and interference with ADAs. Immunogenicity in non-human primates is not considered predictive for the clinical situation as ADA a formation is an expected reaction after administration of a human antibody.

In vitro pharmacology assays to compare the PD mechanisms attributed to adalimumab between BI 695501 and Humira were performed using a tiered approach based on the criticality of quality attributes. Paramount importance is conceded to the reported main mechanisms of adalimumab, the neutralization of sTNFα and binding to mTNFα, which could be demonstrated to be similar for BI 695501 and Humira in highly sensitive assays (sTNFα neutralization assay and TNFα binding SPR-based assay). Deduced from clinical findings with different TNFα-targeting modalities (e.g., certolizumab, etanercept) differences in effectiveness were observed in indications other than RA, PsA, PPso and AS (Tracey D. et al., 2008; Taylor P.C. et al., 2010). For the well-known indications binding/neutralization of s/mTNFα has been attributed as the main MoA.

Besides the mTNFα competitive binding assay and SPR-based TNFα affinity assay, reverse signaling, SPR-based FcRn-binding, CD16a-binding, ADCC, CDC and ADCC were performed as Tier 2 assays. In addition, alternative mechanisms of action, such as reverse signalling and Fc-related functions, are considered to contribute to a number of indications, such as CD, UCD, PCD, HS and UV. These additional mechanisms have been addressed in a panel of assays using the commercial formulation of BI 695501. Comparability with Humira could be demonstrated, however, the direct evidence of the Tier 2 and Tier 3 (binding to CD1q, CD16a, CD16b, CD32a, CD32b/c and CD64a) assays maintains to be a matter of research. As such the selected evaluation criteria are acceptable.

Clinical

There are no significant differences in the pharmacokinetic characteristics of Humira between healthy subjects and patients across the various approved Humira indications; hence comparatively evaluating PK in single dose healthy volunteer studies and in a subset of patients with RA provides a solid base for extrapolation. In the absence of immunosuppressive concomitant medication, steady-state trough concentrations of Humira are similar across indications (RA, Pso, PsA, AS, CD, UC, UV) treated with 40 mg Humira every other week, ranging from 5 to 10 µg/mL. In HS, where Humira is given once weekly,

slightly higher exposure levels are observed, ranging from 8 to 10 µg/mL. Steady-state trough concentrations are also comparable between adults and paediatric patients.

PK evaluation for BI 695501 contains data from trials in healthy volunteers (in the absence of immunosuppressive concomitant medication) as well as from patients with RA with background MTX treatment. Comparable PK of Cyltezo and Humira has principally been demonstrated in both models, a pivotal comparative PK study in healthy volunteers supported by similar results of mean C_{trough} levels in a representative set of patients with RA. Adalimumab serum concentrations are considered to be an important and predictive determinant of adalimumabs efficacy across all its authorised indications. A drug level of 5 µg/mL has been reported to have predictive value of good clinical response, in both RA and PsA patients (Pouw et al., 2015; Vogelzang et al., 2014). Also in CD and UC patients, adalimumab serum levels were related to clinical response (Karimiris et al., 2009; Roblin et al., 2014). Hence, showing PK similarity in two different populations supports the evidence that Cyltezo will demonstrate a similar clinical profile in all indications, for which Humira is indicated.

For the choice of an efficacy and safety model, EU guidance recommends comparative parallel design studies in treatment-naïve patients as the most sensitive design for a premarketing study to assess potential differences in the risk of immunogenicity (EMA "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues"). For the applicant´s pivotal comparative clinical efficacy/safety study the choice of patient population has also been endorsed during scientific advice.

RA is the indication for which Humira obtained initial marketing authorization and it is the indication for which most clinical trial experience has been accumulated, hence external validity of results can be considered high. The disease pathology of RA and the role of TNF-α inhibition are known. Furthermore adalimumab exhibits a reasonable effect size in moderate to severe RA.

Bearing this in mind, the chosen model together with the clinical similarity data is considered sensitive enough to allow for extrapolation to all other indications of Humira.

Safety related outcomes mediated by TNFα suppression are considered comparable across indications. Comparative immunogenicity has clinically been evaluated in two populations (healthy volunteers and patients with RA) in addition to structural and functional testing in earlier development stages.

In summary, the totality of data suggest that Cyltezo is biosimilar to Humira. Complemented by the results obtained by functional assays to comparatively study the mechanism of action proposed for IBD indications, it is considered that the submitted data allows for extrapolation to all other indications.

2.5.1. Discussion on clinical efficacy

One pivotal study was performed to evaluate equivalence in efficacy between BI 695501 and US-licensed Humira in patients with active Rheumatoid arthritis.

Design and conduct of clinical studies

The study was designed to be sufficiently sensitive to detect potential differences in efficacy between Cyltezo and US licensed Humira, in accordance with applicable EMA guidance ("Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues").

Use of US-licensed Humira as the only comparator in this study is deemed acceptable due to a successful bridging exercise on the quality level, indicating similarity between EU and US reference, and successful bridging on PK level as demonstrated in study 1297.8 (see clinical pharmacology).

The choice of a patient population with moderate to severe RA is considered a suitable and sensitive model to study similarity of efficacy between Cyltezo and Humira. Eligibility criteria of study 1297.2 are considered adequate. Baseline characteristics were balanced between the treatment groups regarding age, ethnicity, gender, BMI, and prior exposure to biologics. Baseline disease characteristics in terms of duration and severity of RA were well balanced (at initial and at re-randomisation) and representative for a patient population with moderately to severely active Rheumatoid arthritis.

The primary objective of this study was to demonstrate equivalence of Cyltezo and US-Humira at Week 12 and Week 24 in terms of American College of Rheumatology 20% (ACR20) response rate. Secondary and further objectives included scores such as ACR50, ACR70 and DAS28, responses at weeks 12, 24 and 48, as well as EULAR response, and change in individual ACR parameters among other endpoints of rather exploratory nature. The choice of primary and secondary endpoints is acceptable in principle, despite the limitation that it is hard to define clinically relevant equivalence margins on a responder criterion since relevance cannot be assessed on an individual level.

Choice and analysis of the primary endpoint were subject to several amendments introducing some specifics, which were not discussed in Scientific Advice (nor would they have been endorsed). This mainly concerns the initial choice of ACR20 instead of DAS28 at Week 12 as a co-primary endpoint, where an asymmetric equivalence margin was introduced [-12%; 15%]. Furthermore, a 90% CI was used for this measure while using 95% CIs for the co-primary endpoint at Week 24. Since European biosimilar guidance gives preference to the 95% CI in similarity assessment, the assessment was mainly based on this range for both time points. A blinded evaluation of sample size assumptions by an independent IDMC has been performed and possible consequences for the type I error rate have been addressed.

As regards statistical analysis, the methods have been clearly and sufficiently described in the analysis plans and are overall appropriate. The primary efficacy analysis for the two time points based on the FAS (treatment difference of all randomised subjects at the two time points irrespective of whether some subjects have discontinued treatment) and the PPS (treatment difference if all patients adhered to the initial treatment) are considered equally important. The definition of these analyses has been discussed and a comprehensive sensitivity analysis has been presented demonstrating robustness of the primary efficacy analysis.

Protocol deviations and use of permitted/prohibited concomitant medication seem equally distributed between treatment groups, with only minor differences: Fewer patients with protocol deviations leading to exclusion from the PPS in the BI 695501 group (4.0%) as opposed to the US-licensed Humira group (7.9%). This difference stems from an imbalance in the most common deviation “restricted DMARD therapy prior to primary endpoint assessment” (Week 24). Severe violations of this criterion were 2.8% more common in the Humira group. The applicant provided results of primary measures for the FAS and the PPS, supporting that small differences in protocol deviations/use of prohibited concomitant medication do not to hamper similarity assessment. All other protocol deviations leading to exclusion from the PPS were very rare (≤ 9 patients in total).

After 24 weeks (primary endpoint), patients on US-Humira treatment were re-randomized 1:1 to either continue receiving Humira or to switch to Cyltezo till end of study (Week 48). From an efficacy point of view this is acceptable since enough patients (n=148) remained on US -Humira treatment.

In summary, the model chosen by the applicant can be considered sufficiently sensitive to study similarity of efficacy between Humira and Cyltezo. Considerate overviews of time versus response over the whole study duration were also provided in the course of the procedure.

Efficacy data and additional analyses

BI 695501 was similar to Humira in the proportion of patients achieving ACR after 12 weeks and 24 weeks in the primary analysis (FAS) and the sensitivity analysis (PPS): The treatment difference in ACR20 response rate at Week 12 was 5.9%, the 95% CI of the adjusted treatment difference [-2.2; 14.0] was completely contained within the pre-defined equivalence margin of [−12%;15%]. After 24 weeks the treatment difference in ACR20 response was 4.5%; the 95% CI of the adjusted treatment difference [-3.5;12.4] completely within the equivalence margin of [−15%;15%].

These results indicate similarity, however with a trend for a higher response in BI 695501 treated patients. Similarity was also shown in the PPS: the difference between both products in ACR20 at Week 12 and 24 ranges from 4.2% (12 weeks) to 1.6% (24 weeks). At both time points the adjusted treatment difference was completely contained within the pre-defined equivalence margins.

In order to get a more thorough impression whether the efficacy profile of Cyltezo is truly comparable to Humira, as opposed to only comparing two certain time points for a specific measure, the Applicant was asked to provide efficacy data over time for ACR20, but also for ACR 50 and ACR70. The provided efficacy-over time graphs and tables show overall similarity between Cyltezo and Humira US across the different measures and time points. A few uncertainties are however noticed: the primary endpoint results for ACR20 at week 12 and 24 display a trend for higher efficacy of Cyltezo. This trend is similarly seen at week 4, which is considered a very sensitive time point, since it is in the steep part of the dose response curve: 6.9% more patients in the Cyltezo than in the Humira arm reach ACR20 at week 4 (no confidence intervals provided). Differences between the two arms are much smaller however when looking at ACR50 (1.02%) and ACR 70 (-0.65%) and do not persist over time.

Data presented in the final study report suggests that the numerical imbalances observed at Week 12 and 24 for ACR20 and at Week 24 for ACR70 do not persist in the long term. The mean proportion of patients meeting the ACR20 response criteria at Week 48 was 67.85%, 70.23% and 63.95% in the BI 695501 to BI 695501, US-Humira to US-Humira and US-Humira to BI 695501 group, respectively. Regarding durability of efficacy in ACR20 response it is noted that 74.3% of patients in the Cyltezo arm reached ACR20 at week 24, but only 67.9% at week 48. The same tendency is noted for patients who switched from US Humira to Cyltezo (72.3% w24 vs. 64% at w48), while ACR20 seems to increase over time for US Humira (66.8% w24 vs. 70.2% w48). This finding is however not confirmed by other efficacy measures like DAS-ESR, EULAR response, ACR 50m and ACR 70, and is also due to its small magnitude most likely a chance finding.

Data for ACR70 over the whole study duration was requested, since a higher response rate for ACR70 was noted for US-Humira at Week 24 (18.16% vs. 13.75%). The ACR 70 vs. time graph clearly illustrates that the imbalance is only notable at Week 24 and is not observed at other time points, namely Week 4, 12, 40, and 48. At end of study, Cyltezo exhibits a slightly higher ACR 70 response rate (25.22% vs. 21.69). Overall these results suggest similarity in ACR70 between Cyltezo and Humira.

Most other secondary and further endpoints (such as DAS28-ESR, DAS28-CRP, and the change in individual ACR parameters) can be considered supportive of similarity although no confirmatory equivalence testing was applied.

Efficacy and ADA response

The applicant provided a thorough review concerning ADA status and its correlation with ACR20 response at Week 24. At this specific time point, despite the numerically slightly higher impact of ADA positivity on ACR20 responses on Cyltezo- versus Humira treated patients a disadvantage for ADA positive patients treated with Cyltezo is not recognisable.

ACR20 responses:

- ADA positive patients: Cyltezo 69.3% versus US Humira 64.6%; numerical difference 4.7%
- ADA negative patients: Cyltezo 78.4% - versus US Humira 71.3%; numerical difference 7.1%

Neutralising antibodies seem to dramatically reduce the percentage of ACR20 responders, however to a similar degree in both treatments [-16.8% vs. -15.6%].

The Applicant was asked to provide graphs and tables for ACR 20/50/70 over time for the ADA positive and negative cohort. Tables for the same efficacy measures evaluating potential impact of low/medium/high ADA titres on efficacy were also presented. For all three efficacy measures that were evaluated over time (ACR 20/50/70), no relevant differences were noted between Cyltezo and Humira in the ADA positive and the ADA negative subgroup at any given time point. The numerical difference in ACR70 as observed at week 24 in the overall population seems to be derived from the ADA positive collective only. However, also in this subgroup, the numerical difference vanishes towards the end of the study.

When looking at ADA titres it seems that, not surprisingly, high ADA titres cause the highest differences in efficacy as compared to the ADA negative collective. However, these are not more than trends, mostly derived from only a very low number of patients and need to be interpreted with care. The impact on ADA status on efficacy (ACR20/50/70) over time seems to be comparable between treatments.

2.5.2. Conclusions on the clinical efficacy

From a clinical efficacy point of view, data of the comparative efficacy trial in moderate to severe RA supports similarity between Cyltezo and Humira.

2.6. Clinical safety

As outlined in the EMA “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues” (EMEA/CHMP/BMWP/42832/2005 Rev. 1) and “Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues” (EMA/CHMP/BMWP/403543/2010), clinical evidence on comparability/similarity needs to be provided with respect to safety.

Safety data for BI 695501 have been collected in 5 clinical studies:

2 Phase I PK trials:

1297.8: double-blind, randomized, single-dose, parallel-group trial in healthy male volunteers, using the commercial formulation of BI 695501 (PFS).

1297.1: open-label, randomized, single-dose, parallel-group trial in healthy male volunteers, conducted with a trial formulation of BI 695501 (PFS).

1 pivotal Phase III trial:

1297.2: double-blind, randomized, parallel-group, multiple-dose, active comparator trial in patients with moderately to severely active RA receiving MTX (115 sites in 14 countries). Two parallel treatment groups were investigated: BI 695501 and US-licensed Humira.

2 trials supporting the autoinjector:

1297.6: open-label, randomized, single-dose, parallel-group trial in healthy male volunteers. The primary objective was to characterize and compare the PK of BI 695501 (commercial formulation) after subcutaneous injection using either a PFS or an AI.

1297.11: 7-week, open-label, single-arm, uncontrolled, multiple dose trial in patients with moderately to severely active RA using the BI 695501 AI (AI assessment period), followed by an optional 42-week extension phase with BI 695501 PFS (extension phase).

The amount of safety data as well as the duration of the studies is considered adequate and in line with applicable guidance. Safety data were not pooled across trials but analysed by trial. The focus of safety assessment is on study 1297.2.

The analysis of adverse events was based on the concept of treatment-emergent adverse events: all adverse events with onset or with worsening between the date of the first trial drug administration up to the end-of-trial visit (1297.1) or up to 70 days after the date of the last administration (1297.2, 1297.6, 1297.8, and 1297.11) were considered as treatment-emergent.

The analysis of adverse events was furthermore based on the number of patients/subjects with adverse events, not the number of adverse events.

The types of adverse events analysed included all adverse events, serious adverse events, and adverse events leading to discontinuation from trial medication, all adverse events by intensity, investigator-defined drug-related adverse events, and adverse events leading to death. In addition, particular attention was given to adverse events of special interest (AESIs) and other selected adverse events.

The safety endpoint was defined as 'the number/proportion of patients with drug-related AEs during the treatment phase'. Other safety endpoints were the number/proportion of patients with infections/serious infections (seriousness of infection defined as requirement of IV antibiotics fir with treatment and/or meeting seriousness criteria to be qualified as an SAE); who experience anaphylactic reaction; who experience hypersensitivity reactions; and who experience DILI.

Patient exposure

Overall

	N (receiving at least 1 dose)			
	BI 695501	**Humira US**	**Humira EU**	**Total**
Phase I PK Healthy Subjects:				
1297.8 (VOLTAIRE®-PK) completed	108	108	108	**324**
1297.1 * completed	67	62	64	**193**

Phase III efficacy, patients with RA:				
1297.2 (VOLTAIRE®-RA) completed	324	321	0	**645**
Trials supporting the autoinjector				
1297.6 (VOLTAIRE®-AI) completed	AI: 33 PFS: 33	0	0	**66**
1297.11 (VOLTAIRE®-RL) ongoing	70	0	0	**70**
Total	**635**	**491**	**172**	**1298**

* Trial 1297.1 was conducted with a trial formulation (TF) of BI 695501, which was not considered for further development. Safety information from the TF of BI 695501 is only included in this SCS for completeness.

Trial 1297.2

Table: Exposure to trial drug (SAF)

Exposure	Period 1 (Day 1 to Week 24)		Period 2 (Week 24 to Week 58)		Overall (Day 1 to Week 58)	
	BI 695501 (N=324)	Humira US (N=321)	Humira US to Humira US (N=148)	Humira US to BI 695501 (N=146)	BI 695501 continuously (N=324)	Humira US continuously (N=175)
Number of patients treated at (n [%])						
Day 1	324 (100.0)	321 (100.0)	-	-	324 (100.0)	175 (100.0)
Week 2	319 (98.5)	315 (98.1)	-	-	319 (98.5)	169 (96.6)
Week 4	319 (98.5)	313 (97.5)	-	-	319 (98.5)	168 (96.0)
Week 6	317 (97.8)	309 (96.3)	-	-	317 (97.8)	163 (93.1)
Week 12	311 (96.0)	300 (93.5)	-	-	311 (96.0)	155 (88.6)
Week 24	294 (90.7)	288 (89.7)	145 (98.0)	143 (97.9)	294 (90.7)	145 (82.9)
Week 32	-	-	142 (95.9)	142 (97.3)	290 (89.5)	142 (81.1)
Week 34	-	-	144 (97.3)	142 (97.3)	286 (88.3)	144 (82.3)
Week 40	-	-	140 (94.6)	140 (95.9)	282 (87.0)	140 (80.0)
Week 48	-	-	137 (92.6)	131 (89.7)	276 (85.2)	137 (78.3)

In the pivotal trial 1297.2, all safety analyses were carried out using the SAF, which was defined as all patients who received at least one dose of trial drug.

Trials 1297.8 and 1297.1:

All subjects were administered a single SC dose of 40 mg of BI 695501, US-licensed Humira, or EU-approved Humira. In trial 1297.8, 324 healthy volunteers were randomized, while in trial 1297.1, 193 were included. Trial 1297.1 was conducted with a trial formulation of BI 695501.

Trial 1297.6

71 subjects were treated with a single SC dose of 40 mg BI 695501 (PFS: 36 subjects [50.0%], AI: 35 subjects [50.0%]).

Trial 1297.11

A dose of 40 mg BI 695501 was self-injected using an autoinjector by 77 patients on Day 1, 72 patients (93.5%) on Day 15, 73 patients on Day 29, and 73 patients on Day 43.

Overall, it is concluded that the number of patients included in the studies, as well as the dose and duration of exposure to BI 695501 and/or Humira US/EU is considered adequate for the purpose of a safety evaluation.

Adverse events

PIVOTAL TRIAL 1297.2

AE results have been presented separately for 3 different treatment periods:

Overall: cumulative AEs are displayed for patients who continuously received BI 695501 or continuously received US-licensed Humira, from Day 1 up to Week 58;

Period 1: safety data from the first administration of trial drug on Day 1 up to trial drug administration at Week 24;

Period 2: safety data from the administration of trial drug at Week 24 Week 58; it focuses on patients who were initially randomized to US-licensed Humira and either continued taking US-licensed Humira or had a single transition from US-licensed Humira to BI 695501.

The separate illustration of safety results by treatment period is endorsed. The focus of assessment was on the overall safety analysis.

Overview of AEs

The **overall** analysis showed that the frequency of patients with at least 1 AE was similar between the BI 695501 continuously and the US-licensed Humira continuously treatment groups (59.6% vs. 60.0%). The majority of AEs were non-serious. Investigator-assessed drug-related AEs (safety endpoint) and AEs leading to discontinuation of trial medication were also reported for similar proportions of patients (19.1% vs. 22.9%; and 4.0% vs. 6.9%, respectively). Slightly lower proportions of patients in the BI 695501 continuously group than in the US-licensed Humira continuously group were reported with SAEs (5.6% vs. 9.7%). Few of these patients were reported with drug-related SAEs (1.2%). No patient died during the course of the trial.

Table: Trial 1297.2, overview of TEAEs in continuous treatment groups (SAF)

	BI 695501 continuously (N=324)	Humira US continuously (N=175)
Number of patients (n [%]) with:		
At least one TEAE	193 (59.6)	105 (60.0)
At least one TEAE related to trial drug	62 (19.1)	40 (22.9)
At least one non-serious TEAE	188 (58.0)	102 (58.3)
At least one serious TEAE	18 (5.6)	17 (9.7)
At least one serious TEAE related to trial drug	2 (0.6)	6 (3.4)
A TEAE leading to trial drug discontinuation	13 (4.0)	12 (6.9)
A TEAE leading to death	0	0

Source: Table 14.3.1.1
n = number of patients; N = number of patients in SAF; SAF = safety set; TEAE = treatment-emergent adverse event.
Percentage of patients was calculated relative to the total number of patients in the SAF.
Relationship to trial drug was reported according to Investigator judgement.

In **Period 1**, the frequencies of patients with at least 1 AE, serious AEs, investigator-assessed drug-related AEs, AEs leading to discontinuation and serious drug-related AEs were similar between the BI 695501 treatment group and the US-licensed Humira treatment group, with lower AEs in the biosimilar arm in general (refer to table below).

Table: Overview of TEAEs in Period 1 (up to Week 24) (SAF)

	BI 695501 (N=324)	Humira US (N=321)
Number of patients (n [%]) with:		
At least one TEAE	138 (42.6)	148 (46.1)
At least one TEAE related to trial drug	36 (11.1)	44 (13.7)
At least one non-serious TEAE	135 (41.7)	141 (43.9)
At least one serious TEAE	12 (3.7)	18 (5.6)
At least one serious TEAE related to trial drug	1 (0.3)	5 (1.6)
A TEAE leading to trial drug discontinuation	8 (2.5)	11 (3.4)
A TEAE leading to death	0 (0.0)	0 (0.0)

Source: Table 14.3.1.6.
n = number of patients; N = number of patients in SAF; SAF = safety set; TEAE = treatment-emergent adverse event.
Percentage of patients was calculated relative to the total number of patients in the SAF.
Relationship to trial drug was reported according to Investigator judgement.

In **Period 2** the frequencies of patients within the different AE categories were as follows:

Table: Overview of TEAEs in Period 2 (from Week 24 up to Week 58)-(SAF)

	Humira US to Humira US (N=148)	Humira US to BI 695501 (N=146)
Number of patients (n [%]) with:		
At least one TEAE	51 (34.5)	62 (42.5)
At least one TEAE related to trial drug	17 (11.5)	17 (11.6)
At least one non-serious TEAE	51 (34.5)	59 (40.4)
At least one serious TEAE	5 (3.4)	6 (4.1)
At least one serious TEAE related to trial drug	2 (1.4)	0 (0.0)
A TEAE leading to trial drug discontinuation	1 (0.7)	6 (4.1)
A TEAE leading to death	0 (0.0)	0 (0.0)

Source: Table 14.3.1.14
n = number of patients; N = number of patients in SAF; SAF = safety set; TEAE = treatment-emergent adverse event.
Percentage of patients was calculated relative to the total number of patients in the SAF.
Relationship to trial drug was reported according to Investigator judgement.

In conclusion, the summary results of TEAE suggest similarity. The focus of this assessment was mainly laid on the overall analysis (BI 695501 or Humira continuously). Nevertheless it is noted that in

Period 2, the frequency of patients with at least 1 AE was slightly higher for patients who were re-randomized to BI 695501.

Investigator-assessed drug-related AEs (Safety endpoint)

The proportion of patients with investigator-assessed drug-related AEs during the treatment period was defined as a secondary safety endpoint.

In the **overall** analysis, the frequencies of investigator-assessed drug-related AEs were reported to be 19.1% for the BI 695501 continuously group and 22.9%for the Humira US continuously group (see table below).

Most patients with AEs assessed as drug-related by the investigator were reported in the SOC 'infections and infestations': continuous BI 695501 11.7%; continuous US-licensed Humira 9.1%. While this represents a slight difference between both arms, it is however not considered clinically relevant. At the PT level, the most frequently reported investigator-assessed drug-related AEs were 'bronchitis' and 'nasopharyngitis'; both AEs were reported in similar proportions of patients in the BI 695501 continuously group and in the US-licensed Humira continuously group.

Drug-related AEs associated with injection site reactions were reported for slightly more patients in the US-licensed Humira continuously group than in the BI 695501 continuously group. For all other investigator-assessed drug-related AEs reported in >1% of patients, no clinically relevant differences in the frequencies between both treatment groups were observed.

Table: Frequency of Investigator-assessed drug-related TEAEs overall by SOC and PT with an incidence of ≥ 1% based on preferred term level (up to Week 58) (SAF)

	BI 695501 continuously (N=324)		Humira continuously (N=175)	
	n	(%)	n	(%)
Number of patients with at least one related TEAE	62	(19.1)	40	(22.9)
Infections and infestations	38	(11.7)	16	(9.1)
Upper respiratory tract infection	5	(1.5)	1	(0.6)
Nasopharyngitis	4	(1.2)	5	(2.9)
Pharyngitis	3	(0.9)	2	(1.1)
Bronchitis	10	(3.1)	4	(2.3)
Sinusitis	4	(1.2)	2	(1.1)
Oral herpes	4	(1.2)	0	(0.0)
Acute sinusitis	1	(0.3)	2	(1.1)
Pneumonia	0	(0.0)	4	(2.3)
Nervous system disorders	4	(1.2)	2	(1.1)
Headache	4	(1.2)	2	(1.1)
Gastrointestinal disorders	2	(0.6)	6	(3.4)
Nausea	0	(0.0)	3	(1.7)
Skin and subcutaneous tissue disorders	5	(1.5)	7	(4.0)
Urticaria	0	(0.0)	3	(1.7)
General disorders and administration site conditions	6	(1.9)	10	(5.7)
Injection site reaction	3	(0.9)	3	(1.7)
Injection site erythema	0	(0.0)	3	(1.7)
Injection site pruritus	0	(0.0)	4	(2.3)
Injection site pain	1	(0.3)	2	(1.1)
Investigations	14	(4.3)	6	(3.4)
Alanine aminotransferase increased	4	(1.2)	3	(1.7)
Neutrophil count decreased	1	(0.3)	2	(1.1)

Source: Table 14.3.1.3

n = number of patients; N = number of patients in SAF; SAF = safety set; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Percentage of patients was calculated relative to the total number of patients in the SAF.

TEAEs with a missing relationship were classified as related to trial drug. Patients with one related TEAE and one unrelated TEAE were counted once in the related causal relationship category.

AEs by intensity

AEs were classified as mild, moderate, or severe.

In the **overall** analysis, mild, moderate, and severe TEAEs were reported by similar proportions of patients within the continuous treatment groups. Moderate TEAEs were reported in 27.2% of patients in the BI 695501 continuously group and 28.6% of patients in the US-licensed Humira continuously group. Severe TEAEs were reported in 3.4% of patients in the BI 695501 continuously group and 5.1% of patients in the US-licensed Humira continuously group.

Adverse events of special interest (AESI), other safety endpoints and further selected AEs

AEs that were considered of special interest (AESIs), based on knowledge from other compounds of the same class or on universal concern (e.g. hepatic impairment), were evaluated in trial 1297.2.

Investigator-reported AESIs: these AESIs were reported using the following method: AESIs were collected via a tickbox on the eCRF and this was based on the Investigator's opinion.

Investigator-reported AESIs and CTP-specified: these AESIs were classified as events that were both collected via a tickbox on the eCRF and also met objective criteria (e.g. classification under specific SOCs and SMQs). They could be classified as serious or non-serious but all AESIs had to be reported in an expedited manner similar to SAEs on an SAE form.

The following events were defined as "Investigator-reported protocol-specified AESI": Serious infections, hypersensitivity reactions, anaphylactic reactions and drug-induced liver injury (DILI).

Other safety endpoints: these events were classified via objective criteria only (e.g. classification under specific SOCs and SMQs), irrespective of the Investigator's assessment.

The following events were defined as "Other safety endpoints": Serious infections, hypersensitivity reactions, drug-induced liver injury, and infections and injection site reactions.

Further events of interest: these events were not pre-specified in the CTP, but were identified for the class of drugs employed in this trial.

In general, the BI 695501 continuously and US-licensed Humira continuously groups were similar with regard to the proportions of patients reported with AESIs, other safety endpoints, and further selected AEs, with the exception of haematological disorders (please see below).

The proportion of patients with at least 1 ***investigator-reported protocol-specified AESI*** was slightly lower in the BI 695501 continuously treatment group (1.2 %) than in the US-licensed Humira continuously treatment group (6.3 %). These proportions were generally equally distributed across the different AESIs, with a slightly higher number of patients with 'infections and infestations' and 'injection site reactions' for the Humira group in Period 1.

Overall, 1 patient had an anaphylactic reaction AESI in the US-licensed Humira continuously group in Period 1. The event was reported as an SAE.

For most of the ***other safety endpoints***, the proportion of patients with serious infections (0.6% versus 4.0%), hypersensitivity reactions (2.8% versus 4.6%), and injection site reactions (1.5% versus 5.1%) was lower in the BI 695501 than in the Humira US continuously group. Infections were the most commonly reported other safety endpoint and were reported for a similar proportion of patients in each group (35.2% and 34.3%, respectively). DILI and anaphylactic reactions were only single occurrences in both arms.

Table: Overview of AESIs and other safety endpoints (up to Week 58) (SAF)

Analysis datasets	Period 1 (Day 1 to Week 24)		Period 2 (Week 24 to Week 58)		Overall (Day 1 to Week 58)	
	BI 695501 n (%)	Humira n (%)	Humira to Humira n (%)	Humira to BI 695501 n (%)	BI 695501 continuously n (%)	Humira continuously n (%)
Number of patients with at least one AESI reported by Investigators[a]	7 (2.2)	16 (5.0)	3 (2.0)	2 (1.4)	9 (2.8)	15 (8.6)
Number of patients with at least one AESI reported by Investigators[a] and CTP-specified[b]	3 (0.9)	11 (3.4)	2 (1.4)	1 (0.7)	4 (1.2)	11 (6.3)
At least one serious infection AESI	1 (0.3)	8 (2.5)	1 (0.7)	1 (0.7)	1 (0.3)	7 (4.0)
At least one hypersensitivity reaction AESI	1 (0.3)	4 (1.2)	1 (0.7)	0 (0.0)	2 (0.6)	5 (2.9)
At least one DILI AESI	1 (0.3)	0	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
At least one anaphylactic reaction AESI	0	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Number of patients with at least one other safety endpoint [b]						
Infection	71 (21.9)	83 (25.9)	28 (18.9)	33 (22.6)	114 (35.2)	60 (34.3)
Serious infection	1 (0.3)	8 (2.5)	1 (0.7)	1 (0.7)	2 (0.6)	7 (4.0)
Hypersensitivity reaction	7 (2.2)	8 (2.5)	2 (1.4)	2 (1.4)	9 (2.8)	8 (4.6)
DILI	2 (0.6)	0	0 (0.0)	0 (0.0)	3 (0.9)	0 (0.0)
Injection site reaction	5 (1.5)	10 (3.1)	2 (1.4)	0 (0.0)	5 (1.5)	9 (5.1)
At least one TEAE Occurring During 10 Weeks After Re-Randomization	-	-	25 (16.9)	28 (19.2)	62 (19.1)	25 (14.3)
At least one AE occurring after the last injection for subjects discontinued due to lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
At least one non-serious adverse events leading to discontinuation of treatment	2 (0.6)	7 (2.2)	1 (0.7)	2 (1.4)	4 (1.2)	8 (4.6)

Source: Table 14.3.1.22, Table 14.3.1.28, and Table 14.3.1.48

AESI = adverse event of special interest; DILI = drug-induced liver injury; N = number of patients; SAF = safety set; BIcMQs = BI customized MedDRA query; SMQ = Standardized MedDRA Queries; eCRF = electronic case report form; SOC = system organ class. Percentage of patients was calculated relative to the total number of patients in the SAF.

(a) Event equal to AESI equal to 'yes' on the eCRF

(b) Identified based on objective criteria (e.g. SMQs/BIcMQs) (see Section 9.7.1.3.5.2).

The BI 695501 continuously and US-licensed Humira continuously groups were similar with regard to the proportions of patients reported with ***further events of interest*** in each category with the exception of 'hematological disorders' and 'bone fractures'. For more details, please see below.

Furthermore, 'systemic lupus erythematosus' was reported for 1 patient in the BI 695501 group in Period 1. The AE was classified as serious and assessed as not related to trial drug by the investigator.

Malignancies were reported for 2 patients in the US-licensed Humira group in Period 1: 'Non-Hodgkin's lymphoma' and 'breast cancer'; both AEs were classified as serious and not related to trial drug by the investigator.

Table: Overview of all further events of interest (up to Week 58) (SAF)

Analysis datasets	Period 1 (Day 1 to Week 24)		Period 2 (Week 24 to Week 58)		Overall (Day 1 to Week 58)	
	BI 695501 n (%)	Humira n (%)	Humira to Humira n (%)	Humira to BI 695501 n (%)	BI 695501 continuously n (%)	Humira continuously n (%)
Number of patients with at least one						
HBV reactivation	0	0	0	0	0	0
Hematological disorder	10 (3.1)	4 (1.2)	4 (2.7)	3 (2.1)	17 (5.2)	5 (2.9)
Neurological events (demyelinating disorders)	0	0	0	0	0	0
Systemic lupus erythematosus	1 (0.3)	0	0	0	1 (0.3)	0
Sarcoidosis	0	0	0	0	0	0
Stevens-Johnson syndrome	0	0	0	0	0	0
Erythema multiforme	0	0	0	0	0	0
Autoimmune hepatitis	0	0	0	0	0	0
Malignancies	0	2 (0.6)	0	3 (2.1)	0	2 (1.1)
Congestive heart failure	0		0	0	0	0
Fracture	3 (0.9)	1 (0.3)	0	1 (0.7)	7 (2.2)	0 (0.0)

Source: Table 14.3.1.22, Table 14.3.1.28, and Table 14.3.1.48
HBV = hepatitis B virus; n = number of patients; SAF = safety set.
Percentage of patients was calculated relative to the total number of patients in the SAF.

Haematological disorders

The higher proportion of patients with 'haematological disorders' in the BI 695501 continuously group than in the US-licensed Humira continuously group was driven by events reported in the medical concept of anaemia. The **PTs 'anaemia'** and **'haemoglobin decreased'** were exclusively reported for patients in the BI 695501 continuously group.

All of these AEs were non-serious and of mild (8 patients) or moderate (2 patients) intensity, and none of them led to discontinuation of trial medication. One case of decreased haemoglobin was assessed as drug related by the investigator. Five of the patients reported with 'anaemia' or 'decreased haemoglobin' had haemoglobin levels below the lower limit of normal at screening and/or baseline. However, there were no protocol violations regarding the inclusion/exclusion criteria.

Taking also into account the higher frequencies of bone fractures and, most importantly, positive TB tests (the latter being a new finding reported during the evaluation procedure), there was initially concern about the comparative safety profile. For better traceability, the Company was asked to elaborate the totality of medical information related to risk-factors for anaemia/decreased Hb, bone fractures, and TB, for patients under question. The Company showed that risk factors were generally equally distributed over the treatment arms and that no explanation for the observed differences could be found at the population level.

It is noted that the listed factors indeed represent risk factors for anaemia/bone fracture/TB, and also agreed that the relative proportions of patients with these events (and the differences between treatment arms) are rather small, due to the considerably lower number of patients in the US-Humira continuous arm as compared to the BI 695501 continuous arm. Against this background the observed differences are attributed to chance and are hence not considered a finding questioning similarity between the treatment arms.

Bone fractures

Overall, a total of 9 patients (1.4%) were reported with bone fractures; 7 patients in the BI 695501 continuously treatment group, 1 patient who was treated with BI 695501 in Period 2 after re-randomization from US-licensed Humira, and 1 patient who was treated with US-licensed Humira in Period 1

Of the 8 patients who experienced bone fracture while on treatment with BI 695501, 4 patients were ≥ 64 years and postmenopausal, 6 patients had received long-term treatment with glucocorticoids, and 5 patients had osteoporosis or osteopenia. None of the reported bone fracture adverse events was assessed as drug related by the investigators. In total, 5 patients were reported with SAEs and 5 patients with non-serious AEs. All 5 cases of SAEs (femoral neck fracture, lumbar vertebral fracture, rib fracture, ulna fracture, left hip fracture) were following a road traffic accident, fall, or slipping on wet floor. The 5 cases of non-serious AEs were pelvic fracture (mild intensity), wrist fracture (mild intensity), radius fracture (mild intensity), foot fracture (2 cases of moderate intensity), spinal compression fracture (1 moderate and 1 severe intensity).

The exposure-adjusted incidence rate of 20.8 per 1000 patient-years for all bone fractures reported in the BI 695501 continuously treatment group is within the range of bone fracture risk in the general population of 8.5 and 36.0 per 1000 patient-years although for patients with RA, a 2- to 3-fold increased risk of fractures is known. Furthermore, the frequency of non-spontaneous bone fractures in the BI 695501 continuously treatment group (N=324) is in line with historical data from Humira (expected as per the Humira USPI at a frequency of <5% in patients with RA).

Nevertheless, the difference between the treatment arms was considered noteworthy and the Applicant was therefore asked to provide comparative information relating to risk factors for these events. The same comments as for the anaemia cases apply (please refer to the section above): the observed differences might be attributable to chance and are not considered a finding questioning similarity between the treatment arms.

AEs occurring after the last injection for patients who discontinued due to lack of efficacy

No TEAEs occurred after the last injection for patients who discontinued due to lack of efficacy.

PHASE I TRIAL 1297.8

In trial 1297.8, the proportions of subjects reported with at least 1 AE, AEs assessed as drug-related, SAEs and AESIs were similar across the 3 treatment groups. The majority of AEs were of mild or moderate intensity. No death was reported during the trial.

Table: Summary of adverse events in the Phase I PK trial 1297.8 – SAF

Number of subjects, N (%)	BI 695501	Humira US	Humira EU
Total number of subjects	108 (100.0)	108 (100.0)	108 (100.0)
Subjects with any AE	76 (70.4)	79 (73.1)	77 (71.3)
Drug-related AEs[1]	21 (19.4)	29 (26.9)	28 (25.9)
Severe AEs	4 (3.7)	1 (0.9)	0
SAEs	3 (2.8)	3 (2.8)	2 (1.9)
Protocol-specified AESIs[2]	2 (1.9)	2 (1.9)	1 (0.9)

[1] As assessed by the investigator
[2] For the definition of protocol-specified AESIs, see Table 50

The **most common AEs** were 'headache' and 'upper respiratory tract infection', with comparable frequencies in the 3 treatment groups (Headache: 23.1, 23.1, 25.9%; upper respiratory tract infection: 17.6, 15.7, 20.4%; for BI 695501, Humira US, or Humira EU, respectively).

AEs of severe intensity were single occurrences of 'ankle fracture', 'concussion', 'joint dislocation', and 'abdominal pain' in the BI 695501 treatment group and a single occurrence of 'laceration' in the

US-licensed Humira treatment group. It is commented that except from one patient, these patients in the BI 695501 treatment group showed orthopaedic traumata. Please refer to assessor´s comment on AEs in trial 1297.2.

Most **AEs assessed as drug-related** by the investigator were reported in the SOC 'nervous system disorders' (BI 695501: 7.4%, US-licensed Humira: 11.1%, EU-approved Humira: 12.0%), which was mainly driven by the PT 'headache'.

The reported **protocol-specified AESIs** were 'injection site hypersensitivity' (2 subjects) in the BI 695501 group, 'hypersensitivity' (1 subject) and 'urticaria' (1 subject) in the US-licensed Humira group, and 'injection site hypersensitivity' (1 subject) in the EU-approved Humira group. All AESIs were of mild or moderate intensity and were considered drug related by the investigator. No AESIs were reported for subjects with ADA positive results on Day 8. The 2 serious cases of 'appendicitis' that were reported for 2 subjects in the US-licensed Humira group were not reported as AESIs by the investigators. As serious infections qualify as an AESI, they were classified as such by the sponsor irrespective of the investigators' assessment.

The assessment of **local tolerability** based on swelling, induration, heat, redness, pain, or other findings resulted in the BI 695501 group in 2 subjects with findings, in the US-licensed Humira group in 2 subjects with findings, and in the EU-approved Humira group in 4 subjects with findings.

In conclusion, the comparison of AEs between Humira US and Humira EU shows similar frequencies of subjects with any AE, drug-related, severe, serious AEs and AESIs. This finding supports the concept of bridging from the EU- to the US-licences reference product, and vice versa.

PHASE I TRIAL 1297.1

Trial 1297.1 was conducted with a trial formulation (TF) of BI 695501 that was not considered for further development.

The majority of subjects were reported with at least 1 AE during the course of the trial. Slightly higher proportions of AEs in general, drug-related AEs and severe AEs were reported for the BI 695501 group than for the US-licensed Humira or EU-approved Humira treatment groups.

TRIALS SUPPORTING THE AUTOINJECTOR: 1297.6 AND 1297.11

Trial 1297.6

Overall summary of AEs in the AI assessment period of trial 1297.6 is provided in the table:

	BI 695501 PFS (N=36)	BI 695501 AI (N=35)	Total (N=71)
Number of subjects (n [%]) with:			
At least one TEAE	29 (80.6)	29 (82.9)	58 (81.7)
At least one TEAE related to trial drug	16 (44.4)	20 (57.1)	36 (50.7)
At least one non-serious TEAE	29 (80.6)	29 (82.9)	58 (81.7)
At least one serious TEAE	0	0	0
At least one serious TEAE related to trial drug	0	0	0
A TEAE leading to death	0	0	0

Source: Table 14.3.1.1
AI = autoinjector; PFS = prefilled syringe; TEAE = treatment-emergent adverse event.
MedDRA Version 19.1 was used to code adverse events.
% = percentage of subjects calculated relative to the total number of subjects in the analysis set (N).
TEAEs are defined as AEs that started or worsened in intensity on or after the first and single dose of trial medication up to 10 weeks (70 days) post dose.
A related TEAE is defined as a TEAE with a relationship to trial drug according to the Investigator.

Trial 1297.11

Overall summary of AEs in the AI assessment period of trial 1297.11 is provided in the table:

Number of patients, N (%)	BI 695501 AI
Total number of patients	77 (100.0)
Patients with any AE	31 (40.3)
Drug-related AEs[1]	9 (11.7)
Severe AEs	2 (2.6)
SAEs	2 (2.6)
AEs leading to discontinuation of trial medication	2 (2.6)
Protocol-specified AESIs[2]	2 (2.6)

[1] As assessed by the investigator
[2] For the definition of protocol-specified AESIs, see Table 52

As can be seen from the tables, there was a large difference in the proportion of patients with any AEs between trials 1297.6 and 1297.11. It was questioned how far the AE incidences of around 80% in trial 1297.6 versus a frequency of around 40% in trial 1297.11 are plausible. The Company was asked to discuss this. With the Day 121 Responses, the Company discussed plausible reasons for the numerical differences. Especially the facts that trial 1297.6 was conducted in healthy volunteers not used to parenteral therapies and that these patients stayed at the trial site for a 24-hour observation period, in contrast to patients in trial 1297.11, represent convincing arguments.

Serious adverse events and deaths

PIVOTAL TRIAL 1297.2

Overall: The frequency of patients with SAEs who continuously took BI 695501 or Humira US reported in >1% of patients (PT level) in either of the treatment groups is shown in the following table:

	BI 695501 continuously (N=324) n (%)	Humira continuously (N=178) n (%)
Number of patients with at least one SAE	18 (5.6)	17 (9.7)
Infections and infestations	2 (0.6)	7 (4.0)
Pneumonia	0	3 (1.7)
Pyelonephritis acute	0	2 (1.1)

Source: Table 14.3.1.5
n = number of patients; N = number of patients in the analysis set; SAF = safety set; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Percentage of patients was calculated relative to the total number of patients in the SAF.

As can be seen from the table, most frequently reported SAEs were SOC 'infections and infestations', which is in line with that known for the reference product. All other SAEs were individual occurrences.

SAEs assessed as drug related by the investigator were reported for 2 patients (0.6%) in the BI 695501 continuously group and for 6 patients (3.4%) in the US-licensed Humira continuously group, which is also in favour of the biosimilar product.

In **Period 1**, 3.7% SAEs were reported in the BI 695501 group and 5.6% in the US-licensed Humira group. The most common SAEs were reported in the SOC 'infections and infestations' (0.3% for BI 695501 and 2.5% for US-licensed Humira). SAEs assessed as drug related by the investigator were reported for 1 patient (0.3%) in the BI 695501 group and for 5 patients (1.6%) in the US-licensed Humira group.

In **Period 2**, few patients were reported with SAEs (3.4% for Humira US to Humira US; 4.1% for Humira US to BI 695501), and all SAEs reported in either the 'Humira US to Humira US' or in the 'Humira US to BI 695501' group were individual occurrences. SAEs assessed as drug related by the investigator were reported for 2 patients (1.4%) in the 'Humira US to Humira US' group and for none of the patients in the 'Humira US to BI 695501' group.

In conclusion, more SAEs were generally reported for Humira US, which favours BI 695501.

No **deaths** were reported in the trial results included in this submission.

PHASE I TRIAL 1297.8

SAEs were reported for 3 subjects in the BI 695501 group ('concussion': 1 subject, hand and ankle fractures: 1 subject, drug-related 'abdominal pain': 1 subject), for 3 subjects in the US-licensed Humira group ('laceration': 1 subject, 'appendicitis': 2 subjects, of which 1 case was assessed as drug related by the investigator), and for 2 subjects in the EU-approved Humira group ('nephrolithiasis': 1 subject, abdominal pain: 1 subject). For any comment related to these AEs, please refer to the comment in the section “Adverse events” – “Analysis of AEs by organ system or syndrome”.

No **deaths** were reported in the trial.

PHASE I TRIAL 1297.1

No **SAEs** or **deaths** were reported during the trial.

TRIALS SUPPORTING THE AUTOINJECTOR: 1297.6 AND 1297.11

1297.6

No SAEs or deaths were reported during the trial.

1297.11

Two patients were reported with severe AEs. The same 2 patients were reported with SAEs ('depression' and 'drug hypersensitivity' [allergic reaction to Cymbalta [rash]]: 1 patient, 'oesophageal carcinoma' and 'anaemia': 1 patient).

Two patients were reported with protocol-specified AESIs. Both patients were reported with hypersensitivity reactions; 1 patient was reported with 'rash' and 1 patient was reported with an allergic reaction to Cymbalta (rash) (PT 'drug hypersensitivity').

No **death** was reported during the trial.

However, as these trials were uncontrolled, the findings can only be regarded as supportive.

Laboratory findings

PIVOTAL TRIAL 1297.2

As for AE reporting, the main assessment of safety laboratory evaluations focuses on the pivotal trial 1297.2, for patients who continuously received BI 695501 or continuously received US-licensed Humira (long-term safety analysis).

Chemistry

There were no clinically meaningful changes from baseline to endpoint/during the trial for chemistry parameters within the treatment groups. No important treatment group differences were noted in the mean change from baseline for any chemistry parameter.

Haematology

There were no clinically meaningful changes from baseline to endpoint/during the trial for haematology parameters within the treatment groups. No important treatment group differences were noted in the mean change from baseline for any haematology parameter.

For **haemoglobin**, decreases (i.e. a change of > 2 RCTC grades) from normal at baseline were reported at Weeks 24 and 40 for the US-licensed Humira to US-licensed Humira group and at Weeks 4, 12, 40, and 48 for the US-licensed Humira to BI 695501 group. 1 patient in the US-licensed Humira to BI 695501 group had a decrease in haemoglobin from normal at baseline to RCTC grade 4 at Weeks 4, 12, and 24, and 3 patients (1.0%) in the BI 695501 to BI 695501 group had a decrease in haemoglobin from normal at baseline to RCTC grade 4 at Week 4, 3 patients (1.0%) at Week 40 and 1 patient (0.3%) at Week 48.

Decreases in haematocrit from normal at baseline to low (i.e. below the reference range) were reported for ≥ 2% of patients for all treatment groups; at Weeks 4, 12, 24, 40, and 48 for the BI 695501 to BI 695501 group, Weeks 12, 24, 40, and 48 for the US-licensed Humira to US-licensed Humira group and at Weeks 12, 24, and 40 for the US-licensed Humira to BI 695501 group.

Of the serum haematology parameters that were reported as AEs, 'haemoglobin decreased' was reported for 2 patients in the BI 695501 continuously treatment group; for 1 patient, decreased haemoglobin was assessed as drug related by the investigator.

No haematology abnormalities were reported as treatment-emergent SAEs and no patients discontinued due to haematology abnormalities that were reported as non-serious TEAEs.

C-reactive protein and erythrocyte sedimentation rate

Median change in CRP from baseline at Week 24 and Week 48 was similar between the BI 695501 continuously and the US-licensed Humira continuously treatment groups.

All treatment groups showed a decrease from baseline in ESR over the course of the trial. Median change in ESR from baseline at Week 24 and Week 48 was similar between the BI 695501 continuously and in the US-licensed Humira treatment groups.

Laboratory evaluation of liver parameters

A total of 5 patients had a least 1 potential DILI finding during the trial (3 patients in the BI 695501 to BI 695501 group, 1 patient in the US-licensed Humira to US-licensed Humira group and 1 patient in the Humira US to BI 695501 group). One of these patients in the BI 695501 to BI 695501 group also had potential Hy's law findings.

Four patients had marked peak aminotransferase (ALT and/or AST) elevations ≥ 10-fold ULN; 2 patients in the BI 695501 to BI 695501 group and 1 patient in the US-licensed Humira to US-licensed Humira group, and 1 patient in the US-licensed Humira to US-licensed Humira group.

While it is generally concluded that slightly more patients experienced abnormal liver parameters with potential DILI finding in the BI 695501 than in the Humira US continuously group (3 vs. 1 patient), the small sample size as well as the general low number of these abnormal parameters severely hampers any meaningful interpretation.

TRIALS 1297.8, 1297.1, 1297.6 AND 1297.11

No clinically relevant findings with respect to the clinical laboratory evaluation were observed in trials 1297.8, 1297.1, 1297.6, and 1297.11.

Vital signs, physical findings, and other observations related to safety

Trial 1297.2

No notable findings with respect to vital signs, physical examination, and electrocardiograms were observed. However, 17 patients had a positive tuberculosis test at Week 48/early termination visit, 8 patients (2.8%) in the BI 6958501 to BI 695501 group, 1 patient (0.7%) in the Humira to Humira group, and 8 patients (5.7%) in the Humira to BI 695501 group. All patients had a negative result at screening. No TEAEs of tuberculosis were reported during the trial.

The positive TB tests – together with the anaemia and bone fracture findings – initially raised concern about the comparative safety profile. The Applicant was asked to discuss possible explanations for the slight imbalance in positive TB tests and to analyse whether any imbalances with regard to risk factors could explain the difference. In addition, as TB screening was only performed at baseline and at end of treatment, it was unclear whether the positive test in the 8 patients in the Humira to BI 695501 group could be linked to the reference or the biosimilar product. Additional information with regard to the possible time of infection was requested.

The additional patient information on diagnostic procedures, antibiotic therapies, TB related symptoms, and environmental TB risks showed that there was no active TB in either treatment arm; due to the absence of clinical symptoms, the time of infection could not be determined retrospectively. As a consequence, the TB positive patients in the switching arm cannot be attributed to either of the products.

It is concluded that the provided information and subsequent discussion with regard to the observed imbalances in positive TB tests is sufficient and adequate. Although still no plausible explanation

resolving the concern could be found, there seems to be no further work that could be done premarketing in order to settle the issue. Furthermore, while the absolute differences (numbers of patients with AEs) between treatment arms appear noteworthy, the respective relative proportions are rather small, due to the considerably lower number of patients in the US-Humira continuous arm as compared to the BI 695501 continuous arm. Against this background, the observed difference could indeed be a chance-finding.

There were no notable findings with respect to vital signs and electrocardiogram recordings in **trials 1297.1, 1297.8, 1297.6,** and **1297.11.**

Safety in special populations

In accordance with regulatory guidance, safety studies in special groups and situations are not required and were not conducted**.**

Immunological events

The main studies contributing to the clinical immunogenicity database are the 48-Week therapeutic equivalence trial in patients with RA receiving concomitant methotrexate (trial 1297.2) and the comparative single-dose PK trial in healthy volunteers (trial 1297.8).

PIVOTAL TRIAL 1297.2

The extent of immunogenicity data available is illustrated in the table below:

Visit		Period 1 (Day 1 to Week 24)		Period 2 (Week 24 to Week 58)		
		BI 695501 (N=324)	Humira (N=321)	BI 695501 to BI 695501 (N=298)	Humira US to Humira US (N=148)	Humira US to BI 695501 (N=146)
Baseline	Total reportable[a]	323	321	-	-	-
	Not reportable[b]	1	0	-	-	-
	Total[c]	324	321	-	-	-
Week 24	Total reportable[a]	294	301	292	147	146
	Not reportable[b]	10	2	6	1	0
	Total[c]	304	303	298	148	146
Week 48	Total reportable[a]	-	-	282	139	138
	Not reportable[b]	-	-	1	1	3
	Total[c]	-	-	283	140	141

Source: Table 14.3.5.7.1

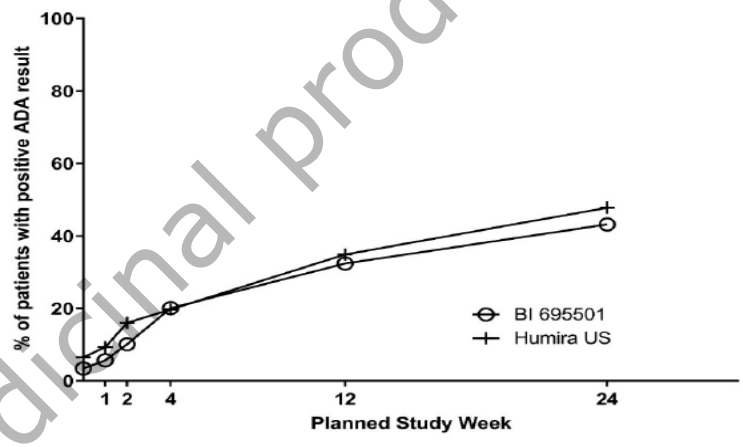
a. Total Reportable = sum of Negative and Positive categories per visit (= total number of subjects in the analysis set with data per visit).

b. Not Reportable = no sample available or invalid sample.

c. Total = sum of Total Reportable and Not Reportable categories

ADA and nAb results for Period 1

The frequencies of ADA and nAb positive patients up to week 24 are presented in the figure below. The frequency of ADA positive patients was 43.2 % for BI 695501 vs. 47.8 % for US-licensed Humira after 24 weeks of treatment. The frequency of nAb positive patients was 16.0 % for BI 695501 vs. 20.6 % for US-licensed Humira after 24 weeks of treatment. Considering the slightly lower proportion of patients with ADA/nAb positive samples at baseline, the reported frequencies can be described as being similar between treatment groups.



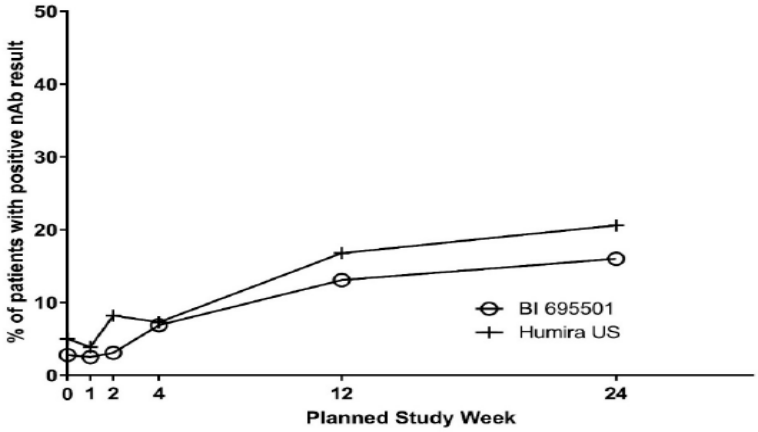


Figure: Time course of ADA (top) and nAb (bottom) development (percentage of positive tested patients) over time in Period 1 of the pivotal trial 1297.2

The median titre values at the different time points were similar between the treatment groups. The corresponding results at the different time points in form of boxplots are presented below. Mean titre values as well as upper whiskers were generally higher for the US Humira treatment groups, which is favourable for the biosimilar product.

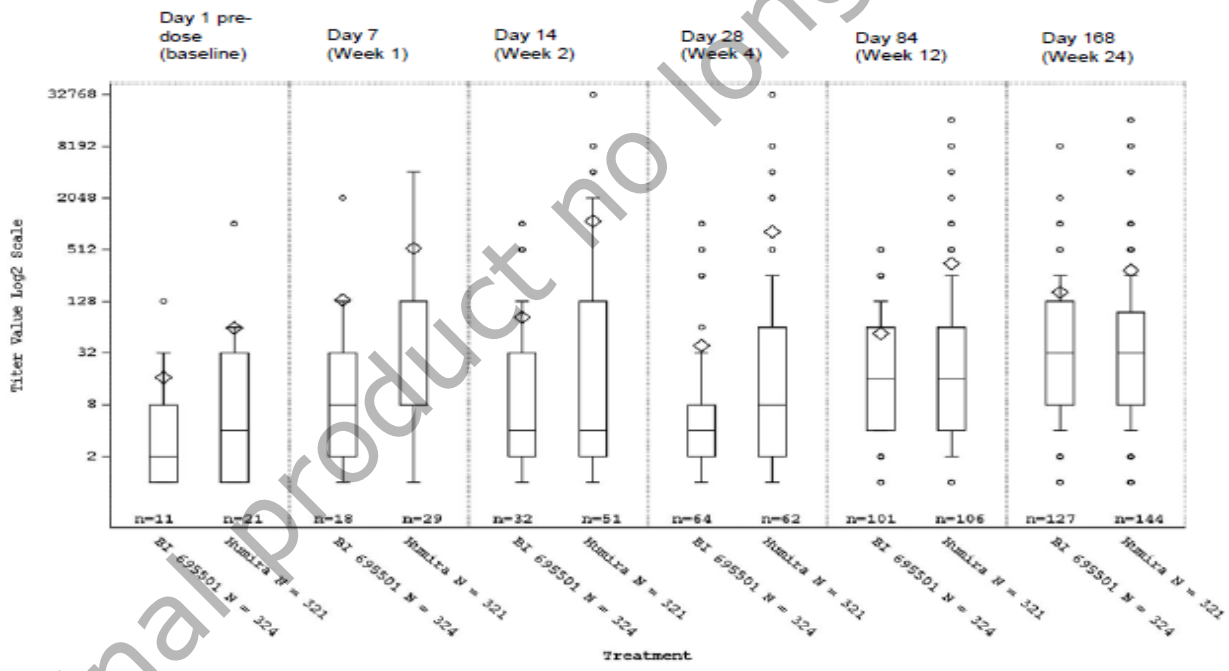


Figure: Box and whisker plot of ADA titre vs time during Period 1, indicating the median (line) within the 25th to 75th percentile box, the arithmetic mean (diamond), outliers as individual points (circle), as well as the 10th and 90th percentile for whiskers. n = the number of patients with a value displayed. N= the number of patients in the analysis set.

ADA and nAb results for Period 2

In the BI 695501 and US-licensed Humira continuous groups, the ADA frequencies and titres were similar and did not further increase between Week 24 and Week 48. At Week 48, frequencies of ADAs were 41.8 % vs. 49.6 %; frequencies of nAbs 19.1 % vs. 21.6 % in both groups, respectively. As can be seen from the figures, the proportion of ADA and nAb positive patients was slightly higher in the Humira group.

Table: Frequency of patients with positive ADA response at different visits in Period 2 (SAF)

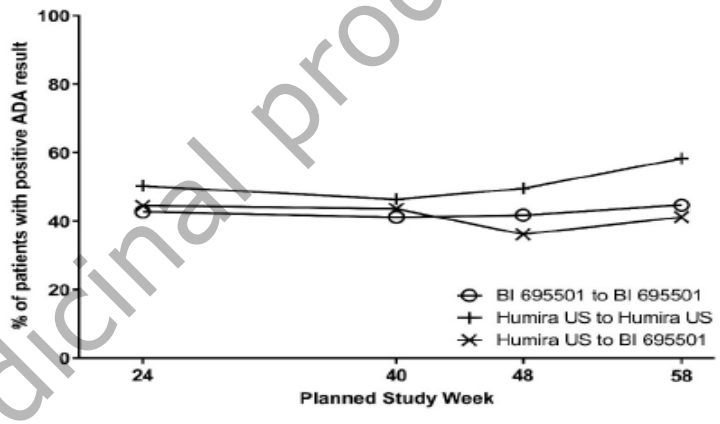
Visit	Period 2 (Week 24 to Week 58)		
	BI 695501 to BI 695501 (N=298[1]) n/N[2] (%)	Humira US to Humira US (N=148[1]) n/N[2] (%)	Humira US to BI 695501 (N=146[1]) n/N[2] (%)
Week 24	125/292 (42.8)	74/147 (50.3)	65/146 (44.5)
Week 40	117/284 (41.2)	65/140 (46.4)	61/140 (43.6)
Week 48	118/282 (41.8)	69/139 (49.6)	50/138 (36.2)
Week 58	21/47 (44.7)	21/36 (58.3)	14/34 (41.2)

Source: Table 14.3.5.7.1
ADA = anti-drug antibody; SAF = safety set.
1. N = number of patients in the SAF in each treatment group.
2. n = number of patients with a positive ADA response. N = total reportable patients.

Table: Frequency of patients with positive nAb response at different visits in Period 2 (SAF)

Visit	Period 2 (Week 24 to Week 58)		
	BI 695501 to BI 695501 (N=298[1]) n/N[2] (%)	Humira US to Humira US (N=148[1]) n/N[2] (%)	Humira US to BI 695501 (N=146[1]) n/N[2] (%)
Week 24	46/292 (15.8)	35/147 (23.8)	23/146 (15.8)
Week 40	38/284 (13.4)	22/140 (15.7)	25/140 (17.9)
Week 48	54/282 (19.1)	30/139 (21.6)	21/138 (15.2)
Week 58	16/47 (34.0)	14/36 (38.9)	10/34 (29.4)

Source: Table 14.3.5.7.2
ADA = anti-drug antibody; SAF = safety set.
1. N = number of patients in the SAF in each treatment group.
2. n = number of patients with a positive ADA response. N = total reportable patients.



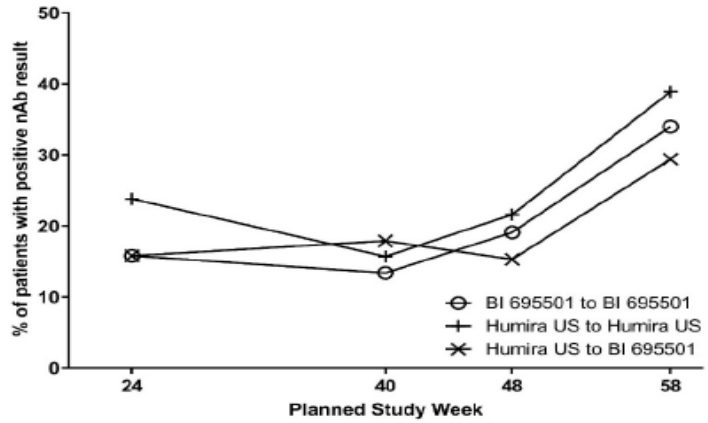


Figure: Time course of ADA development (top) and nAb (bottom) development (percent positive patients) over time for all treatments – Period 2 (SAF)

Regarding the **overall treatment period**, it is noted that those treatment arms continuing on either BI 695501 or US-licensed Humira showed a comparable frequency of ADA positive patients at baseline and Week 48: from 3.4% to 41.8% in the BI 695501 group, and from 6.5% to 49.6% in the Humira US group. The same applies for nAb: from 2.8% to 19.1% in the BI 695501 group, and from 5.0% to 21.6% in the Humira US group.

Relationship of ADA and nAb response to clinical PK, efficacy, and safety parameters during Period 1 and 2.

The mean **drug plasma concentration** was remarkably lower in the ADA positive subpopulation compared with the ADA negative population from the 4-week (672 hours) time point onwards. Nevertheless, the PK profiles for the ADA positive and ADA negative subpopulations were similar for the BI 695501 and US-licensed Humira treatment groups.

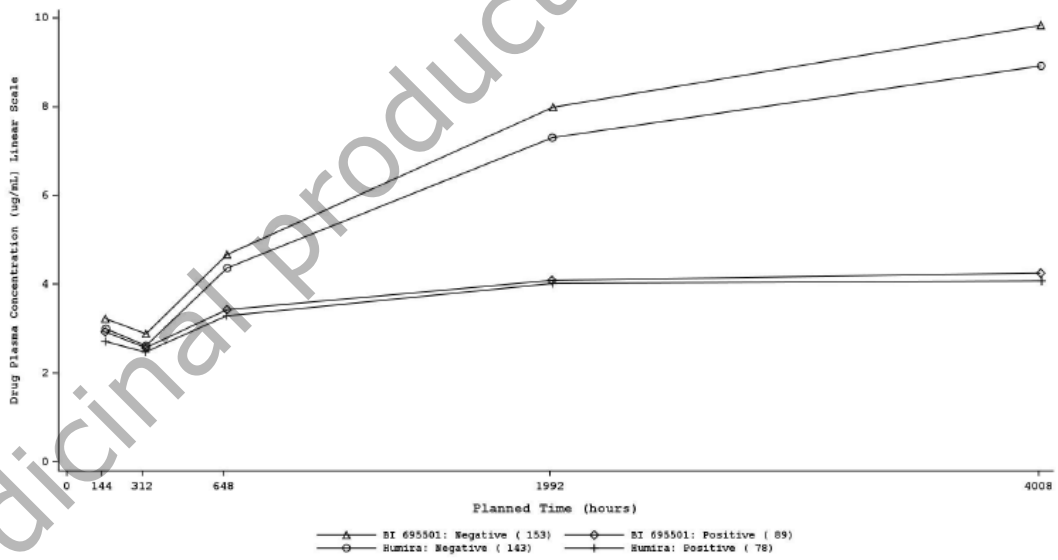


Figure: Geometric mean drug plasma concentration-time profiles per treatment group and ADA group (negative/positive at Week 48) over time (PKFS)

Analysis of the mean drug plasma concentration by ADA titre quartile showed an equivalent impact of the ADA response to each treatment on the drug plasma concentration.

Regarding impact on **efficacy**, please refer to the section on clinical efficacy.

The potential relationship between ADA response and possible immune-mediated **adverse events** that have been reported for Humira was assessed by the number of patients with reported hypersensitivity or injection site reactions by ADA category and treatment group. The results show a very low incidence of hypersensitivity in both treatment groups: ≥ 1 treatment-emergent hypersensitivity AESI in 1 patient with positive ADA results and with high ADA titre for the BI695501 group vs. 2 patients with positive ADA results with low ADA titre for the Humira group.

In the BI 695501 to BI 695501 group, of the patients who were ADA positive at Week 48, 1 patient (0.8%) had >1 injection site reactions during the trial. Of the patients who were ADA negative at Week 48, 2 patients (1.2%) also had 1 injection site reaction during the trial and 1 patient (0.6%) had >1 injection site reactions.

In the US-licensed Humira to US-licensed Humira group, of the patients who were ADA positive at Week 48, 4 patients (5.8%) also had 1 injection site reaction during the trial. Of the patients who were ADA negative, 1 patient (1.4%) also had >1 injection site reaction during the trial.

The low incidences preclude any reliable conclusion about a potential relationship of these adverse events to treatment-emergent ADA. The same applies for the reported very low incidence of injection site reactions in both treatment groups.

PK TRIAL 1297.8

ADA results

The time-course of detected ADA positive samples following the single administration of the test drug shows an overall high frequency (84 to 93 %) of ADA positive subjects at Day 71 (End-of-Study) with a similar frequency of ADA positive subjects and median ADA titre across each treatment group. A higher frequency of ADA positives at day 8 after a single dose of BI 695501 compared with subjects receiving either US-licensed Humira or EU-approved Humira was detected (32.7% vs. 5.6% and 4.6%) (see figure).

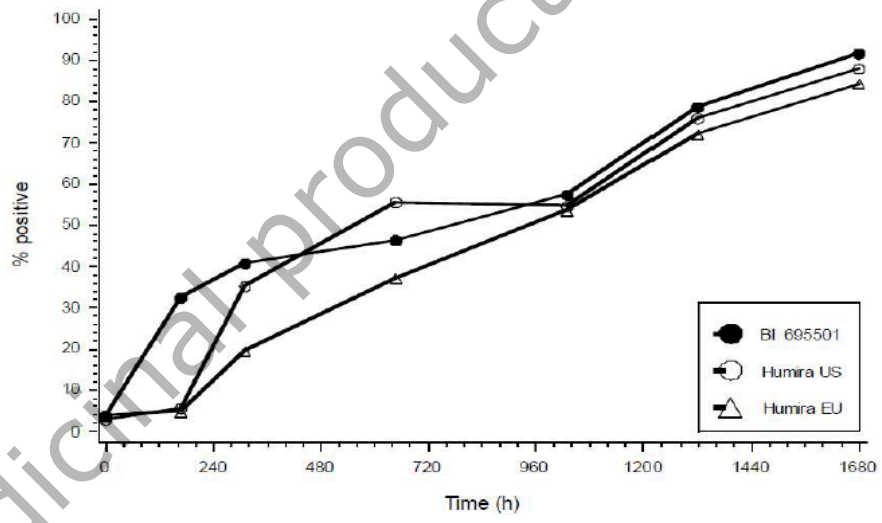


Figure: Percentage of ADA positive subjects (%) by treatment and time (h) in clinical trial 1297.8

The majority of positive samples in the BI 695501 group at Day 8 represented titre values in the range of 1 to 2, while similar numbers of subjects with ADA titres >2 were measured in the three treatment groups (5 subjects in BI 695501, 5 in US-licensed Humira, 3 in EU-approved Humira). It is also noted that this finding did not translate into differences between treatment groups with regard to PK or ADA parameters at the end of the trial (please see below). The Company was nevertheless asked to further

substantiate the potential reasons for this difference. The Company provided a discussion on a quality, preclinical, and clinical level, specifically substantiating potential reasons for the observed difference. It is agreed that the comparison between test and reference lots used in the trial 1297.8 does not raise any concern that a product-related attribute had caused the differences in immunogenicity incidences observed at Day 8. Furthermore, re-analysis with assays applying US- or EU-licensed Humira as detecting reagents show far less differences. On a clinical level, it was again emphasised that the overall development of ADA responses was similar during the course of study 1297.8 and study 1297.2 and it is agreed that the result could be coincidental.

At Day 71 (End-of-Study), the box and whisker plots of ADA titres by treatment group showed similar titre values for all groups at all time-points.

nAb results

On Day 71, 59.8% of subjects in the BI 695501 group, 63.9% of subjects in the US-licensed Humira group and 58.3% in the EU-approved Humira group had developed nAb responses after single dose injection. The time-course of nAb detection in each treatment group is illustrated in the figure below. The results show similar profiles for the three treatment groups over the time-course of monitoring. At the Day 8 and 14, where higher proportion of ADA positive patients were found for the BI 695501 group, the corresponding values for nAb were 1.9% vs. 0% and 0% at Day 8, and 4.7%, 4.6% and 4.7% at Day 14, respectively.

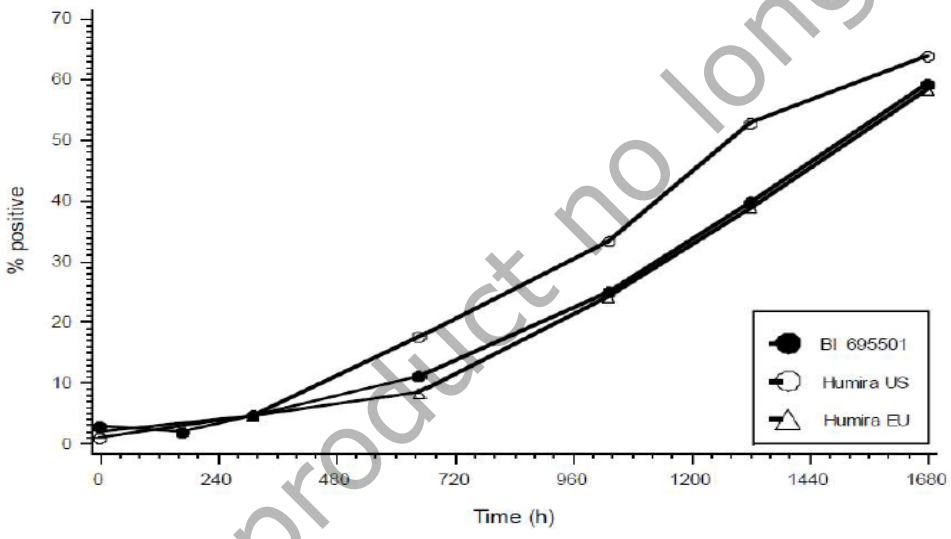


Figure: Percentage of nAb positive subjects by treatment and time in clinical trial 1297.8

It is generally noted that US-licensed Humira generally seems to be more immunogenic than the EU sourced product, with notable differences especially during the first month. This aspect is considered relevant with regard to the use of US-licensed Humira in the pivotal confirmative efficacy trial 1297.2 together with the provision of bridging data between US- and EU-sourced products. However, as the frequency of ADA and nAb positive patients was generally slightly lower in the BI 695501 group than in the Humira US group in trial 1297.2, this concern is insignificant.

Relationship of ADA and nAb response to clinical PK and safety parameters

Regarding impact on **PK parameters**, the predicted $AUC_{0\text{-}inf}$ value was lower for the high ADA titre subpopulation in all treatment groups. This is likely to reflect binding of ADA to the epitopes in the CDRs of adalimumab, thereby reducing the level of unbound drug available for binding to the capture TNF-alfa antigen in the PK assay.

Predicted $AUC_{0\text{-}inf}$ values for both the high and low Day 71-ADA titre subpopulations, respectively, were substantially overlapping across the different treatment groups. Thus, the impact of the ADA response on $AUC_{0\text{-}inf}$ was highly similar for BI 695501, US-licensed Humira, and EU-approved Humira, regardless of the ADA titre sub-population.

At Day 8, where a higher frequency of ADA positive samples had been detected for subjects receiving a single-dose of BI 695501 (n=35) compared with US-licensed Humira (n=6) and EU-approved Humira (n=5), the relationship of ADA positive vs. negative status to predicted $AUC_{0\text{-}inf}$ and C_{max} was also analysed. The results showed that positive ADA status at Day 8 in the BI 695501 did not reduce the predicted $AUC_{0\text{-}inf}$ value below that for the ADA-negative subjects treated with either US-licensed or EU-approved Humira. While this is generally acknowledged, it has to be commented that the aim of a biosimilar exercise is to show similarity between both respective groups (BI 695501 low titre vs. Humira low titre, and BI 695501 high titre vs. Humira high titre). However, the small sample size of ADA positive patients at Day 8 hampers any meaningful interpretation and therefore, no concern has been raised.

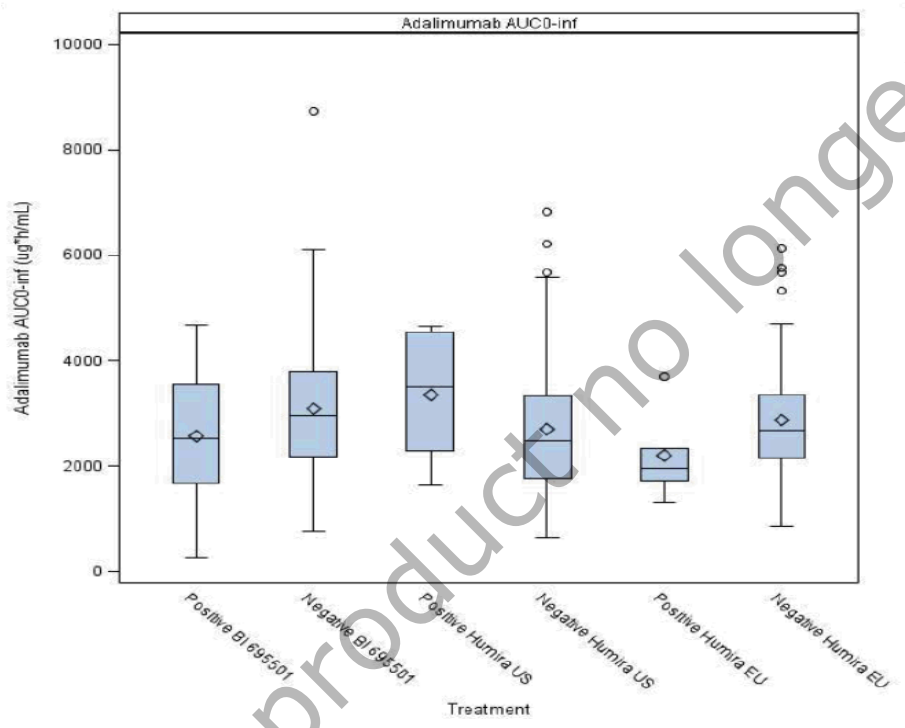


Figure: Box plot of AUC0-inf for adalimumab for all treatments by ADA positive and negative subjects on Day 8.

The mean C_{max} value for the ADA positive subjects on Day 8 was also comparable to that for the ADA negative population in the BI 695501 treatment group, while the distribution of individual C_{max} values was substantially overlapping those calculated for the other treatment groups.

Regarding **safety** parameters, analysis of the incidence of injection site reactions by treatment group indicated a similar profile for BI 695501, US-licensed Humira, and EU-approved Humira.

The following hypersensitivity reactions were reported:

- Injection site hypersensitivity: 2 subjects (1.9%) in the BI 695501 group and 1 subject (0.9%) in the EU-approved Humira group
- Hypersensitivity: 1 subject (0.9%) in the US-licensed Humira group
- Urticaria: 1 subject (0.9%) in the US-licensed Humira group

Very low incidence of hypersensitivity and injection site reactions in all three treatment groups was reported. In addition, a high percentage of subjects were ADA positive at end-of-study (>80%), precluding a reliable conclusion about a potential relationship of these adverse events to treatment-emergent ADA.

PK TRIAL 1297.1

Immunogenicity results of trial 1297.1 are supportive only. Nevertheless, it is noted that as for study 1297.8, a significant higher proportion of patients were detected ADA positive at Day 8 (20.9% vs. 12.9% and 6.5% for BI 695501, Humira US and Humira EU, respectively). This strengthens the concern raised before, requesting further substantiation regarding this difference.

PK TRIAL 1297.6

Trial 1297.6 is a relative BA clinical trial to compare PK parameters for the BI 695501 AI presentation with the BI 695501 PFS presentation. Since the primary container and formulation are identical for the BI 695501 AI and PFS presentations, no additional extrinsic product quality-related variables for immunogenicity risk were identified. The only variable that might influence the immune response would be potential differences in the rate of delivery into the local subcutaneous tissue.

Monitoring for ADA and nAb formation in trial 1297.6, demonstrated a similar profile of the two groups in terms of ADA frequency, ADA titre, and nAb frequency.

Discontinuation due to adverse events

PIVOTAL PHASE III TRIAL 1297.2

In the **overall** analysis, the frequency of patients with AEs leading to discontinuation of trial medication was comparable between patients who continuously took either BI 695501 or US-licensed Humira (4.0% for the BI 695501 continuously group and 6.9% for the Humira US continuously group).

Most AEs leading to discontinuation of trial medication were reported in the SOC 'infections and infestations' (0.6% vs. 2.3% for the BI 695501 or US-licensed Humira groups, respectively). At the PT level, the only AEs leading to discontinuation of trial medication that were reported for >1 patient were 'pyelonephritis acute' and 'urticaria', which were both reported in the US-licensed Humira continuously group. All other AEs leading to discontinuation of trial medication were individual occurrences.

PHASE I TRIAL 1297.8

No AEs leading to discontinuation from the trial medication administration were reported.

PHASE I TRIAL 1297.1

No AEs leading to discontinuation from the trial medication administration were reported.

2.6.1. Discussion on clinical safety

Safety data for BI 695501 have been collected in 5 clinical studies: 2 Phase I PK trials, 1 pivotal confirmative efficacy trial, and 2 trials supporting the autoinjector. This amount of data is considered adequate and in line with applicable guidance. The focus of safety assessment is on the pivotal, confirmative efficacy trial in patients with RA (study 1297.2), which was designed to assess the equivalence between BI 695501 and US-Humira regarding efficacy and safety. As the trials are differed in trial design, trial treatments, treatment duration and population, the safety data were not pooled across trials.

276 vs. 137 patients in the continuously BI 695501 and Humira US group, respectively, were exposed to the drug in the pivotal trial 1297.2. A sufficient number of subjects was followed for an adequate duration, allowing an adequate assessment of safety profile.

The analysis of AEs was based on the concept of treatment-emergent AEs and was illustrated as the number of patients/subjects with AEs.

Overall in **trial 1297.2,** the frequency of AE was similar between BI 695501 and Humira groups:

Similar proportions between the BI 695501 continuously and the US-licensed Humira continuously treatment groups were observed for patients with at least 1 AE (59.6 vs. 60.0%), investigator-assessed drug-related AEs (safety endpoint), and AEs leading to discontinuation of trial medication. Among AEs assessed as drug-related, most were reported in the SOC 'infections and infestations' (again with similar frequencies). Also overall the most common AEs were reported in the SOC 'infections and infestations', with almost equal frequencies for both arms: 35.2% (BI 695501) versus 34.3% (US-licensed Humira). These findings mirror the safety profile as described in the SmPC of Humira.

The comparison of AEs by intensity shows also similar frequencies for the BI 695501 and US Humira groups. Slightly lower proportions of patients in the BI 695501 continuously group than in the US-licensed Humira continuously group were reported with SAEs (5.6 vs. 9.7%), which is in favour for the biosimilar product. Most frequently reported SAEs were – again - SOC 'infections and infestations'. Also SAEs reported by the investigator as being drug-related occurred more frequently in the Humira US group.

The definition of AESIs is supported. AESIs, `other safety endpoints´ and `further selected AEs´ were also equally distributed across treatment groups. The frequencies of patients with serious infections, hypersensitivity reactions, and injection site reactions were lower for the BI 695501 continuously group than for the US Humira continuously groups. DILI and anaphylactic reactions were only single occurrences in both arms.

However, a numerical difference was observed for SOC `haematological disorders´, driven by the PT 'anaemia'. This was exclusively reported in patients who continuously took BI 695501 (8 patients, 2.5%).' Haemoglobin decreased' was also only reported for 2 patients (0.6%) in the BI 695501 continuously group. Furthermore, a total of 7 patients in the BI 695501 continuously group compared with none of the patients in the US-licensed Humira continuously group were reported with bone fractures (2.2%). Single occurrences of orthopaedic traumata were also found only for the BI 695501 group in trial 1297.8. In addition, 17 patients were reported to have a positive tuberculosis test at Week 48/EoT visit: 8 patients (2.8%) in the BI 695501 to BI 695501 group, 1 patient (0.7%) in the US-licensed Humira to US-licensed Humira group, and 8 patients (5.7%) in the US-licensed Humira to BI 695501 group; all patients had a negative result at screening.The TB cases – together with the anaemia and bone fracture findings mentioned above – initially raised the concern about the comparative safety profile.

The Applicant was requested to provide additional information and to discuss the numerical differences between the 3 arms. Furthermore, it was requested to analyse whether there were any population imbalances with regard to risk factors potentially explaining the difference in anaemia, bone fracture, and TB frequencies (e.g. region, co-medication, but not limited to these ones). After reviewing the Applicant's response, it was concluded that no imbalances in risk factors that could have contributed to the differences could be identified and there was no active TB in either of the treatment arms. Furthermore, the respective relative proportions of these events (and their differences) are considered rather small, due to the considerably lower number of patients in the US-Humira continuous arm as compared to the BI 695501 continuous arm. Although still no plausible explanation resolving the

concern could be found, the findings could be attributed to chance and there seems however to be no further work that could be done premarketing. Haematological disorders and tuberculosis are listed as "important identified risks" in the RMP and will be monitored in the scope of routine pharmacovigilance.

Laboratory findings were elevated cholesterol and AST/ALT values as well as decreased haemoglobin values. Cholesterol abnormalities are expected laboratory findings, as stated in EU-approved Humira SmPC. Elevated liver enzymes are also in line with what is known from the reference product. Potential DILI was reported for single patients (3 for BI 695501 vs. 1 for US Humira).

Immunogenicity was monitored for the 48 study weeks (+10 weeks safety follow-up) period under double-blind treatment conditions for the two sequential periods 1 and 2. The frequencies of ADA and nAb positive patients were similar between BI 695501 and US-licensed Humira at the different time points. A low number of patients being tested ADA positive and/or with high titres showed hypersensitivity or injection site reactions, with similar frequencies across treatment groups. The median titre values at the different time points were also similar between BI 695501 and US-licensed Humira.

In **trial 1297.8,** the proportion of subjects with any TEAE and drug-related AEs was generally similar across treatment groups.

Immunogenicity results show an overall high frequency of ADA positive subjects at Day 71 (End-of-Study) with a similar frequency of ADA positive subjects across the 3 treatment groups.

2.6.2. Conclusions on the clinical safety

Overall, the elucidated safety and immunogenicity profiles for Cyltezo seem to be comparable to the established characteristics of Humira, supporting the notion of biosimilarity for the two products. The slight differences in anaemia, bone fracture, and positive TB tests are most probably a chance finding.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Autoimmune hepatitis Cerebrovascular accident Congestive heart failure Cutaneous vasculitis Demyelinating disorders (including multiple sclerosis, Guillain-Barre syndrome, and optic neuritis) Elevated ALT levels Erythema multiforme Haematologic disorders Hepatosplenic T cell lymphoma Immune reactions (including lupus-like

Summary of safety concerns	
	reactions and allergic reactions) Interstitial lung disease Intestinal perforation Intestinal stricture in Crohn's disease Leukaemia Liver failure and other liver events Lymphoma Medication errors and maladministration Melanoma Merkel cell carcinoma (neuroendocrine carcinoma of the skin) Myocardial infarction Non-melanoma skin cancer Pancreatitis Pulmonary embolism Reactivation of hepatitis B Sarcoidosis Serious infections including diverticulitis and opportunistic infections, e.g. invasive fungal infections, parasitic infections, legionellosis, and tuberculosis Stevens-Johnson syndrome Worsening and new onset of psoriasis
Important potential risks	Adenocarcinoma of colon in ulcerative colitis patients Amyotrophic lateral sclerosis Infections in infants exposed to BI 695501 *in utero* Off-label use Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma) Progressive multifocal leukoencephalopathy Reversible posterior leukoencephalopathy syndrome Vasculitis (non-cutaneous)
Missing information	Long-term safety data in the treatment of adults with hidradenitis suppurativa Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease and

Summary of safety concerns	
	paediatric enthesitis related arthritis Pregnant and lactating women Remission-withdrawal-retreatment nr-AS data and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis, and juvenile idiopathic arthritis Subjects with immune-compromised conditions either due to underlying conditions (i.e. diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post-cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications Long-term safety data in the treatment of adults with uveitis

Pharmacovigilance plan

Study / activity	Objectives	Safety concerns addressed	Status	Date for submission of interim of final reports
Rheumatoid arthritis patient registry (CORRONA); category 3	To monitor longterm safety of rheumatoid arthritis patients	- Serious infections including diverticulitis and opportunistic infections, e.g. invasive fungal infections, parasitic infections, legionellosis, and tuberculosis - Merkel cell carcinoma - Elevated ALT levels - Autoimmune hepatitis	Planned	Interim report after 2 years of marketing
Psoriasis patient registry study (CORRONA); category 3	To monitor longterm safety of psoriasis patients	- Serious infections including diverticulitis and opportunistic infections, e.g.	Planned	Interim report after 2 years of marketing

Study / activity	Objectives	Safety concerns addressed	Status	Date for submission of interim of final reports
		invasive fungal infections, parasitic infections, legionellosis, and tuberculosis - Merkel cell carcinoma - Elevated ALT levels - Autoimmune hepatitis		
Inflammatory bowel disease patient registry (CORRONA); category 3	To monitor long-term safety of intestinal bowel disease patients	- Serious infections including diverticulitis and opportunistic infections, e.g. invasive fungal infections, parasitic infections, legionellosis, and tuberculosis - Merkel cell carcinoma - Elevated ALT levels - Autoimmune hepatitis - Adenocarcinoma of colon in ulcerative colitis patients	Planned	Interim report after 2 years of marketing
Rheumatoid arthritis patient registry (RABBIT); category 3	To monitor longterm safety of rheumatoid arthritis patients	- Serious infections including diverticulitis and opportunistic infections, e.g. invasive fungal infections, parasitic infections, legionellosis, and tuberculosis - Merkel cell carcinoma - Elevated ALT levels - Autoimmune	Planned	Interim report after 2 years of marketing

Study / activity	Objectives	Safety concerns addressed	Status	Date for submission of interim of final reports
		hepatitis		
Open-label, long-term extension trial of BI 695501 in patients with rheumatoid arthritis (1297.3); category 3	Long-term assessment of safety, efficacy, pharmacokinetics and immunogenicity of BI 695501 in patients with rheumatoid arthritis	None	Started	Final report Q2 2018
BI 695501 versus Humira in patients with active Crohn's disease (1297.4); category 3	To compare efficacy, endoscopic improvement, safety, and immunogenicity of BI 695501 versus Humira in patients with active Crohn's disease	None	Started	Final report Q2 2019
Efficacy, safety, and immunogenicity of BI 695501 versus Humira in patients with moderate to severe chronic plaque psoriasis (1297.12); category 3	To compare efficacy, safety, and immunogenicity of BI 695501 versus Humira in patients with moderate to severe chronic plaque psoriasis	None	Started	Final report Q3 2018

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Autoimmune hepatitis	Labelling in SmPC section 4.8; prescription-only medicine	None
Cerebrovascular accident	Labelling in SmPC section 4.8; prescription-only medicine	None
Congestive heart failure	Labelling in SmPC sections 4.3, 4.4, and 4.8; prescription-only medicine	Patient alert card, HCP educational material
Cutaneous vasculitis	Labelling in SmPC section 4.8; prescription-only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Demyelinating disorders (including multiple sclerosis, Guillain-Barre syndrome, and optic neuritis)	Labelling in SmPC sections 4.4 and 4.8; prescription-only medicine	Patient alert card, HCP educational material
Elevated ALT levels	Labelling in SmPC section 4.8; prescription-only medicine	None
Erythema multiforme	Labelling in SmPC section 4.8; prescription-only medicine	None
Haematologic disorders	Labelling in SmPC section 4.4; prescription-only medicine	None
Hepatosplenic T-cell lymphoma	Labelling in SmPC section 4.4; prescription-only medicine	Patient alert card, HCP educational material
Immune reactions (including lupus-like reactions and allergic reactions)	Labelling in SmPC sections 4.4 and 4.8; prescription-only medicine	None
Interstitial lung disease	Labelling in SmPC section 4.8; prescription-only medicine	None
Intestinal perforation	Labelling in SmPC section 4.8; prescription-only medicine	None
Intestinal stricture in Crohn's disease	Labelling in SmPC section 4.4; prescription-only medicine	None
Leukaemia	Labelling in SmPC section 4.4; prescription-only medicine	Patient alert card, HCP educational material
Liver failure and other liver events	Labelling in SmPC section 4.8; prescription-only medicine	None
Lymphoma	Labelling in SmPC section 4.4 and 4.8; prescription only medicine	Patient alert card, HCP educational material
Medication errors and maladministration	Prescription-only medicine	None
Melanoma	Labelling in SmPC sections 4.4 and 4.8; prescription-only medicine	Patient alert card, HCP educational material
Merkel cell carcinoma	Labelling in SmPC sections 4.4 and 4.8; prescription-only medicine	Patient alert card, HCP educational material
Myocardial infarction	Labelling in SmPC section 4.8; prescription-only medicine	None
Non-melanoma skin cancer	Labelling in SmPC sections 4.4 and 4.8; prescription-only medicine	Patient alert card, HCP educational material
Pancreatitis	Labelling in SmPC section 4.8; prescription-only medicine	None
Pulmonary embolism	Labelling in SmPC section 4.8; prescription-only medicine	None
Reactivation of hepatitis B	Labelling in SmPC sections 4.4 and 4.8; prescription-only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Sarcoidosis	Labelling in SmPC section 4.8; prescription-only medicine	None
Serious infections (including diverticulitis and opportunistic infections, e.g. invasive fungal infections, parasitic infections, legionellosis, and tuberculosis)	Labelling in SmPC sections 4.3, 4.4, and 4.8; prescription-only medicine	Patient alert card, HCP educational material
Stevens-Johnson syndrome	Labelling in SmPC section 4.8; prescription-only medicine	None
Worsening and new onset of psoriasis	Labelling in SmPC sections 4.4 and 4.8; prescription-only medicine	None
Important potential risks		
Adenocarcinoma of colon in ulcerative colitis patients	Labelling in SmPC section 4.4; prescription-only medicine	None
Amyotrophic lateral sclerosis	Prescription-only medicine	None
Infections in infants exposed to BI 965501 in utero	Labelling in SmPC section 4.6; prescription-only medicine	None
Off-label use	Prescription-only medicine	None
Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma)	Labelling in SmPC sections 4.4 and 4.8; prescription-only medicine	Patient alert card, HCP educational material
Progressive multifocal leukoencephalopathy	Prescription-only medicine	None
Reversible posterior leukoencephalopathy syndrome	Prescription-only medicine	None
Vasculitis (non-cutaneous)	Labelling in SmPC section 4.8, prescription-only medicine	None
Missing information		
Long-term safety data in the treatment of adults with hidradenitis suppurativa	Labelling in SmPC section 4.2, prescription-only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease and paediatric enthesitis-related arthritis	Labelling in SmPC section 4.2, prescription-only medicine	None
Pregnant and lactating women	Labelling in SmPC section 4.6, prescription-only medicine	None
Remission-withdrawalretreatment nr-AS data and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis, and juvenile idiopathic arthritis	Prescription-only medicine	None
Subjects with immunecompromised conditions either due to underlying conditions (i.e. diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post-cancer chemotherapy, antirejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications	Labelling in SmPC section 4.4; prescription-only medicine	None
Long-term safety data in the treatment of adults with uveitis	Labelling in SmPC section 4.2; prescription-only medicine	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The applicant has provided a short “bridging report” in which as parent PL for content and key messages the package leaflet of the reference product “Humira 40 mg/0.8 mL solution for injection in pre-filled syringe and 40 mg solution for injection in pre-filled pen” was defined. A tabulated overview of the differences in the package leaflet between Cyltezo and Humira was provided, including a justification of the differences with regards to the content of the package leaflet.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Humira. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Cyltezo (adalimumab) is included in the additional monitoring list as biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Applicant claims the same therapeutic indications for Cyltezo as granted for Humira in the EU, i.e. Rheumatoid arthritis, Juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), Axial spondyloarthritis (ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS), Psoriatic arthritis, Psoriasis, paediatric plaque Psoriasis, Hidradenitis suppurativa, Crohn’s disease, paediatric Crohn's disease, Ulcerative colitis and Non-infectious Uveitis.

As Cyltezo is currently only available as a 40 mg prefilled syringe (PFS) presentation, the Applicant claims the paediatric indications only for patients who can administer the full 40 mg dose, depending on age, weight, or body surface area.

3.1.2. Main clinical studies

Table 1 Overview of clinical trials with BI 695501

Trial No. Report No.	Trial Objective (Trial brand name)	Trial design	Trial Population	Duration of treatment	Treatment groups, trial medication formulation, and number of treated subjects	Trial status
Phase I PK trials						
1297.8 Final CTR [c03070713]	Comparative pharmacokinetics and safety of BI 695501 versus Humira (VOLTAIRE®-PK)	Double-blind, randomized, parallel-group, active-controlled	Healthy subjects	Single dose	BI 695501 PFS (CF): 108 Humira US: 108 Humira EU: 108	Completed
1297.1 Final CTR [U13-1096]	Comparative pharmacokinetics and safety of BI 695501 versus Humira	Open-label, randomized, parallel-group, active-controlled	Healthy subjects	Single dose	BI 695501 PFS (TF): 67 Humira US: 62 Humira EU: 64	Completed
Pivotal Phase III trial 1297.2						
1297.2 Primary analysis CTR [c08934295]	Comparative efficacy, safety and immunogenicity of BI 695501 versus US-licensed Humira (VOLTAIRE®-RA)	Double-blind, randomized, parallel-group, active-controlled	Patients with moderately to severely active RA (and MTX background therapy)	48 weeks	Initial Randomization BI 695501 PFS (CF): 324 Humira US: 321 Re-randomization at Week 24 BI 695501 PFS (CF) to BI 695501 PFS (CF): 298 Humira US to BI 695501 (CF): 147 Humira US to Humira US: 148	Ongoing (261 patients), LPO expected in Oct 2016
Trials supporting the autoinjector						
1297.6 Final primary analysis CTR [c09477818]	PK, safety, and tolerability of BI 695501 administered s.c. via pre-filled syringe or autoinjector (VOLTAIRE®-AI)	Open-label, randomized, parallel-group	Healthy subjects	Single dose	BI 695501 PFS (CF): 33 BI 695501 AI (CF): 33	Ongoing[1] LPO expected in Oct 2016
1297.11 Primary analysis CTR [c08933683]	Assessment of real-life patient handling experience of BI 695501 administered s.c. with an autoinjector (VOLTAIRE®-RL)	Open-label, single-arm, uncontrolled	Patients with moderately to severely active RA (MTX or any other DMARD therapy)	50 weeks	Autoinjector Assessment Phase BI 695501 AI (CF): 77 Extension Phase BI 695501 PFS (CF): 72	Ongoing (70 patients); LPO expected in June 2017

Abbreviations: AI: autoinjector; CF: commercial formulation; CTR: clinical trial report; Humira EU: EU-approved Humira; Humira US: US-licensed Humira; LPO: last patient out; MTX: methotrexate; PFS: pre-filled syringe; PK: pharmacokinetics; RA: rheumatoid arthritis; TF: trial formulation

[1] All patients included in the Final Primary Analysis Report have completed the trial. Further subjects (in the low BMI group) are being recruited.

Table 1 Overview of clinical trials with BI 695501

Trial No. Report No.	Trial Objective (Trial brand name)	Trial design	Trial Population	Duration of treatment	Treatment groups, trial medication formulation, treated subjects	Trial status
Phase I PK trials						
1297.8 Final CTR [c03070713]	Comparative pharmacokinetics and safety of BI 695501 versus Humira (VOLTAIRE®-PK)	Double-blind, randomized, parallel-group, active-controlled	Healthy subjects	Single dose	BI 695501 PFS (CF): 108 Humira US: 108 Humira EU: 108	Completed
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Pivotal Phase III trial 1297.2						
1297.2 Primary analysis CTR [c08934295]	Comparative efficacy, safety and immunogenicity of BI 695501 versus US-licensed Humira (VOLTAIRE®-RA)	Double-blind, randomized, parallel-group, active-controlled	Patients with moderately to severely active RA (and MTX background therapy)	48 weeks	Initial Randomization BI 695501 PFS (CF): 324 Humira US: 321 Re-randomization at Week 24 BI 695501 PFS (CF) to BI 695501 PFS (CF): 298 Humira US to BI 695501 (CF): 147 Humira US to Humira US: 148	Ongoing (261 patients), LPO expected in Oct 2016
Final CTR [c15074004]						Completed
Trials supporting the autoinjector						
1297.6 Final primary analysis CTR [c09477818]	PK, safety, and tolerability of BI 695501 administered s.c. via pre-filled syringe or autoinjector (VOLTAIRE®-AI)	Open-label, randomized, parallel-group	Healthy subjects	Single dose	BI 695501 PFS (CF): 33 BI 695501 AI (CF): 33	Ongoing[1] LPO expected in Oct 2016
Final CTR [c08933656]						Completed
1297.11 Primary analysis CTR [c08933683]	Assessment of real-life patient handling experience of BI 695501 administered s.c. with an autoinjector (VOLTAIRE®-RL)	Open-label, single-arm, uncontrolled	Patients with moderately to severely active RA (MTX or any other DMARD therapy)	50 weeks	Autoinjector Assessment Phase BI 695501 AI (CF): 77 Extension Phase BI 695501 PFS (CF): 72	Ongoing (70 patients); LPO expected in June 2017

Abbreviations: AI: autoinjector; CF: commercial formulation; CTR: clinical trial report; Humira EU: EU-approved Humira; Humira US: US-licensed Humira; LPO: last patient out; MTX: methotrexate; PFS: pre-filled syringe; PK: pharmacokinetics; RA: rheumatoid arthritis; TF: trial formulation

[1] All patients included in the Final Primary Analysis Report have completed the trial. Further subjects (in the low BMI group) are being recruited.

Note that final data for trials 1297.6 and 1297.2 were provided during the procedure.

The applicant performed two single-dose PK studies comparing Cyltezo, EU- and US-Humira in healthy volunteers; study **1297.8** used the final, to be commercialised formulation of Cyltezo. The PK trials also investigated similarity between US- and EU-Humira in order to allow for bridging to the US originator used in the pivotal efficacy and safety trial.

In addition, supportive PK data was generated in patients with active RA (study 1297.2). Trough drug concentrations were determined for a descriptive pharmacokinetic comparison of Cyltezo and US-licensed Humira and for a population PK analysis.

The pivotal study **1297.2** was a double-blind, randomised, parallel group trial investigating comparative efficacy, safety and immunogenicity of Cyltezo and US Humira over a 48-weeks treatment period. The trial enrolled female and male patients aged 18 to 80 years (n=324) with moderately to severely active RA receiving MTX as background therapy. At Week 24, all patients were re-randomized in a blinded fashion: Patients who were originally randomized to US-licensed Humira were re-randomized (1:1) to either continue on US-licensed Humira or transition to Cyltezo. The primary objective was to evaluate similarity in the proportion of patients meeting the ACR20 response criteria at Week 12 and 24 in the two treatment arms.

Two additional clinical trials were conducted to assess the performance of the autoinjector. Trial 1297.6 was an open-label, randomized, single-dose, parallel-group trial in healthy male volunteers comparing the PK of BI 695501 after subcutaneous injection using either a PFS or an AI. Trial 1297.11 was a 7-week, open-label, single-arm, uncontrolled, multiple dose trial in patients with moderately to severely active RA assessing real-life patient handling experience of self-injecting BI 695501 with an AI.

3.2. Favourable effects

From a quality perspective a robust and well-controlled manufacturing process for drug substance as well as for drug product is in place, which can perform effectively and reproducibly to produce drug substance respective drug product meeting its predetermined specifications and quality attributes. The provided drug substance and drug product batch analyses data support this conclusion. An appropriate control strategy ensures that material of sufficient high quality will enter the market.

The applicant performed a sound and very comprehensive biosimilarity exercise at the quality level. A quite exhaustive panel of standard and state-of-the-art techniques has been used for characterisation and comparison of relevant quality attributes of the adalimumab molecule. This panel includes analytical tests for physicochemical features as well as biological characteristics. Biosimilarity could be sufficiently demonstrated and observed differences in physicochemical quality attributes have been appropriately justified to have no impact on efficacy and safety. Additional biological and in vitro pharmacological assays have been included to characterise and compare biological mechanisms relevant for psoriasis and the inflammatory bowel diseases (and likely/potentially relevant for HS and UV). These additional biological characterisation data provide further evidence for the claimed extrapolation from the clinically investigated RA indication to all other indications granted for Humira.

From a non-clinical perspective it is considered that overall results of the in vitro Fab- and Fc-related biological assays and additional biological assays demonstrated similarity between Cyltezo and Humira. In vivo PK and toxicology studies also showed comparable results.

Pharmacokinetics:

In study 1297.8 PK similarity was demonstrated for the primary PK parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}tz}$ and C_{max} of Cyltezo, EU-Humira and US Humira: Ratios [90%CIs]: $AUC_{0\text{-}inf}$: 101.27% [92.45; 110.94];

AUC_{0-tz}: 99.93% [92.15; 108.37]; C_{max}: 96.39% [91.06; 102.03]. The 90% CIs of the geometric means ratios of the AUC_{0-inf}, AUC_{0-tz} and C_{max} for Cyltezo vs. EU Humira fell within the predefined equivalence margin of 80.00 to 125.00.

Study 1297.8 also established PK similarity between EU and US originator products, supporting the use of US licensed product in the comparative efficacy/safety study. Ratio [90% CI] for US-Humira/ EU-Humira: AUC_{0-inf}: 94.02% [86.01; 102.78]; AUC_{0-tz}: 93.66% [86.76; 101.11]; C_{max}: 95.93% [90.83; 101.33].

An exploratory PK analysis from efficacy study 1297.2 revealed no major differences in C_{trough} values between Cyltezo and US Humira.

Efficacy:

In the pivotal trial 1297.2 in patients with RA, Cyltezo was similarly effective as US-Humira in reaching the primary endpoints, ACR20 at 12 and 24 weeks. The proportion of patients achieving ACR20 after 12 and 24 weeks was similar for Cyltezo and US Humira in the primary analysis (FAS) and the sensitivity analysis (PPS). The treatment difference (Cyltezo vs Humira) in ACR20 response rate at Week 12 was 5.9%; the 90% CI of the adjusted treatment difference was [-0.9;12.7], completely contained within the pre-defined equivalence margin [−12%, 15%]. In addition, the 95% CI of the adjusted treatment difference, which is considered more relevant by CHMP, was [-2.2;14.0], also completely contained within the pre-defined equivalence margin.

After 24 weeks the difference in ACR20 response was 4.5%, the 95% CI [-3.5;12.4] completely contained within the equivalence margin [−15%, 15%].

The similarity in the primary endpoint is supported by most secondary efficacy measures at Week 12 and 24, e.g. DAS28-ESR (treatment difference and 95% CI at Week 12: -0.1 [−0.28, 0.08] and at Week 24: 0 [−0.16, 0.23]), but also in ACR 50, DAS28-CRP, and change in individual ACR parameters (compared only numerically without providing CIs).

In addition, the Applicant presented a discussion on the extrapolation of the different indications, justified by physicochemical and structural analyses as well as *in vitro* functional tests, complemented by clinical data (efficacy, safety and/or PK/PD data) in patients with RA and a literature review of the mechanisms of action of adalimumab to justify extrapolating efficacy and safety data across all approved therapeutic indications.

This extrapolation is in agreement with the “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues” (EMEA/CHMP/BMWP/42832/2005 Rev. 1) as well as former CHMP Scientific Advice.

Hence, the same favourable effects demonstrated for Humira can be assumed to be in place for Cyltezo.

3.3. Uncertainties and limitations about favourable effects

In the non-clinical PK evaluation a higher exposure was observed in BI 695501-treated compared with Humira treated animals. The difference in exposure was not statistically significant and most probably due to small group size, subcutaneous route of administration, and relatively rapid emergence of ADAs.

PK trial 1297.1 failed to demonstrate similarity between Cyltezo and EU-Humira in the primary endpoints. The main driver for the observed dissimilarity in PK in this trial was an unexpected low exposure of EU-Humira that was not observed in the second PK trial and could not be explained, e.g.

by differences in shelf-life, shipment and storage conditions, or molecular/pharmacological properties of the Humira lots used in the 2 PK studies.

3.4. Unfavourable effects

The safety characteristics of Cyltezo seen in the clinical studies mostly overlap with the established safety profile of Humira. TNF-antagonists such as Humira can be associated with fatal and life-threatening infections (including sepsis, opportunistic infections, and TB), HBV reactivation, and various malignancies (including leukaemia, lymphoma, and HSTCL) as well as serious haematological, neurological, and autoimmune reactions.

3.5. Uncertainties and limitations about unfavourable effects

The occurrence of product-related and foreign particles in the final product was initially a major quality concern. This has been appropriately addressed as additional information provided with the responses allowed a conclusive and in-depth assessment; potential safety issues arising from the presence of particles could be ruled out.

The safety and immunogenicity profiles of Cyltezo and Humira seen in the clinical programme seem to be comparable. However, in trial 1297.2 in patients with RA, adverse events of 'anaemia' and 'haemoglobin decreased' were exclusively reported in patients who continuously took Cyltezo (10 patients, 3.1%). Bone fractures were reported in 7 patients (2.2%) in the Cyltezo continuously group compared with none of the patients in the US-Humira continuously group. 17 patients had a positive tuberculosis test at Week 48/EoT visit: 8 patients (2.8%) in the Cyltezo to Cyltezo group, 1 patient (0.7%) in the US-Humira to US-Humira group, and 8 patients (5.7%) in the US-Humira to Cyltezo group; all patients had a negative result at screening. These findings initially raised concern about the comparative safety profile. Review of additional patient data did not identify differences in baseline risk factors or other plausible explanations; the relative proportions/differences are small and the slight imbalances might be attributable to chance.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The applicant provided a comprehensive dossier evaluating similarity between Cyltezo and Humira on the quality, preclinical and clinical level.

A robust and well-controlled manufacturing process for drug substance as well as for drug product is in place, which is expected to meet the predetermined specifications and quality attributes for the production of drug substance and drug product. The provided DS and DP batch analyses data supports this conclusion. The proposed control strategy is considered appropriate and ensures that material of sufficiently high quality will enter the market.

Initially, the occurrence of product-related and foreign particles in the final product was viewed as a major concern. Based on provided information and a thorough discussion including risk assessment and corrective measures taken so far, potential safety issues arising from the presence of particles can be ruled out.

Concerning the biosimilarity exercise a comparable profile for the majority of the critical quality attributes could be shown. Potential impact of differences in certain characteristics has been ruled out

by demonstrating similarity in biological activity, which was investigated by a broad panel of binding and in vitro assays, structure function relationship studies and reformulation studies.

Similarity of BI 695501 and Humira at the non-clinical level was shown with regard to in vitro PD, in vivo PK and toxicology. Statistically non-significant differences in the PK of BI 695501 and Humira are most probably attributable to the small group size of experimental animals and, thus, of no clinical relevance.

PK trial 1297.1 in HV failed to demonstrate similarity between Cyltezo and EU-Humira in the primary endpoints. The study used a trial formulation of the biosimilar candidate, which differs only minimally from the to-be-commercialised formulation used in the rest of the clinical program. During further assessment, differences in design of both PK studies (1297.1 and 1297.8) regarding their potential sensitivity were discussed. It became clear that some observations that probably decreased sensitivity in trial 1297.1 (such as a slight imbalance in body weight, differences in protein concentrations and variable injection sites), were better controlled in trial 1297.8; sample size was increased to account for the unexpected high variability in the first trial. It is thus plausible that study 1297.8 is the more relevant and sensitive model to detect true, product related differences. Moreover, the main driver for the observed results in trial 1297.1 was an unexpected low exposure of EU-Humira.

Overall it is concluded that trial 1297.8 clearly demonstrating similarity between treatments is the more sensitive and relevant study and Cyltezo is biosimilar to Humira in terms of PK.

The pivotal efficacy and safety study 1297.2 in patients with RA demonstrated comparability to Humira in the primary endpoints (ACR20, Week 12 and 24) substantiated by secondary efficacy measures, such as DAS28, and persistence of similar efficacy could also be demonstrated with the final dataset. Additional reassurance on comparable clinical performance was gained by comparing efficacy over the whole trial duration, including time/response graphs, and also earlier time points.

The final dataset neither revealed major differences in number and kind of AEs nor in incidence and quality of ADA. Efficacy and pharmacokinetics were equally influenced by incidence and quality of ADA between Cyltezo and Humira. Safety concerns pertained to small differences in anaemia, bone fracture, and positive TB tests (mainly occurring in the biosimilar arm), which have been analysed and addressed by the Applicant as far as possible based on the available data. Haematological disorders and tuberculosis are listed as “important identified risks” in the RMP and will be monitored in the scope of routine pharmacovigilance.

Extrapolation to all indications of Humira seems acceptable. Results obtained from relevant functional assays (ADCC, CDC, binding to mTNFα, apoptosis assay, Fcγ-receptor binding triggering regulatory macrophage function, ADCP) showed comparative results concerning the putative mechanism of action in IBD, which is also relevant for the Hidradenitis Suppurativa and Uveitis indication.

3.6.2. Balance of benefits and risks

The totality of the presented data supports biosimilarity of Cyltezo and Humira.

3.7. Conclusions

The overall B/R of Cyltezo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cyltezo is favourable in the following indication:

Rheumatoid arthritis

Cyltezo in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Cyltezo can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Cyltezo reduces the rate of progression of joint damage as measured by X ray and improves physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Adalimumab is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Cyltezo is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Cyltezo is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Cyltezo is indicated for the treatment of active and progressive psoriatic arthritis in adults when the

response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

Cyltezo is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Cyltezo is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Cyltezo is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of agewith an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn’s disease

Cyltezo is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Cyltezo is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Cyltezo is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6 mercaptopurine (6 MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Cyltezo is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Cyltezo in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Cyltezo is marketed, all healthcare professionals who are expected to prescribe Cyltezo have are provided with the following educational package:

- Physician educational material
- Patient information

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient alert card

The Guide for healthcare professionals shall contain the following key elements:

- Relevant information on the safety concerns of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies to be

addressed by the additional risk minimisation measures (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable).

The patient alert card shall contain the following key messages:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Cyltezo.
- That Cyltezo treatment may increase the potential risks of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies.
- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the prescriber

The patient information pack should contain:

- Patient information leaflet

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.