CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761216Orig1s000

MULTI-DISCIPLINE REVIEW

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	761216
Received Date	December 18, 2020
BsUFA Goal Date	December 18, 2021
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)/Office of Immunology and Inflammation (OII) in collaboration with the Division of Dermatology and Dentistry (DDD/OII) and Division of Gastroenterology (DG/OII)
Review Completion Date	See DARRTS stamped date
Product Code Name	CHS-1420
Proposed Nonproprietary Name[1]	Adalimumab-aqvh
Proposed Proprietary Name[1]	Yusimry
Pharmacologic Class	Tumor Necrosis Factor (TNF) blocker
Applicant	Coherus Biosciences, Inc.
Applicant Proposed Indication(s)	• Rheumatoid arthritis (RA): reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. • Juvenile idiopathic arthritis (JIA): reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ≥2 years of age and older. • Psoriatic arthritis (PsA): reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. • Ankylosing spondylitis (AS): reducing signs and symptoms in adult patients with active AS. • Crohn's disease (CD): treatment of moderately and severely active Crohn's disease in adults and pediatric patients 6 years of age and older. • Ulcerative colitis (UC): treatment of moderately to severely active ulcerative colitis in adult patients. Limitations of Use: Effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers. • Plaque psoriasis (Ps): treatment of adult patients with moderate to severe chronic plaque psoriasis who are

[1]The proposed nonproprietary and proprietary names are conditionally accepted until such time that the application is approved.

	candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
Recommendation on Regulatory Action	Approval

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSIS = Office of Study Integrity and Surveillance
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DMAMES = Division of Mitigation Assessment & Medication Error Surveillance
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
U.S.-Humira	U.S.-licensed Humira

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1. Executive Summary

1.1. Product Introduction

Coherus (also referred to as the "Applicant" in this review) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for CHS-1420 as a proposed biosimilar to U.S.-licensed Humira (adalimumab). CHS-1420 is a fully humanized anti-TNFα IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells using recombinant DNA technology. The following bullet points include the basic information about the CHS-1420 product and its proposed indications for which U.S.-Humira has been previously approved.

- The proposed nonproprietary name is adalimumab-aqvh and proposed proprietary name is Yusimry.
- The pharmacologic class is tumor necrosis factor blocker.
- The proposed indications as described in Section 1 of the proposed USPI correspond to those for which U.S.-Humira[2] has been licensed for and are:
    - 1.1 Rheumatoid Arthritis. YUSIMRY is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. YUSIMRY can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).
    - 1.2 Juvenile Idiopathic Arthritis. YUSIMRY is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. YUSIMRY can be used alone or in combination with methotrexate.
    - 1.3 Psoriatic Arthritis. YUSIMRY is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. YUSIMRY can be used alone or in combination with non-biologic DMARDs.
    - 1.4 Ankylosing Spondylitis. YUSIMRY is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.
    - 1.5 Crohn's Disease. YUSIMRY is indicated for the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

[2] FDA-approved U.S.-Humira labeling

- 1.6 Ulcerative Colitis. YUSIMRY is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients.
  Limitations of Use. The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers [see *Clinical Studies (14.7)*].
- 1.7 Plaque Psoriasis. YUSIMRY is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. YUSIMRY should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician [see *Warnings and Precautions (5)*].

- The proposed strength is 40 mg/0.8 mL, dosage forms is solution, and route of administration is subcutaneous.

- The proposed dosing regimen(s) are:

  - Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS):
    Adults: 40 mg every other week.
    Some patients with RA not receiving methotrexate may benefit from increasing the dosage to 40 mg every week or 80 mg every other week.

  - Juvenile Idiopathic Arthritis (JIA):

Pediatric Weight 2 Years of Age and Older	**Recommended Dosage**
30 kg (66 lbs) and greater	40 mg every other week

  - Crohn's Disease (CD):
    Adults: 160 mg on Day 1 (given in one day or split over two consecutive days); 80 mg on Day 15; and 40 mg every other week starting on Day 29.
    Pediatric Patients 6 Years of Age and Older:

Pediatric Weight	**Recommended Dosage**	
	Days 1 and 15	**Starting on Day 29**
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week

  - Ulcerative Colitis (UC):
    Adults: 160 mg on Day 1 (given in one day or split over two consecutive days), 80 mg on Day 15 and 40 mg every other week starting on Day 29.

Discontinue in patients without evidence of clinical remission by eight weeks (Day 57).

- Plaque Psoriasis (Ps):
  Adults: 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

Although the Division of Rheumatology and Transplant Medicine (DRTM) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology (DG), and the Division of Dermatology and Dentistry (DDD) during the course of the review.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

The BLA contains sufficient data and information to conclude that the proposed product and the U.S.-licensed reference product, Humira, utilize the same mechanism(s) of action (MOA(s)) for the conditions of use in the proposed labeling to the extent the MOA(s) are known for U.S.-Humira. Additionally, the conditions of use for which the applicant is seeking licensure have been previously approved for U.S.-Humira.

CHS-1420 binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. It also lyses surface TNF expressing cells in vitro in the presence of complement. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques.

The CHS-1420 drug product is a sterile liquid solution with one proposed strength and presentation: 40 mg/0.8 mL in a single-dose prefilled glass syringe. This strength of CHS-1420 in prefilled syringes is the same as that of U.S.-Humira. CHS-1420 also has the same dosage form (solution) and route of administration (subcutaneous) as that of U.S.-Humira.

1.4. Inspection of Manufacturing Facilities

FDA's Office of Pharmaceutical Manufacturing Assessment (OPMA) conducted an assessment of the manufacturing facilities for this BLA.

(b) (4), is responsible for the manufacture of the CHS-1420 drug substance (DS). A pre-license inspection (PLI) was conducted from (b) (4). No FDA Form 483 was issued, and the inspection was classified as no action indicated (NAI) and no potential approvability issues were identified.

(b) (4) is responsible for manufacturing the CHS-1420 drug product (DP). OPMA determined that the drug product manufacturing facilities were adequate.

The final facility recommendation from OPMA was that BLA 761216 be approved from the standpoint of facilities assessment.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not Applicable

1.6. Biosimilarity Assessment

Table 1. Summary and Assessment of Biosimilarity

Comparative Analytical Studies[3]	
Summary of Evidence	• CHS-1420 is highly similar to U.S.-Humira notwithstanding minor differences in clinically inactive components. • CHS-1420 prefilled syringes (40 mg/0.8 mL) have the same strength as that of U.S.-Humira. • The dosage form and route of administration are also the same as those of U.S.-Humira.

[3] Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical data.

Assessment of Residual Uncertainties	• No residual uncertainties from the product quality assessment
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment support the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties for CHS-1420 from the pharmacology/toxicology assessment.
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• A PK similarity study (Study CHS-1420-03) evaluated PK similarity between CHS-1420 and US-Humira in healthy subjects. • PK similarity between CHS-1420 and U.S.-Humira was established, and supports a demonstration of no clinically meaningful differences between CHS-1420 and U.S.-Humira. • Similar incidence of ADA and Nab formation between CHS-1420 and U.S.-Humira in healthy subjects and patients with PsO supports a demonstration of no clinically meaningful differences between CHS-1420 and U.S.-Humira.
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding PK and immunogenicity assessment.
Additional Clinical Studies	

Summary of Evidence	• In Study CHS-1420-02 on patients with plaque psoriasis, there were no meaningful differences in terms of efficacy between CHS-1420 and U.S.-Humira. • In clinical studies presented in this BLA, the frequency of treatment emergent adverse events, serious adverse events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. • In Study CHS-1420-02 on patients with plaque psoriasis, no clinically meaningful differences were observed between the immunogenicity of CHS-1420 and U.S.-Humira, or the impact of immunogenicity on efficacy, PK, and safety.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical perspective regarding the demonstration of no clinically meaningful differences between CHS-1420 and U.S.-Humira.
Extrapolation	

Summary of Evidence	• DG, DDD and DRTM teams have determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data, and information submitted, including clinical data from the studied population (Ps), to support licensure of CHS-1420 as a biosimilar, under section 351(k) of the PHS Act, for the following indications for which U.S.-licensed Humira has been previously approved: o Treatment of inflammatory bowel disease indications (adult Ulcerative colitis and Crohn's disease ages 6 and above) o Treatment of moderate to severe plaque psoriasis in adults o Treatment of juvenile idiopathic arthritis ages 2 and above o Treatment of adult psoriatic arthritis o Treatment of adult ankylosing spondylitis o Treatment of adult rheumatoid arthritis
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of CHS-1420 as biosimilar to U.S.-Humira for the above indications.

1.7. Conclusions on Approvability

In considering the totality of the evidence, the data submitted by the Applicant show that CHS-1420 is highly similar to U.S.-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CHS-1420 and U.S.-Humira in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of CHS-1420 for JIA in patients 2 years and older, CD in patients 6 years and older, and adult patients with RA, PsA, AS, UC, and Ps. The information submitted by the Applicant demonstrates that CHS-1420 is biosimilar to U.S.-Humira for each of the following indications for which U.S.-Humira is currently licensed and the Applicant is seeking licensure for CHS-1420: JIA in patients 2

years and older, CD in patients 6 years and older, and adult patients with RA, PsA, AS, UC, and Ps[4].

Authors:
Hon-Sum Ko, Cross-Discipline Team Leader
Nikolay Nikolov, Division Director

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

Coherus submitted IND 119540 on November 15, 2013 (received November 20, 2013) for development of CHS-1420 as a proposed biosimilar product to U.S.-Humira (adalimumab), and submitted a biologics license application (BLA) under Section 351(k) of the Public Health Service (PHS) Act on December 18, 2020.

A summary of the important landmarks and agreements with FDA after IND submission has been summarized by the Applicant in the following Table.

Table 2. Summary of FDA Interactions Related to CHS-1420 Clinical Development Program

Meeting	Outcome
BPD Type 2 Meeting, 25 Feb 2015 (Reference ID: 3725835)	• Coherus gained agreement with the Agency for Study CHS-1420-02 on the following: o Using PASI-75 as the primary endpoint o The patient population and exclusion and inclusion criteria o The similarity margin of 15% o The safety monitoring, immunogenicity, and PK assessment plan • The Agency agreed that CHS-1420-03 is adequately designed to assess PK similarity between CHS-1420 and U.S.-Humira

[4] The proposed CHS-1420 labeling states: "Biosimilarity of YUSIMRY has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

BPD Type 4 Meeting, 17 May 2017 (Reference ID: 4112911)	• The bioanalytical and analytical methods for human studies should be submitted in Module 5.3.1.4 • Gained agreement with the Agency on the Extrapolation of Indication document: o Submitted under Module 2 o Submit scientific justification for extrapolating data to support demonstration of biosimilarity for condition of use for which U.S.-Humira has unexpired orphan exclusivity in the original 351(k) BLA (the protected indications will be approved when exclusivity expires) • No integrated analysis of safety data from pooled results will be submitted[a] • The Agency agreed with plan to characterize ADA of CHS-1420 and U.S.-Humira • The Agency agreed with the competitive ligand-binding NAb assay to characterize and compare CHS-1420 and U.S.-Humira
BPD Type 3 Meeting, 02 Jul 2019 (Reference ID: 4498121)	• Purpose of the meeting was to gain agreement on the ADA and NAb assay suitability and strategy for the immunogenicity assessment of CHS-1420 and U.S.-Humira. Specific agreements are summarized as follows: o The ADA assay performance is similar for CHS-1420 and U.S.-Humira, and validation and cross-validation exercises appear to be appropriately performed. o Selection of confirmatory assays for the clinical studies is acceptable o ADA assay cut-point selection strategy, sample selection and statistical methods are appropriate for cut-point determination in the clinical studies o The NAb assay performance was similar for CHS-1420 and U.S.-Humira, and validation exercise appear to be appropriately performed. The NAb assay appears to have acceptable drug tolerance.
BPD Type 4 Meeting, 27 October 2020 (Preliminary comments Reference ID: 4691579)	• Purpose of the meeting was to gain an agreement on content and format of a complete application to support a future 351(k) BLA submission of CHS-1420 as a proposed biosimilar to U.S.-licensed Humira. The preliminary comments from the Agency received on 25October 2020 are summarized as follows: o The proposed structure and content appear acceptable. o The Agency provided updated recommendationsto also include in the CSR an evaluation of the percent change in PASI at Week 16, using a 90% confidence interval with margins of ±10. • During the meeting held on 27 October 2020, the Agency acknowledged that the safety data and data presentation was acceptable.

ADA = anti-drug antibody, BDS = Biologics Development Services, BLA = Biologics License Application, (b) (4) EU = European Union, FDA = Food and Drug Administration, ID = identification, NAb = neutralizing antibody PASI = psoriasis area and severity index, PASI-75 = 75% improvement in PASI, PK = pharmacokinetic, US = United States.

[a]Since this FDA Meeting, Coherus has decided to change its strategy for presenting safety data. Pooled analysis will be presented for single dose studies.
Source: BLA 761216 Module 2 Section 2.5 Clinical Overview Subsection 1.2, Regulatory History. Link: \\cdsesub1\evsprod\BLA761216\0001\m2\25-clin-over\clinical-overview.pdf

Coherus obtained an agreement on the initial Pediatric Study Plan on 18 May 2017. An amendment to the Agreed Initial Pediatric Study Plan was submitted on 16 January 2020 to reflect the then current U.S.-Humira prescribing information, with agreement by FDA on November 23, 2020.

2.2. Studies Submitted by the Applicant

Regarding comparative analytical data, refer to the Comparative Analytical Assessment (CAA) Chapter of the Integrated Quality Assessment (IQA) for additional information.

Table 3. CHS-1420 (Process C) Nonclinical Studies Submitted

Study	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration/Dose
PK Study: A Single Dose Subcutaneous Pharmacokinetic Study in Cynomolgus Monkeys with CHS-1420 and Adalimumab					
IND 119540	*20043567*	*Cynomolgus Monkey*	*3*	*Single dose*	*Subcutaneous; 1 mg/kg* CHS-1420 (Process C) or U.S.-Humira
Toxicity/TK Study: A 1-month Subcutaneous Toxicity Study in Cynomolgus Monkeys with CHS-1420 and Adalimumab with a 6-week Recovery Period					
IND 119540	20026996 -1420-004	*Cynomolgus Monkey*	*3*	*1 month*	*Subcutaneous;* 30 or 100 mg/kg/week CHS-1420 (Process C), or 30 mg/kg/week U.S.-Humira

Table 4. CHS-1420 Relevant Clinical Studies Submitted*

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study: "A Randomized, Double-Blind, Single-Dose, Parallel-Group Study to Assess the Pharmacokinetic Similarity of CHS-1420 DP and Humira® (US) in					

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Healthy Male and Female Subjects"					
CHS-1420-03	n/a	Assess PK similarity by comparing CHS-1420 and U.S.-Humira after a single dose of 40 mg SC administered to healthy subjects	randomized, double blind, single-dose, parallel-group	Healthy Subjects	CHS-1420 40 mg (40 mg/0.8 mL solution) PFS for SC injection vs. U.S.-Humira 40 mg (40 mg/0.8 mL solution) PFS for SC injection
Comparative Clinical Study: "A Double-Blind, Randomized, Parallel-Group, Active-Control Study to Compare the Efficacy and Safety of CHS-1420 Versus Humira® in Subjects with Chronic Plaque Psoriasis (PsOsim)"					
CHS-1420-02	NCT02489227	Comparative safety, efficacy, and immunogenicity of Coherus-1420 and U.S.-Humira	randomized, double-blind, active-control (followed by open-label safety), parallel-group, multicenter study across 97 sites worldwide	Plaque psoriasis	CHS-1420/CHS-1420/CHS-1420 vs U.S.-Humira/U.S.-Humira/CHS-1420 vs U.S.-Humira/CHS-1420/CHS-1420 over 3 treatment periods

*The following submitted clinical studies are not listed because they are not considered relevant to support a demonstration of biosimilarity for CHS-1420 PFS:
CHS-1420-01 (single-dose PK study using an earlier formulation of CHS-1420),
CHS-1420-05 (single-dose PK study comparing AI and PFS presentations of CHS-1420),
CHS-1420-07 (single-dose study PK comparing with EU-approved Humira as comparator), and
CHS-1420-04 (3-dose study testing use of autoinjector by RA patients and caregivers).

Authors:

Xiaochun Chen Non-Clinical Reviewer	Carol Galvis Non-Clinical Team Leader
Priya Brunsdon Clinical Pharmacology Reviewer	Ping Ji Clinical Pharmacology Team Leader
Hon-Sum Ko Clinical Reviewer	Hon-Sum Ko Acting Clinical Team Leader & CDTL

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Products, OPQ, CDER, recommends approval of BLA 761216 for CHS-1420 manufactured by Coherus. Refer to the integrated quality assessment and related primary reviews for detailed information. The OPQ team determined that the data submitted in this application are adequate to support the following conclusions:

- The manufacture of CHS-1420 is well-controlled and leads to a product that is pure, potent, and safe.
- There are three manufacture process iterations during the commercial developent stage of CHS-1420. The comparability is demonstrated between the late development lots (used for PK similarity study CHS-1420-03 and comparative clinical study CHS-1420-02), pre-commercial and commercial lots.
- CHS-1420 is highly similar to U.S.-Humira notwithstanding minor differences in clinically inactive components.
- The strength of CHS-1420 (0 mg/0.8 mL) in a prefilled syringe is the same as that of U.S.-Humira. CHS-1420 also has the same dosage form and route of administration as that of U.S.-Humira.

3.2. Devices

CHS-1420 product is a sterile liquid solution with the following proposed strength and presentation:

- Prefilled syringe
  Injection: 40 mg/0.8 mL in a single-dose prefilled plastic syringe

Container closure:

- CHS-1420 PFS: The container closure system (CCS) consists of [redacted] (b) (4) 1-mL-long syringe barrel with a 29 gauge, ½-inch needle with [redacted] (b) (4) rigid needle shield (RNS), and [redacted] (b) (4) plunger stopper.

3.2.1. Center for Devices and Radiological Health (CDRH)

As PFS without additional safety device can be reviewed by OPQ alone, CDRH was not consulted for the device component of CHS-1420.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

In October, 2019, Coherus requested review of their Human Factors (HF) Threshold Analysis, Use-Related Risk Analysis (URRA), Instructions for Use (IFU), and Quick Reference Guide (QRG).

DMEPA reviewed the submission and subsequent materials submitted, including a human factors validation study protocol in December, 2019. DMEPA noted that since the proposed product is a combination product, the device constituent should comply with the Quality System regulation, 21 CFR Part 820. In particular, Section 30, Design Controls, includes requirements relevant to human factors. However, based on review of Coherus' URRA, comparative analyses, and justification, DMEPA determined that results from a human factors validation study do not need to be submitted for CHS-1420 prefilled syringe with the BLA.

DMEPA has also provided recommendations on labeling. The CDTL and Divisions Signatory concur that additional data are not needed, and the proposed labeling is appropriate and sufficient to ensure the safe and effective use of the PFS presentation ofCHS-1420.

3.3. Office of Study Integrity and Surveillance (OSIS)

OSIS conducted an Remote Record Review (RRR) of the bioanalytical portion of Study CHS-1420-03 performed at [redacted] (b) (4). OSIS noted that [redacted] (b) (4) Based on the outcome of the RRR and review of the firm's response, the objectionable condition had no impact on the integrity of the pharmacokinetic (PK) data reviewed from Study CHS-1420-03. Therefore, OSIS has concluded that the PK data from the reviewed study are acceptable.

Refer to the review memo by Drs. Gajendiran Mahadevan/Amanda Lewin dated September 23, 2021 for additional information.

3.4. Office of Scientific Investigations (OSI)

Based on the information submitted and evaluation of the sites for the clinical studies, Clinical and Statistical Reviewers have determined that site audits are not needed. Thus, OSI audits were not conducted.

Author:

Hon-Sum Ko
Clinical Reviewer

Hon-Sum Ko
Acting Clinical Team Leader & CDTL

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

According to FDA Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April, 2015), *a 351(k) application should include information demonstrating biosimilarity based on data derived from animal studies (including the assessment of toxicity), unless FDA determines that such studies are not necessary in a 351(k) application*. However, the Applicant did not request a pre-IND meeting prior to the submission of IND 119540 on November 21, 2013. In the opening IND, the Applicant provided comparative analytical data among CHS-1420 (Process C) and U.S.-Humira including the assessment of physicochemical, potency, and biological activity attributes for several lots. In addition, results from a single subcutaneous (SC) dose pharmacokinetic (PK) study and a one-month repeat SC dose toxicity/toxicokinetics (TK) study of CHS-1420 (Process C) in cynomolgus monkeys were provided.

On November 17, 2014, the CHS-1420 Process D product was proposed for further clinical development and to be the intended commercial product. Since CHS-1420 Process C and D products were determined to have similar pharmacological activity compared to U.S.-Humira (see the CMC review by Dr. Jun Park, dated October 15, 2015 under IND 119540), there is an adequate analytical bridge allowing the nonclinical studies comparing CHS-1420 Process C and U.S.-Humira to be used to assess the

safety of CHS-1420 Process D. According to the same guideline above, *animal toxicity data are considered useful when, based on the results of extensive structural and functional characterization, uncertainties remain about the safety of the proposed product that need to be addressed before initiation of clinical studies in humans*. Therefore, animal PK/TK and toxicity results for CHS-1420 (Process C) are summarized below and in Section 13.3 to support a demonstration of biosimilarity.

In the single SC dose PK study of CHS-1420 (Process C) in cynomolgus monkeys, the serum concentration-time profiles for 1 mg/kg of CHS-1420 and U.S.-Humira over 240 hrs postdose were similar.

In the one-month repeat-dose general toxicity study of CHS-1420 (Process C) in cynomolgus monkeys, the toxicity and TK profiles of CHS-1420 and U.S.-Humira were considered to be similar at the 30 mg/kg level, except for females on Day 29 where exposure to 30 mg/kg CHS-1420 was about +50% higher compared to 30 mg/kg U.S.-Humira, likely due to limited number of animals with large variation; this observation was not considered to be meaningful. Anti-drug antibody (ADA) was detected in both CHS-1420 and U.S.-Humira -treated groups.

Overall, the toxicity and PK/TK profiles of CHS-1420 (Process C) and U.S.-Humira were considered to be similar. The information in the pharmacology/toxicology assessment support the demonstration of biosimilarity. See Sections **Error! Reference source not found.** and 13.3 for additional information from the nonclinical assessment.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The commercial CHS-1420 (Process D) drug products will be supplied as a sterile solution designed for SC injection with (b) (4) The drug product contains a formulation of 50 mg/mL CHS-1420 drug substance, 0.638 mg/mL L-histidine, 5.43 mg/mL L-histidine HCl monohydrate, 12.0 mg/mL glycine, 2.58 mg/mL sodium chloride, 1 mg/mL polysorbate 80 and water for injection (Error! Reference source not found.). The drug product is presented as a prefilled syringe (PFS) with no overage, ready for injection.

Table 5. Composition of CHS-1420 (Process D) Drug Product, for injection

Ingredients	Reference to Standards	Function	Unit Formula	
			40 mg PFS (mg)	(mg/mL)
CHS-1420	Coherus	Drug Substance	40	50
L-Histidine	USP/ Ph. Eur. /JP	(b) (4)	0.51	0.638
L-Histidine HCl monohydrate	Ph. Eur. / JP		4.34	5.43
Glycine	USP/ Ph. Eur./ JP		9.61	12.0
Sodium chloride	USP/ Ph. Eur.		2.06	2.58
Polysorbate 80	NF/ Ph. Eur.		0.8	1
Water for injection	USP/ Ph. Eur.		qs to 0.8 mL	N/A
Sodium hydroxide*	NF / Ph. Eur. / JP	pH Adjustment	qs to pH 5.3	N/A

USP = United States Pharmacopoeia; Ph. Eur. = European Pharmacopoeia; JP = Japanese Pharmacopoeia; NF = National Formulary; qs = quantum sufficient, HCl = Hydrochloric Acid; N/A = Not Applicable; PFS = Prefilled Syringe
*: Added as necessary for pH adjustment (b) (4)

Comments on Excipients

The excipients in the formulation of the CHS-1420 (Process C) 40 mg/0.8 mL PFS drug product used for nonclinical studies at early drug development is identical to that of U.S.-Humira except for a (b) (4)

The excipients used in the commercial formulation of the CHS-1420 (Process D) 40 mg/0.8 mL PFS drug product differ from that of U.S.-Humira 40 mg/0.8 mL PFS drug product (**Table 6**). The only two excipients found in both formulations were polysorbate 80 (same amount) and sodium choliride (lower for CHS-1420 drug product). All excipients for CHS-1420 (Process D) were compendial and their quality standards met the current version of the USP or NF, Ph. Eur., or JP. None of the excipients used in CHS-1420 were of human or animal origin. The total quantity of histidine from L-histidine and L-histidine hydrochloride monohydrate was combined to accurately assess the total amount of histidine. Excipients are within the ranges that are found in the inactive ingredient database.

Table 6. Excipients of CHS-1420 (Process D) and U.S.-Humira Drug Products, for injection

Ingredients	CHS-1420		U.S.-Humira	
	40mg PFS: Unit Formula		40mg PFS: Unit Formula	
	(mg)	(mg/mL)	(mg)	(mg/mL)
L-Histidine	0.51	0.638	-	-
L-Histidine HCl monohydrate	4.34	5.43	-	-
Citric acid monohydrate	-	-	1.04	1.31
Sodium citrate	-	-	0.244	0.31
Disodium phosphate dihydrate	-	-	1.22	1.53
Monobasic sodium phosphate	-	-	0.688	0.86
Glycine	9.61	12	-	-
Sodium chloride	2.06	2.58	4.93	6.17
Manitol	-	-	9.6	12
Polysorbate 80	0.8	1	0.8	1
Water for injection	qs to 0.8 mL	N/A	qs to 0.8 mL	N/A
Sodium hydroxide*	qs to pH 5.3	N/A	qs to (b) (4)	N/A

qs: quantity sufficient; N/A = Not Applicable
*: Added as necessary for pH adjustment.

Comments on Impurities of Concern

No impurities of concern are identified. No extractables/leachables of safety concern were identified (refer to review report dated Octorber 6, 2021 under BLA 761216 in DARRTS [reference ID: 4868752]).

Authors:

Xiaochun Chen, PhD
Nonclinical Reviewer

Carol Galvis, PhD
Nonclinical Supervisor/Team leader

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 7. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	PK similarity between CHS-1420 and U.S.-Humira was established, and supports a demonstration of no clinically meaningful differences between CHS-1420 and U.S.-Humira.

Pharmacodynamics	Not applicable
Immunogenicity	Comparable incidence of ADA and NAb formation between CHS-1420 and U.S.-Humira in healthy subjects and patients with PsO supports a demonstration of no clinically meaningful differences between CHS-1420 and U.S.-Humira.

The clinical development program for CHS-1420 included 2 studies pertinent to the clinical pharmacology review:

- CHS-1420-03: PK similarity study between CHS-1420 and U.S.-Humira after a single dose of 40 mg SC administered to healthy subjects.
- CHS-1420-02: aComparative clinicalstudy comparing the safety and efficacy (measured by the PASI) of CHS-1420 and U.S.-Humira at 12 weeks in subjects with moderate to severe chronic PsO.

The results of the PK similarity study (Study CHS-1420-03) demonstrated PK similarity between CHS-1420 and US- Humira.

In the PK similarity study (Study CHS-1420-03), the 90% CI for the geometrics means ratios (GMRs) for the maximum observed drug concentration (C_{max}) and area under the serum drug concentration-time curve ($AUC_{0\text{-}inf}$) were contained within the prespecified criteria of (b) (4)% to (b) (4)% (**Table 8**).

Table 8. Summary of statistical analyses for assessment of PK similarity (Study CHS-1420-03)

Parameter	Geometric Mean (%CV)		Geometric Mean Ratio* (90% CI)
	CHS-1420	U.S.-Humira	CHS-1420 vs U.S.-Humira
$AUC_{0\text{-}inf}$ (h*µg/mL)	2041	1988	102.7 (92.23, 114.31)
C_{max} (µg/mL)	3.70	3.75	98.6 (90.66, 107.32)

*Presented as percent. Source: Clinical Study Report CHS-1420-03, Table 9, Page 52, Link \\CDSESUB1\evsprod\bla761216\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\chs-1420-03\study-report.pdf

The immunogenicity of CHS-1420 was comparable to that of U.S.-Humira after a single dose in healthy subjects and after multiple doses in patients with chronic plaque psoriasis.

Note that the biopharmaceutical inspections were requested for the clinical and bioanalytical sites for Study CHS-1420-03. Refer to **Section 3.3** for further details.

The overall incidence of anti-drug antibody (ADA) formation over the course of the study in healthy subjects was 82% and 83% in the CHS-1420 and U.S.-Humira groups, respectively (Study CHS-1420-03). The overall incidence of neutralizing antibodies (nAb) formation over the course of the study in healthy subjects was 60% and 65% for CHS-1420 and U.S.-Humira, respectively (Study CHS-1420-03).

For the study conducted in chronic plaque psoriasis patients (Study CHS-1420-02), some patients in the U.S.-Humira arm underwent a single transition to CHS-1420 after period 1. After multiple 40 mg SC doses in treatment period 1 only, the incidence of ADAs was similar between CHS-1420 and U.S.-Humira (90% and 94%, respectively) in patients with chronic plaque psoriasis. The incidence of nAb formation was also similar between CHS-1420 and U.S.-Humira (33% and 34%, respectively) in treatment period 1. The incidence of ADAs and NAbs was similar between subjects who continued treatment with CHS-1420 or U.S.-Humira in period 2 compared to subjects who switched from U.S.-Humira to CHS-1420 in period 2. In the U.S.-Humira group that was switched to CHS-1420, the incidence of ADAs was 94% before period 2, and 95% by the end of period 2; and the incidence of NAbs was 32% before period 2, and 41% by the end of period 2.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

As PK similarity and comparable immunogenicity was demonstrated between CHS-1420 and U.S.-Humira, there are no residual clinical pharmacology uncertainties.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not applicable.

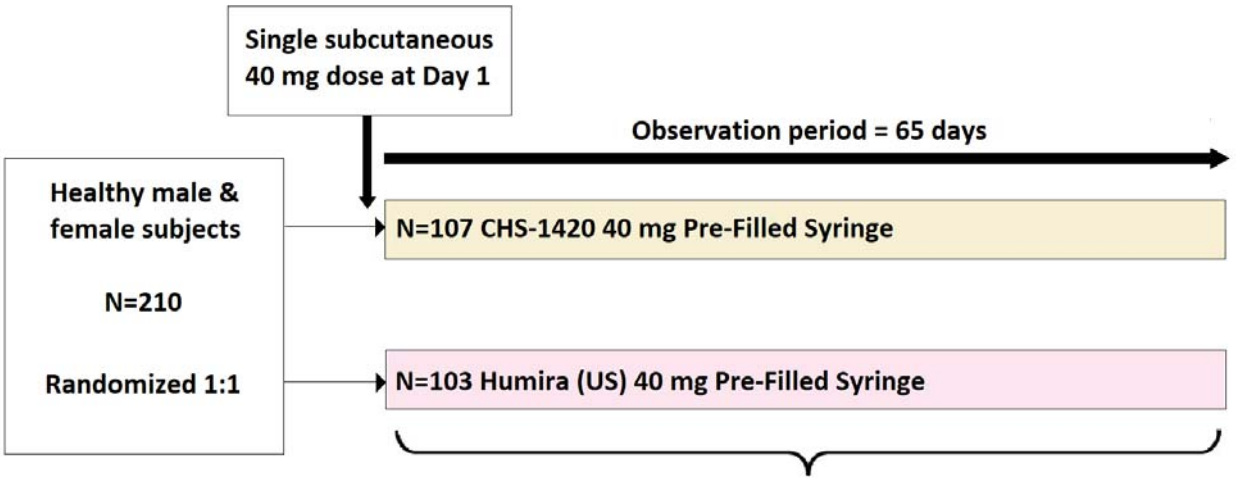
5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1. CHS-1420-03: "A Randomized, Double-Blind, Single-Dose, Parallel-Group Study to Assess the Pharmacokinetic Similarity of CHS-1420 DP and Humira® (US) in Healthy Male and Female Subjects"

Clinical Pharmacology Study Design Features

The PK similarity study comparing CHS-1420 and U.S.-Humira was conducted in healthy subjects (Study CHS-1420-03). The study was conducted at 2 sites in the United States: Medpace Clinical Pharmacology Unit, Cincinnati, Ohio; and West Coast Clinical Trials (WCCT) Global, Cypress, California. (b) (4) The number of subjects randomized in the study was 210.

Figure 1. Study design of the PK similarity study (CHS-1420-03)



Study Procedures	Screening	Admission	Treatment Session				Outpatient Visits					Follow-up/ ET Visit
	Up to Day -21	Day -1	Day 1	Day 2	Day 3	Day 4	Days 5-13	Day 16	Day 23	Day 30	Days 37-58	Day 65 ±4 days
Serum PK sample			X	X	X	X	X	X	X	X	X	X
Serum ADA sample	X		X			X		X		X		X

Source: FDA reviewer-generated schematic

Clinical Pharmacology Study Endpoints

In study CHS-1420-03, the primary PK endpoints were the maximum serum concentrations (C_{max}) of CHS-1420 and U.S.-Humira and the area under the serum concentration versus time curve (AUC) extrapolated from 0 to infinity ($AUC_{0\text{-}inf}$)

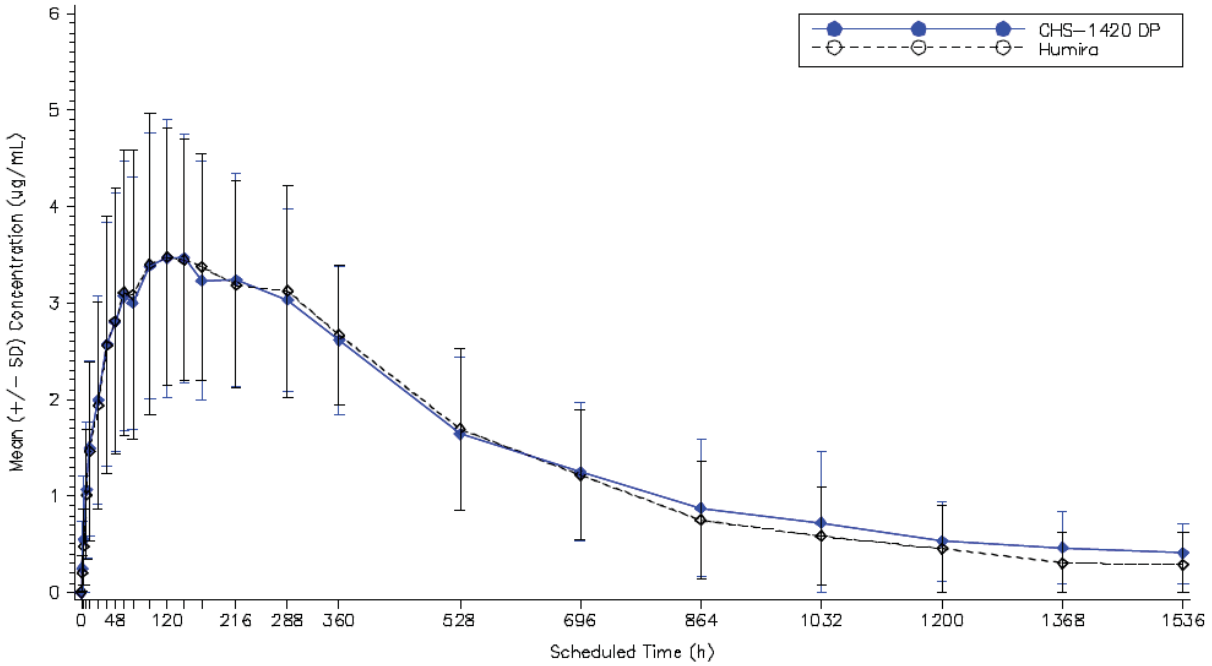
Bioanalytical PK Method and Performance

The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated. Serum concentrations of CHS-1420 and U.S.-Humira were quantified using an anti-idiotype antibody sandwich enzyme-linked immunosorbent assay (ELISA). See Appendix 13.4.1 for further details on the bioanalytical method and performance in Study CHS-1420-03.

PK Similarity Assessment

In the PK similarity study (Study CHS-1420-03), the 90% CI for the geometrics means ratios (GMRs) for the maximum observed drug concentration (C_{max}) and area under the serum drug concentration-time curve ($AUC_{0\text{-}inf}$) were contained within the prespecified criteria of 80% to 125% (
Table 9). The mean concentration-time profiles were similar between CHS-1420 and U.S.-Humira (**Figure 2**).

Figure 2. Mean Concentration-time profiles for CHS-1420 and Humira (Study CHS-1420-03)



Source: Clinical Study Report for CHS-1420-03, Figure 1, page 49, Link \\CDSESUB1\evsprod\BLA761216\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\chs-1420-03\study-report.pdf

Table 9. Summary of PK Parameters for CHS-1420 and Humira (CHS-1420-03)

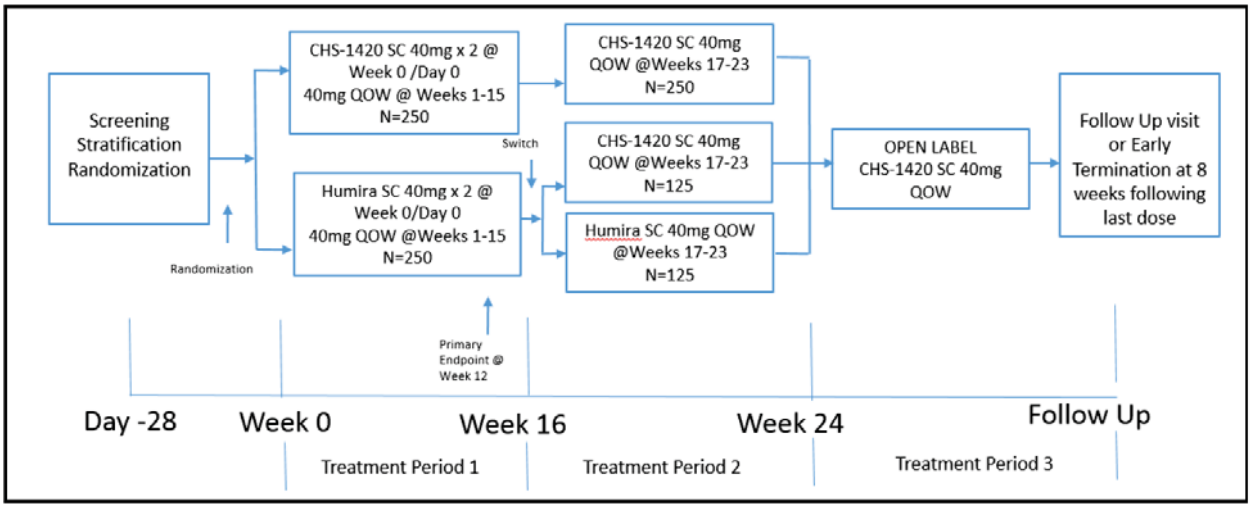
PK Parameters (Unit)	CHS-1420		U.S.-Humira		GMR (%)	90% CI for GMR (%)
	N	Geometric Mean	N	Geometric Mean		
C_{max} (µg/mL)	95	3.70	93	3.75	98.6	90.7, 107.3
$AUC_{0\text{-}inf}$ (h*µg/mL)	91	2041	92	1988	102.7	92.2, 114.3
$AUC_{0\text{-}65day}$ (h*µg/mL)	92	1958	92	1922	101.9	92.5, 112.3

$AUC_{0\text{-last}}$ (h*µg/mL)	95	1903	93	1883	101.1	91.1, 112.1

GMR = Geometric mean ratio
Source: Modified from Clinical Study Report for CHS-1420-03, Table 9, page 52, Link \\CDSESUB1\evsprod\BLA761216\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\chs-1420-03\study-report.pdf

5.3.2. CHS-1420-02: "A Double-Blind, Randomized, Parallel-Group, Active-Control Study to Compare the Efficacy and Safety of CHS-1420 Versus Humira® in Subjects with Chronic Plaque Psoriasis (PsOsim) Clinical Pharmacology Study Design Features"

Figure 3. Study design of the comparative clinical study in chronic plaque psoriasis patients (Study CHS-1420-02)



Source: Clinical Study Report for CHS-1420-02, page 5, Link \\CDSESUB1\evsprod\bla761216\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5351-stud-rep-contr\chs-1420-02\study-report.pdf

Clinical Pharmacology Study Endpoints

Study CHS-1420-02 was a comparative safety and efficacy study for CHS-1420 or U.S.-Humira in chronic plaque psoriasis patients. The primary efficacy endpoint in Study CHS-1420-02 was 75% improvement in PASI (PASI-75) at Week 12 relative to baseline. Serum samples were collected pre-dose and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48 to be used for pharmacokinetic and/or immunogenicity assessments. However, there were no pharmacokinetic or immunogenicity-related endpoints for the study.

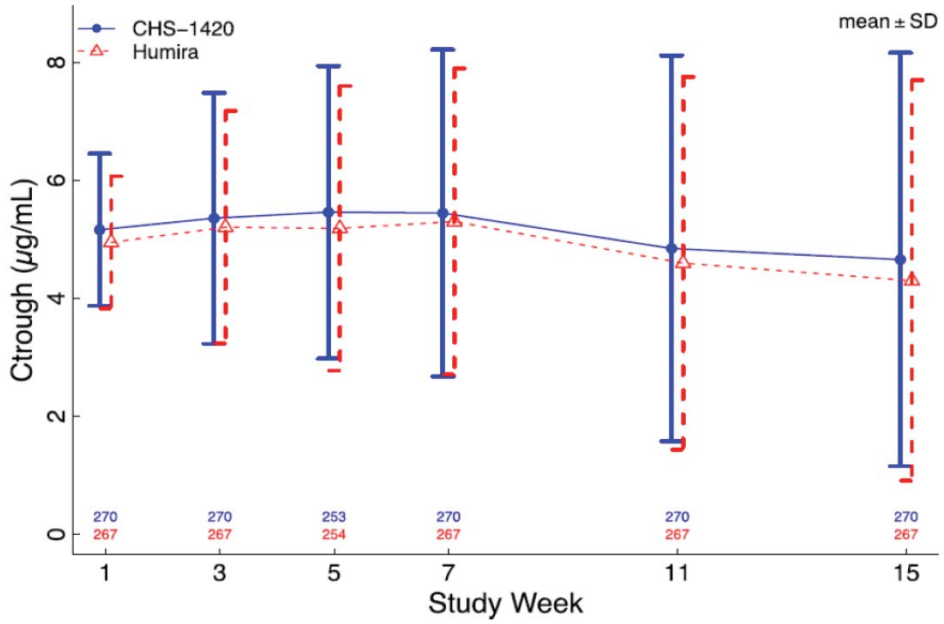
Bioanalytical PK Method and Performance

The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated. Serum concentrations of CHS-1420 and U.S.-Humira were quantified using an anti-idiotype antibody sandwich enzyme-linked immunosorbent assay (ELISA). See Appendix 13.4.1 for further details on the bioanalytical method and performance in Study CHS-1420-02.

PK Assessment

In this comparative clinical study CHS-1420-02 in chronic plaque psoriasis patients, tough concentration (C_{trough}) over time were similar between patients who received CHS-1420 vs. U.S.-Humira (**Figure 4.**). As patients were potentially switched between treatment arms following treatment period 1 (week 16), comparisons in PK between treatment arms could only be evaluated in period 1.

Figure 4. Mean Trough Serum Concentration by Treatment through Week 16



Source: Clinical Study Report for CHS-1420-02, Figure 5, page 114, Link \\CDSESUB1\evsprod\bla761216\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5351-stud-rep-contr\chs-1420-02\study-report.pdf

5.4. Clinical Immunogenicity Studies

5.4.1. Clinical Immunogenicity Overview and Results

Design features of the clinical immunogenicity assessment
Immunogenicity upon single dosing has been evaluated in healthy subjects in Study CHS-1420-03. Immunogenicity after repeat dosing was evaluated in study CHS-1420-02. See **Figure 1** and **Figure 3.** for details on the study designs.

Immunogenicity endpoints
The formation of ADA and the neutralizing activity of ADA was evaluated for immunogenicity assessment.

Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product and U.S.-licensed reference product in the study samples
The ADA assay was an electrochemiluminescence bridging assay that used CHS-1420 as the labeled reagent. The NAb assay was an electrochemiluminescence competitive ligand binding assay that measured the binding of CHS-1420 to its target, TNFα. Refer to the OBP immunogenicity review for more details.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation
The sampling plan was adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation.

Study CHS-1420-03: Serum ADA samples were collected pre-dose and days 1, 4, 16, 30, and the end-of-treatment visit on day 65.

Study CHS-1420-02: Serum ADA samples were collected pre-dose and weeks 2, 4, 8, 12, and 16 during treatment period 1. Samples were collected on weeks 20 and 24 during treatment period 2. Samples were collected on weeks 32, 40, and 48 during treatment period 3, in addition to an end-of-treatment sample at week 55.

Incidence of ADA (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

In Study CHS-1420-03, there was similar incidence of pre-existing antibodies at baseline in the CHS-1420 group (9%, n=10/107) and Humira (7%, n=7/103). Following a single 40 mg subcutaneous dose of CHS-1420 or U.S.-Humira, 88/107 (82.2%) and 85/103 (82.5%) subjects, respectively, developed treatment-emergent ADAs any time post-dose. Overall, the ADA incidence is similar between CHS-1420 and U.S.-Humira treatment arms in healthy subjects (**Table 10**).

In Study CHS-1420-02, 17/268 (6.3%) and 2/271 (10.3%) of chronic plaque psoriasis patients had pre-existing ADAs at baseline. Following multiple 40 mg SC doses of CHS-1420 and U.S.-Humira in period 1 (up until week 16), 89.5% and 93.8%, respectively, of patients developed treatment-emergent ADAs. In treatment period 2, some patients receiving U.S.-Humira were switched to receive CHS-1420 in period 2 (this group is referred to as U.S.-Humira/CHS-1420). In the Humira/CHS-1420 group, the incidence of ADAs was 93.8% at the end of period 1 and 95.2% by the end of period 2. In the open-label period 3, all patients received CHS-1420 and had very similar levels of overall treatment-emergent ADAs by the end of period 3. Overall, incidence of ADAs was similar between all CHS-1420 and U.S.-Humira groups. Switching to CHS-1420 from U.S-Humira did not result in increased ADAs (**Table 11**).

Neutralizing Antibodies (nAb)

The overall incidence of neutralizing antibodies (nAb) formation over the course of the study in healthy subjects was 59.8% and 65.0% for CHS-1420 and U.S.-Humira, respectively (Study CHS-1420-03).

For Study CHS-1420-02 in chronic plaque psoriasis patients, the incidence of nAb formation was also similar between CHS-1420 and U.S.-Humira (33.0% and 33.2%, respectively) in treatment period 1. The incidence NAbs was similar between patients who continued treatment with CHS-1420 (38.5%) or U.S.-Humira (40.4%) in period 2 compared to patients who switched from Humira to CHS-1420 (40.9%) in period 2. By the end of period 3, development of NAbs were similar for all three treatment groups (**Table 11**).

Table 10. Immunogenicity results for binding ADA and NAb in Study CHS-1420-03

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
CHS-1420	107	10/107 (9.3%)	88/107 (82.2%)	64/107 (59.8%)
U.S.-Humira	103	7/103 (6.8%)	85/103 (82.5%)	67/103 (65.0%)

Source: Reviewer-generated table from data in the Integrated Summary of Immunogenicity, Link \\CDSESUB1\evsprod\bla761216\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso-ra\5353-rep-analys-data-more-one-stud\iss\isi.pdf

Table 11. Immunogenicity results for binding ADA and NAb in Study CHS-1420-02

	Treatment-Induced ADA	Treatment-Emergent NAb

	Baseline	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
CHS-1420/ CHS-1420/ CHS-1420	17/268 (6.3%)	230/257 (89.5%)	240/257 (93.4%)	246/157 (95.7%)	90/273 (33.0%)	105/273 (38.5%)	132/273 (48.4%)
Humira/ CHS-1420/ CHS-1420	27/271 (10.3%)	228/243 (93.8)	119/125 (95.2%)	121/125 (96.8%)	89/268 (33.2%)	54/132 (40.9%)	74/132 (56.1%)
Humira/ Humira/ CHS-1420			113/118 (95.8%)	116/118 (98.3%)		55/136 (40.4%)	77/136 (56.6%)

Source: Reviewer-generated table from data in the Integrated Summary of Immunogenicity, Link \\CDSESUB1\evsprod\bla761216\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso-ra\5353-rep-analys-data-more-one-stud\iss\isi.pdf

5.4.2. Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

Impact of ADA and Nab on PK

In single-dose PK Study CHS-1420-03, systemic drug exposure (AUC) was lower in ADA-positive subjects compared to ADA-negative subjects for both CHS-1420 and U.S.-Humira. Similarly, NAb-positive subjects had lower systemic exposure than NAb-negative subjects in both treatment groups. The magnitude of lowered exposure was similar between the CHS-1420 and U.S.-Humira treatment groups (**Table 12**).

Table 12. Summary of PK Parameters by Treatment and ADA Status (Study CHS-1420-03)

PK Parameter (Unit)	CHS-1420				Humira (US)			
	ADA Positive		ADA Negative		ADA Positive		ADA Negative	
	n	Statistic	n	Statistic	n	Statistic	n	Statistic
C_{max} (µg/mL)[1]	87	3.593 (37.0)	8	5.099 (23.3)	84	3.651 (34.1)	9	4.827 (29.7)
t_{max} (h)[2]	87	142.8 (36, 361)	8	143.4 (72, 145)	84	121.1 (36, 361)	9	119.4 (48, 288)
λz (/h)[3]	83	0.0059 (0.00387)	8	0.0014 (0.00034)	83	0.0063 (0.00358)	9	0.0014 (0.00051)
$t_{1/2}$ (h)[3]	83	215.0 (193.98)	8	524.7 (128.81)	83	167.7 (132.22)	9	546.5 (165.13)
$AUC_{0\text{-inf}}$ (h*µg/mL)[1]	83	1924.3 (44.9)	8	3760.3 (24.3)	83	1855.3 (38.1)	9	3753.6 (35.8)
$AUC_{0\text{-65 day}}$ (h*µg/mL)[1]	84	1865.2 (41.6)	8	3264.3 (20.3)	83	1821.5 (36.1)	9	3148.8 (30.9)
$AUC_{0\text{-last}}$ (h*µg/mL)[1]	87	1812.4 (44.5)	8	3238.4 (21.1)	84	1781.9 (40.8)	9	3149.1 (30.9)
AUC extrapolated (%)[3]	83	3.860 (6.6544)	8	13.798 (4.0434)	83	1.972 (4.2340)	9	15.748 (8.1871)
CL/F (mL/h)[3]	83	22.908 (11.8984)	8	10.908 (2.6204)	83	23.066 (8.8563)	9	11.255 (4.0278)

Source: Clinical Study Report for CHS-1420-03, Table 17, page 70, Link

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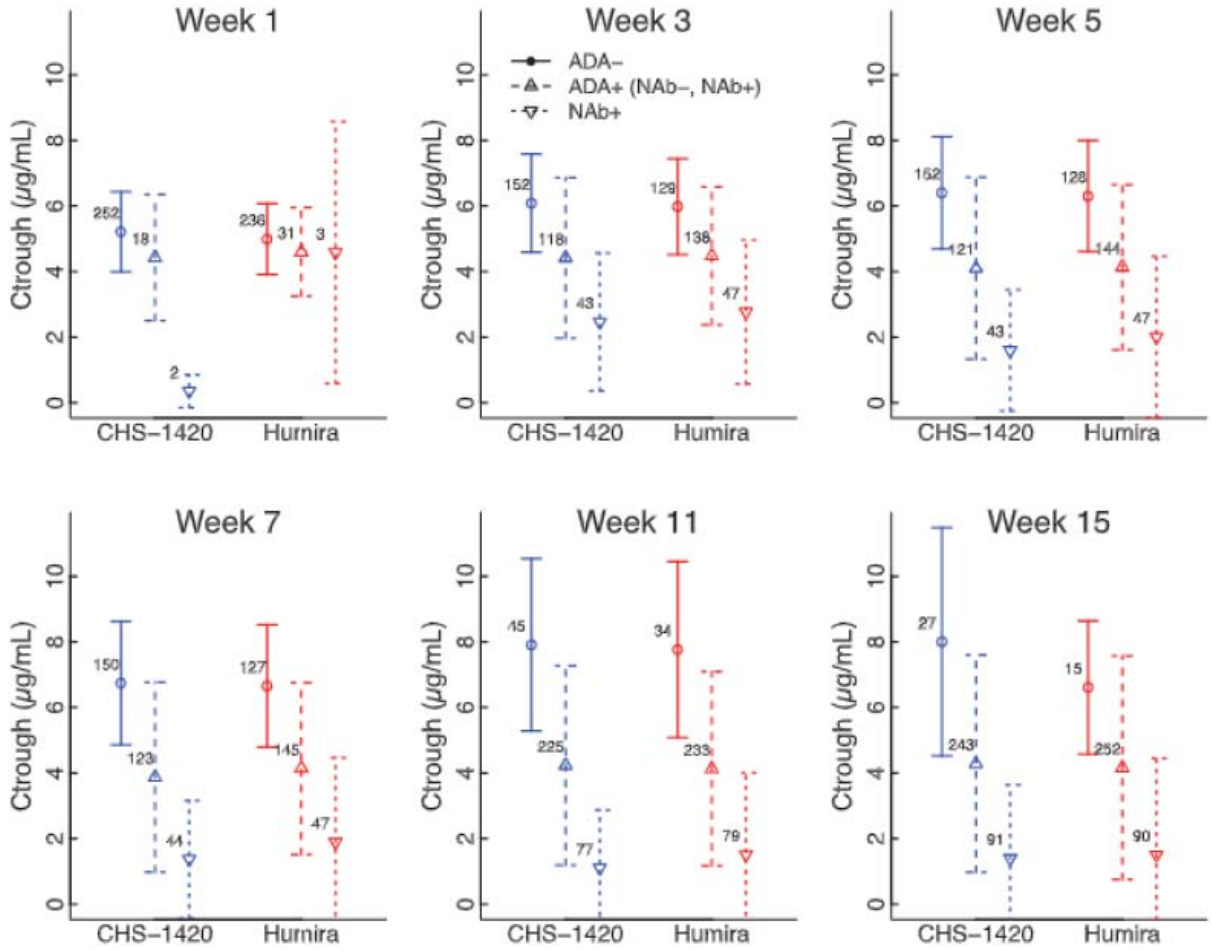
Table 13. Summary of PK Parameters by Treatment and NAb Status (Study CHS-1420-03)

PK Parameter (Unit)	CHS-1420 DP				U.S.-Humira			
	NAb Positive		NAb Negative		NAb Positive		NAb Negative	
	n	Statistic	n	Statistic	n	Statistic	n	Statistic
C_{max} (µg/mL) [1]	63	3.598 (37.0)	32	3.909 (37.9)	66	3.671 (36.4)	27	3.955 (30.1)
t_{max} (h) [2]	63	142.9 (36, 361)	32	131.8 (48, 360)	66	132.2 (36, 361)	27	119.4 (48, 361)
λ_z (/h) [3]	59	0.0076 (0.00335)	32	0.0018 (0.00099)	65	0.0070 (0.00339)	27	0.0028 (0.00254)
$t_{½}$ (h) [3]	59	117.8 (77.96)	32	471.6 (175.17)	65	125.5 (66.79)	27	395.6 (209.29)
$AUC_{0\text{-}65day}$ (h*µg/mL) [1]	60	1674.2 (39.5)	32	2627.1 (32.1)	65	1712.2 (36.2)	27	2537.1 (30.9)
$AUC_{0\text{-}last}$ (h*µg/mL) [1]	63	1617.7 (42.6)	32	2620.9 (32.1)	66	1666.9 (41.7)	27	2535.7 (30.9)
$AUC_{0\text{-}inf}$ (h*µg/mL) [1]	59	1660.0 (38.9)	32	2987.4 (34.0)	65	1718.8 (36.5)	27	2820.7 (37.7)
AUC extrapolated (%) [3]	59	0.831 (1.4535)	32	11.930 (7.5947)	65	0.675 (0.8031)	27	9.688 (8.6741)
CL/F (mL/h) [3]	59	26.038 (12.4726)	32	14.136 (4.9043)	65	24.747 (8.9983)	27	15.084 (5.3017)

Source: Clinical Study Report for CHS-1420-03, Table 18, page 71, Link \\CDSESUB1\evsprod\BLA761216\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\chs-1420-03\study-report.pdf

In Study CHS-1420-02, the presence of ADAs were associated with decreased drug concentrations (Ctrough) in all treatment groups and sequences in the study. Serum drug trough were further lowered in NAb+ patients. The magnitude that serum trough concentrations were lowered for ADA+ and NAb+ patients was similar between CHS-1420 and Humira. Overall, the trough concentrations between the subgroups of each treatment arm is considered similar for each week through week 15 (
Figure 5).

Figure 5. Mean Trough Serum Concentrations by Treatment and ADA and NAb Status through Week 15 (Treatment Period 1, Study CHS-1420-02)



Integers = number of subjects
Source: Integrated Summary of Immunogenicity, Figure 13, page 73, Link \\CDSESUB1\evsprod\bla761216\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso-ra\5353-rep-analys-data-more-one-stud\iss\isi.pdf

Impact of ADA and Nab on Efficacy

In Study CHS-1420-02, the primary efficacy endpoint was 75% improvement in PASI (PASI-75) at week 12 relative to baseline, where baseline was the last assessment prior to beginning study drug. Decreased efficacy was observed by week 12 in NAb+ patients. However, this decreased efficacy was observed in both CHS-1420 and U.S.-Humira treatment arms to a similar degree. For each week that efficacy was assessed in treatment period 1, each ADA/NAb status subgroup had similar efficacy when compared between CHS-1420 and U.S.-Humira (**Table 14**). Some patients who were randomized to receive U.S.-Humira in treatment period 1 were switched to receive CHS-1420 at week 16 (the start of treatment period 2). Patients who switched from U.S.-Humira to CHS-1420 treatments did not have lower efficacy than those who

remained on either CHS-1420 or U.S.-Humira for the entire 24 week treatment. At week 24, there was similar treatment effects in all three treatment arms.

Table 14. Percentage of Subjects Achieving PASI-75 at Weeks 4, 12 and 16 by ADA and NAb Status – Full Analysis Population (Treatment Period 1)

ADA and NAb Status	CHS-1420			Humira (N=271			Treatment Difference
	N'	n	%	N'	n	%	Wald 95% CI
Week 4							
ADA Status							
ADA-positive	119	28	23.5	135	25	18.5	5.0 (-5.0, 15.1)
ADA- negative	153	32	20.9	134	29	21.6	-0.7 (-10.2, 8.8)
NAb Status							
NAb-positive	43	10	23.3	46	5	10.9	12.4 (-3.1, 27.9)
NAb-negative	76	18	23.7	89	20	22.5	1.2 (-11.7, 14.1)
Week 12							
ADA Status							
ADA-positive	228	174	76.3	234	172	73.5	2.8 (-5.1, 10.7)
ADA- negative	46	37	80.4	37	31	83.8	-3.3 (-19.9, 13.2)
NAb Status							
NAb-positive	77	46	59.7	80	43	53.8	6.0 (-9.5, 21.5)
NAb-negative	151	128	84.8	154	129	83.8	1.0 (-7.2, 9.2)
Week 16							
ADA Status							
ADA-positive	247	199	80.6	255	197	77.3	3.3 (-3.8, 10.4)
ADA- negative	27	22	81.5	15	12	80.0	1.5 (-23.5, 26.5)
NAb Status							
NAb-positive	91	59	64.8	90	51	56.7	8.2 (-6.0, 22.3)
NAb-negative	156	140	89.7	165	146	88.5	1.3 (-5.6, 8.1)

Note: N = number of subjects in Full Analysis Population; N' = number of subjects in treatment group within subgroup; n = number of subjects achieving PASI-75; % = percentage of subjects in stratum achieving PASI-75.
Subjects with missing PASI-75 at Week 16 were treated as nonresponders.
1. ADA status: Positive if any positive ADA after first dose through treatment week; Negative, otherwise.
2. NAb status: Positive if any positive NAb after first dose through treatment week; Negative, otherwise.
3. Treatment differences were based on CHS-1420 minus Humira.

Source: Modified from the Clinical Information Amendment submitted on June 17, 2021. Link \\CDSESUB1\evsprod\bla761216\0011\m1\us\clinical-info-amend.pdf

Table 15. Percentage of Subjects Achieving PASI-75 at Week 24 by ADA and NAb Status – Full Analysis Population (Treatment Period 2)

	CHS-1420/CH			Humira/CHS - 1420			Humira/Humira				
Time Point	N'	n	%	N'	n	%	N'	n	%	Treatment Difference (Wald 95% CI)[1]	Treatment Difference (Wald
Week 24 Overall	251	217	86.5	125	103	82.4	129	114	88.4	-1.9 (-8.9,	-6.0 (-14.6, 2.7)
ADA Status											
ADA-Positive	233	199	85.4	119	97	81.5	120	105	87.5	-2.1 (-9.5,	-6.0 (-15.1, 3.2)
ADA-Negative	18	18	100.0	6	6	100.0	9	9	100.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
NAb Status											
NAb-Positive	66	41	62.1	39	28	71.8	37	27	73.0	-10.9 (-29.3,	-1.2 (-21.3, 18.9)
NAb-Negative	167	158	94.6	80	69	86.3	83	78	94.0	0.6 (-5.5, 6.8)	-7.7 (-16.8, 1.4)

N'=number of subjects in Full Analysis Population and in the corresponding Parameter subgroup is used as denominator for calculation of percentages; n=number of subjects achieving PASI-75; %=percentage of subjects achieving PASI-75.
Missing PASI-75 at week 24 are treated as non-responders.
ADA Status: Positive if any positive ADA after Period 1 through Week 24; Negative, otherwise. Note 4): NAb Status: Positive if any positive NAb after Period 1 through Week 24; Negative, otherwise. 1Treatment difference and 95% CI for CHS-1420/CHS-1420 minus Humira/Humira.
Treatment difference and 95% CI for Humira/CHS-1420 minus Humira/Humira.

Source: Clinical Information Amendment submitted on June 17, 2021. Link \\CDSESUB1\evsprod\bla761216\0011\m1\us\clinical-info-amend.pdf

Impact of ADA and Nab on Safety

The incidence of treatment-emergent adverse events (TEAEs) was similar in the ADA-negative, ADA-positive and NAb-positive subjects in both treatment groups for treatment periods 1 and 2. Also, the incidence of hypersensitivity and injection site reactions (ISRs) was low and similar in the ADA-negative, ADA-positive, and NAb-positive subjects in both treatment groups in treatment periods 1 and 2. Overall, no evidence of impact of immunogenicity on safety was observed in Study CHS-1420-02.

Table 16. TEAEs, Hypersensitivity and Injection Site Reactions by ADA/NAb Status – Treatment Period 1

	CHS-1420			U.S.-Humira		
	ADA Negative (N = 27)	ADA Positive (N = 247)	NAb Positive (N = 91)	ADA Negative (N = 16)	ADA Positive (N = 255)	NAb Positive (N = 91)
Any TEAE	15 (55.6)	119 (48.2)	47 (51.6)	7 (43.8)	115 (45.1)	42 (46.2)
Maximum severity of TEAE						

Mild	8 (29.6)	64 (25.9)	28 (30.8)	3 (18.8)	63 (24.7)	24 (26.4)
Moderate	7 (25.6)	52 (21.2)	17 (18.7)	4 (25.0)	48 (18.8)	16 (17.6)
Severe	0	3 (1.2)	2 (2.2)	0	4 (1.6)	2 (2.2)
Study drug-related TEAEs per Investigator[2]	4 (14.8)	26 (10.5)	8 (8.8)	1 (6.3)	33 (12.9)	12 (13.2)
Serious TEAEs	0	4 (1.6)	3 (3.3)	0	6 (2.4)	3 (3.3)
Study drug-related TESAE per Investigator	0	0	0	0	0	0
TEAE leading to study drug discontinuation	1 (3.7)	3 (1.2)	2 (2.2)	0	2 (0.8)	1 (1.1)
Study drug-related TEAEs per Investigator leading to study drug discontinuation[2]	1 (3.7)	0	0	0	2 (0.8)	1 (1.1)
Death	0	0	0	0	0	0
Injection site reaction	1 (3.7)	10 (4.0)	2 (2.2)	1 (6.3)	9 (3.5)	3 (3.3)
Any hypersensitivity (SMQ TEAE)	2 (7.4)	10 (4.0)	5 (5.5)	0	9 (3.5)	1 (1.1)

Source: Modified from Integrated Summary of Immunogenicity, Tables 35-36, pages 79-81, Link \\CDSESUB1\evsprod\bla761216\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso-ra\5353-rep-analys-data-more-one-stud\iss\isi.pdf

Table 17. TEAEs, Hypersensitivity and Injection Site Reactions by ADA/NAb Status – Treatment Period 2

	CHS-1420/CHS-1420 (N = 320)			U.S.-Humira/CHS-1420 (N = 169)			U.S.-Humira/U.S.-Humira		
	ADA Neg (N = 16) n (%)	ADA Pos (N = 234) n (%)	NAb Pos (N = 70) n (%)	ADA Neg (N = 6) n (%)	ADA Pos (N = 119) n (%)	NAb Pos (N = 44) n (%)	ADA Neg (N = 9) n (%)	ADA Pos (N = 121) n (%)	NAb Pos (N = 38) n (%)
Any TEAE	6 (37.5)	48 (20.5)	13 (18.6)	2 (33.3)	24 (20.2)	8 (18.2)	1 (11.1)	21 (17.4)	8 (21.1)
Maximum severity of TEAE									
Mild	5 (31.3)	27 (11.5)	8 (11.4)	1 (16.7)	14 (11.8)	4 (9.1)	0	12 (9.9)	5 (13.2)
Moderate	1 (6.3)	19 (8.1)	5 (7.1)	1 (16.7)	8 (6.7)	3 (6.8)	1 (11.1)	9 (7.4)	3 (7.9)
Severe[1]	0	2 (0.9)	0	0	2 (1.7)	1 (2.3)	0	0	0
Study drug-related TEAEs per PI	1 (6.3)	7 (3.0)	2 (2.9)	0	1 (0.8)	0	0	5 (4.1)	1 (2.6)
Serious TEAEs	0	4 (1.7)	0	0	3 (2.5)	1 (2.3)	0	1 (0.8)	0
Study drug-related TESAE per Investigator	0	0	0	0	0	0	0	1 (0.8)	0

TEAE leading to study drug discontinuation	0	1 (0.4)	0	0	2 (1.7)	0	0	1 (0.8)	0
Study drug-related TEAEs per Investigator leading to study drug discont.	0	1 (0.4)	0	0	0	0	0	1 (0.8)	0
Death	0	0	0	0	0	0	0	0	0
Injection site rxn	1 (6.3)	1 (0.4)	0	0	0	0	0	2 (1.7)	0
Any Hypersensitivity	0	6 (2.6)	0	1 (16.7)	0	0	0	0	0

Source: Modified from Integrated Summary of Immunogenicity, Tables 37-38, pages 83-86, Link \\CDSESUB1\evsprod\bla761216\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso-ra\5353-rep-analys-data-more-one-stud\iss\isi.pdf

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6. Statistical and Clinical Evaluation and Recommendations

The clinical program presented in this BLA includes six clinical studies, and one of them, CHS-1420-02, provides comparative safety, efficacy, and immunogenicity data to support an evaluation of whether clinically meaningful differences exist between CHS-1420 and U.S.-Humira through studying patients with moderate to severe plaque psoriasis[5].

This is further supported by CHS-1420-03, which studied pharmacokinetics (PK) and immunogenicity in healthy humans after a single dose. There are three other single-dose studies in healthy humans for PK: CHS-1420-01 comparing CHS-1420 (manufactured at an early-development stage where the process used a different cell line and different formulation as compared to the late development formulation) and U.S.-Humira, CHS-1420-05 comparing different presentations of CHS-1420 (autoinjector (AI) versus prefilled syringe (PFS)), and CHS-1420-07 comparing CHS-1420 and EU-approved Humira. In addition, there is CHS-1420-04, an open-label observational study for the ability of rheumatoid arthritis (RA) patients to safely and

[5] The clinical development program uses "PsO" as abbreviation for psoriasis. Labeling uses "Ps" as abbreviation for psoriasis because "Ps" is used in labeling of the reference product, U.S.-Humira. In this review, "PsO" will be used for plaque psoriasis in discussions relating to the clinical development program of CHS-1420.

effectively administer three doses of CHS-1420 with the AI. The safety data of CHS-1420 PFS from studies CHS-1420-04, -05 and -07 were reviewed to confirm that those results did not preclude or conflict with conclusions based on Studies CHS-1420-02 and -03.

The current original BLA is for the PFS presentation. The safety data of CHS-1420 PFS have been supplemented with those of CHS-1420 AI from studies CHS-1420-04 and -05. Both the PFS and the AI presentations for CHS-1420 contain the same formulation. Thus, the safety data from use of AI are considered supportive in this application.

The data from three PK studies in healthy humans have also been submitted. CHS-1420-03, which compares CHS-1420 and U.S.-Humira, has been reviewed in detail by the Clinical Pharmacology team (Section 5). Data from CHS-1420-01, where CHS-1420 has a different formulation and was manufactured using a different cell line, will not be further discussed. The safety data of CHS-1420 in CHS-1420-07 was reviewed to confirm that those results did not preclude or conflict with conclusions based on Studies CHS-1420-02 and -03, and the control in this study, which is the EU-approved Humira, was not considered as the comparator for this assessment.

6.1. Statistical and Clinical Executive Summary and Recommendation

Comparative Efficacy: The comparative efficacy of CHS-1420 and U.S.-Humira was evaluated in Study CHS-1420-02, a double-blind, randomized, active control, efficacy and safety study in subjects with moderate to severe psoriasis (PsO). Comparative efficacy were assessed for FDA's currently recommended primary endpoint, the percent improvement in PASI at Week 16 and the applicant's pre-specified primary endpoint, i.e., the originally agreed upon endpoint in 2015, proportion of subjects achieving 75% improvement in PASI (PASI-75) at Week 12. The 90% confidence interval (CI) for the treatment difference based on the mean percent change from baseline in PASI at Week 16 for both the full analysis population (FAP) and the per protocol population (PPP) fall within the prespecified margins of ±10 [FAP: (-4.78, 3.01), PPP: (-3.47, 2.811)]; Similarly, the 90% CI for the treatment difference based on the proportion of subjects with PASI 75 at Week 12 for both the FAP and PPP fall within the prespecified margins of ±15 [FAP: (-3.63, 8.09), PPP: (-2.51, 9.18)]. Thus, the study demonstrated no clinically meaningful differences between CHS-1420 and U.S.-Humira with regard to the primary efficacy endpoint.

Comparative Safety: The safety of CHS-1420 was compared to that of U.S.-Humira in CHS-1420-02, a study in chronic PsO subjects. Safety parameters were also assessed in CHS-1420-04, an open label observational study of the ability of subjects with RA to safely and effectively inject CHS-1420 with the AI. Apart from these multiple-dose studies in patients, data from single-dose PK studies in healthy humans were also submitted in support of safety. The safety data from Study CHS-1420-03 which

compared CHS-1420 and U.S.-Humira in healthy subjects was reviewed. The safety data from two other studies using the CHS-1420 formulation to-be-marketed in the U.S (CHS1420-05, and -07) in healthy subjects were reviewed to confirm that those results did not preclude or conflict with conclusions based on Studies CHS-1420-02. The safety results from CHS-1420 from studies CHS-1420-03, -05 and -07 were pooled as shown in Table 20 below. Note that comparisons between CHS-1420 to EU-Humira were not used to support the determination whether CHS-1420 is biosimilar to U.S.-Humira. As studies were not powered for analyses of safety data, statistical testing have not been applied to such data.

Adverse event rates are summarized in the following three Tables.

Table 18. Overview of Treatment-emergent Adverse Events in CHS1420-02: All Treatment Periods (Periods 1 + 2 + 3), Safety Population

	CHS-1420/ CHS-1420/ CHS-1420 (N = 274) n (%)	Humira/ CHS-1420/ CHS-1420 (N = 134) n (%)	Humira/ Humira/ CHS-1420 (N = 137) n (%)
Subjects with at Least One Event			
Any TEAE	172 (62.8)	85 (63.4)	89 (65.0)
Maximum Severity of TEAE			
Mild	73 (26.6)	37 (27.6)	41 (29.9)
Moderate	91 (33.2)	41 (30.6)	46 (33.6)
Severe [a]	8 (2.9)	7 (5.2)	2 (1.5)
Study drug-related TEAEs per Investigator [b]	45 (16.4)	26 (19.4)	24 (17.5)
TESAEs	9 (3.3)	9 (6.7)	2 (1.5)
Study drug-related TESAE per Investigator [b]	0	1 (0.7)	1 (0.7)
TEAE leading to study drug discontinuation	8 (2.9)	7 (5.2)	2 (1.5)
Study drug-related TEAEs per Investigator leading to study drug discontinuation [b]	4 (1.5)	2 (1.5)	2 (1.5)
Death	1 (0.4)	0	0

N = number of subjects treated in the treatment period; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 1 through study termination;
TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

[a] Events with unknown severity were counted as severe.

[b] Events with unknown relationship to study drug were counted as study drug-related.

Source: CHS-1420-02 CSR Post-text Table 14.3.1.1.32

Table 19. Overview of Treatment-emergent Adverse Events in CHS-1420-04: Safety Population

	CHS-1420 (N = 141) n (%)
Subjects with at Least One Event	
Any TEAE	23 (16.3)
Maximum Severity of TEAE	
Mild	12 (8.5)
Moderate	8 (5.7)
Severe	3 (2.1)
Life-Threatening	0
Study Drug-Related TEAE per Investigator	5 (3.5)
UADE	0
TESAEs	3 (2.1)
Treatment-Related TESAEs	0
TEAEs Leading to Study Drug Discontinuation	3 (2.1)
Death	0

N = number of subjects in treatment group of Safety Population; n = number for the category;
TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event;
UADE = unanticipated adverse device effect.

Source: CHS-1420-04 CSR Post-text Table 14.3.1.1.

Table 20. Overview of Treatment-emergent Adverse Events: Pooled Study Data from CHS1420-03, -05 and -07: Safety Population

	CHS-1420 (N = 437) n (%)	U.S.-Humira (N = 103) n (%)	Humira (EU) (N = 108) [a] n (%)	Overall Total (N = 648) n (%)
Subjects with at Least One Event				
Any AE	169 (38.7)	39 (37.9)	65 (60.2)	273 (42.1)
Any TEAE	165 (37.8)	39 (37.9)	65 (60.2)	269 (41.5)
Maximum severity of TEAE				
Mild	122 (27.9)	34 (33.0)	46 (42.6)	202 (31.2)
Moderate	41 (9.4)	4 (3.9)	19 (17.6)	64 (9.9)
Severe	1 (0.2)	0	0	1 (0.2)

Life-threatening	1 (0.2)	0	0	1 (0.2)
Death	0	1 (1.0)	0	1 (0.2)
Subjects with any study drug-related TEAE per Investigator	74 (16.9)	10 (9.7)	44 (40.7)	128 (19.8)
Maximum severity of any study drug-related TEAE				
Mild	49 (11.2)	8 (7.8)	30 (27.8)	87 (13.4)
Moderate	24 (5.5)	2 (1.9)	14 (13.0)	40 (6.2)
Severe	1 (0.2)	0	0	1 (0.2)
Life-threatening	0	0	0	0
Death	0	0	0	0
Subjects with any SAE	2 (0.5)	2 (1.9)	0	4 (0.6)
Subjects with any study drug-related SAE per Investigator	1 (0.2)	1 (1.0)	0	2 (0.3)
Death due to AE	0	1 (1.0)	0	1 (0.2)
Subjects with TEAE leading to discontinuation from study per investigator	1 (0.2)	1 (1.0)	0	2 (0.3)
Subjects with study drug-related TEAE per Investigator leading to discontinuation from study	1 (0.2)	0	0	1 (0.2)

Studies included: CHS-1420-03, CHS-1420-05, CHS-1420-07

EU = European Union; N = number of subjects in Safety Population was used as the denominator for percentage calculations; n = number of subjects; SAE = serious adverse event; TEAE = treatment-emergent adverse event; US = United States.

[a] The comparison of focus is between CHS-1420 and U.S.-Humira; data for Humira (EU) and Humira Total are provided for informational purposes only. U.S.-Humira was used in CHS-1420-03 and Humira (EU) was used in CHS-1420-07; both studies met the criteria for PK BE. Neither U.S.-Humira nor Humira (EU) were used in CHS-1420-05.
Source: Integrated Table 14.3.1.6.

Source: Module 2 Section 2.7.4 Summary of Clinical Safety Table 22

Review of treatment-related adverse events, deaths, discontinuation due to adverse events, and serious adverse events from the clinical database suggest that their rates are comparable between CHS-1420 and U.S.-Humira.

For special adverse events mentioned in the U.S.-Humira labeling, the following information from the CHS-1420 clinical studies pertain:

- There were no anaphylaxis cases reported in the CHS-1420 clinicalstudies .
- For hypersensitivity,
  - In CHS-1420-02, the proportion of subjects who had at least 1 hypersensitivity TEAE was no more than 4.4% in any treatment group or treatment period
  - In CHS-1420-04 (Yusimry AI administration only), the proportion of subjects who

had at least 1 hypersensitivity was 0.7%.
  - For the Pooled Studies (CHS1420-03, -05, and -07), results of the search for hypersensitivity indicate that the incidence of hypersensitivity is slightly higher with U.S.-Humira (8.7%) than with CHS-1420 (4.3%).
- For immunogenicity,
  - Overall, no clinically meaningful differences were observed between CHS-1420 and U.S.-Humira. CHS-1420-02, the repeat-dose study in subjects with chronic PsO, confirmed the immunogenicity similarity and supports the conclusion of no clinically meaningful differences between CHS-1420 and U.S.-Humira, with incidence, time-course, and magnitude (ADA titer) of ADA and Nab similar between CHS-1420 and U.S.-Humira- groups. CHS-1420-03 confirmed similar immunogenicity (incidence, time-course, and magnitude [ADA titer]) after a single dose of CHS-1420 or U.S.-Humira in healthy subjects.
- For hepatic disorder,
  - A comprehensive search for events related to hepatic disorders was performed for each study in the CHS-1420 clinical program to identify any terms for possible drug-related hepatic events. The incidence rates for reported hepatic disorder are comparable between CHS-1420 and U.S.-Humira through treatment periods in CHS-1420-02 (approximately 1%). These were primarily liver enzyme elevations, and none met Hy's Law criteria.
  - Routine laboratory tests were not performed after baseline in CHS-1420-04.
  - There were no drug-related hepatic disorders recorded in the Pooled Studies CHS-1420-03, -05, and -07.
- For serious infections and tuberculosis,
  - The incidence rates for reported serious infections are comparable between CHS-1420 and U.S.-Humira through treatment periods in CHS-1420-02 (up to 1%). In CHS-1420-04, there were 2 SAEs of infections and infestations (gastroenteritis and acute bronchitis) which were not considered related to the study drug, while in the Pooled Studies (CHS-1420-03, -05, and -07), there was 1 (1.0%) SAE of influenza in the U.S.-Humira group and no SAE infections in the CHS-1420 group.
  - One subject in CHS1420-02, (b) (6) (U.S.-Humira/U.S.-Humira/CHS-1420 group), experienced a re-activation of TB during Treatment Period 2 before use of CHS-1420. There were no positive TB test results in either CHS-1420-04 or the Pooled Studies (CHS1420-03, -05, and -07).
- For cardiac failure,
  - None of the cardiac failure SMQ TEAEs were experienced by >1% of subjects in any of the treatment groups during any of the treatment periods in CHS-1420-02. In CHS-1420-04, no TEAEs were identified by the SMQ search for cardiac failure. One TEAE for cardiac failure was identified by the SMQ search in the Pooled Studies (CHS-1420-03, -05, and -07). The event was peripheral swelling in a subject receiving CHS-1420.
- For injection site reactions,

  - In the CHS-1420 clinical program, the incidence of ISRs to CHS-1420 as recorded on the AE case report forms (AE CRFs) was similar to that for U.S.-Humira, and no new safety signals were identified.
- For neoplasms,
  - There were 7 TEAEs of neoplasm in 6 subjects in the CHS-1420 clinical program, 5 of these events were reported in subjects who had received at least 1 dose of CHS-1420, while the 2 remaining events occurred in subjects who received only U.S.-Humira. The case of glioblastoma multiforme was the only neoplasm considered a SAE. Skin papilloma was the only event which was reported in more than 1 subject.

There were no clinically meaningful changes in vital signs or physical examination in the study subjects in the clinical program for CHS-1420. No notable differences were observed across treatments in clinically significant findings from the 12-lead ECGs during the clinical study CHS-1420-02. ECGs were not conducted in the other clinical studies.

For clinical laboratory testing,

- There were no clinically meaningful changes from baseline in hematology parameters in CHS-1420-02. Routine laboratory tests were not performed after baseline in CHS-1420-04. There were also no clinically meaningful trends in shifts of hematology in the pooled groups from the Safety Population of CHS-1420-03, -05, and -07.
- None of the subjects met the laboratory criteria for Hy's Law in the CHS-1420 clinical program. There were no clinically meaningful changes from baseline in the clinical chemistry parameters in CHS-1420-02. Although there were numerically more cases with elevated levels in liver function tests in the CHS-1420 group than the U.S.-Humira group during Treatment Period 1, new episodes did not occur thereafter. Most episodes that occurred in Treatment Period 1 were resolved during that treatment period. There were no meaningful differences in the frequency or severity of the episodes between the CHS-1420 and U.S.-Humira groups.

Thus, comparative safety data in the clinical program of CHS-1420 support a conclusion that CHS-1420 is highly similar to U.S.- Humira, and there is no clinically meaningful difference between them.

Comparative Immunogenicity: The immunogenicity of CHS-1420 was comparable to that of U.S.-Humira after a single dose in healthy subjects and after multiple doses in patients with chronic plaque psoriasis. See review by Clinical Pharmacology team in Section 5.4. Also refer to Section 6.4 for a summary of comparative immunogenicity.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual clinical or statistical uncertainties that impact a demonstration of no clinically meaningful differences between CHS-1420 and U.S.-licensed Humira.

Authors:

Guoying Sun Clinical Statistics Reviewer	Wanjie Sun Clinical Statistics Team Leader
Kathleen Fritsch Clinical Statistics Reviewer	Mohamed Alosh Clinical Statistics Team Leader
Hon-Sum Ko Clinical Reviewer	Hon-Sum Ko Acting Clinical Team Leader & CDTL

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

The following subsections provide a high-level summary of the clinical studies in this BLA.

6.2.1. STUDY CHS-1420-02

Data and Analysis Quality

There are no concerns regarding data quality and integrity for CHS-1420-02. The applicant has responded to information requests (IRs) with respect to protocol deviations and eDiary records on product administration (IRs dated February 2, 2021 and September 2, 2019, respectively) and the responses are deemed satisfactory (See Appendices 13.2, and 13.5.3).

Clinical and Statistical Reviewers have considered site inspection for the submitted clinical studies and reached consensus that inspection is not needed.

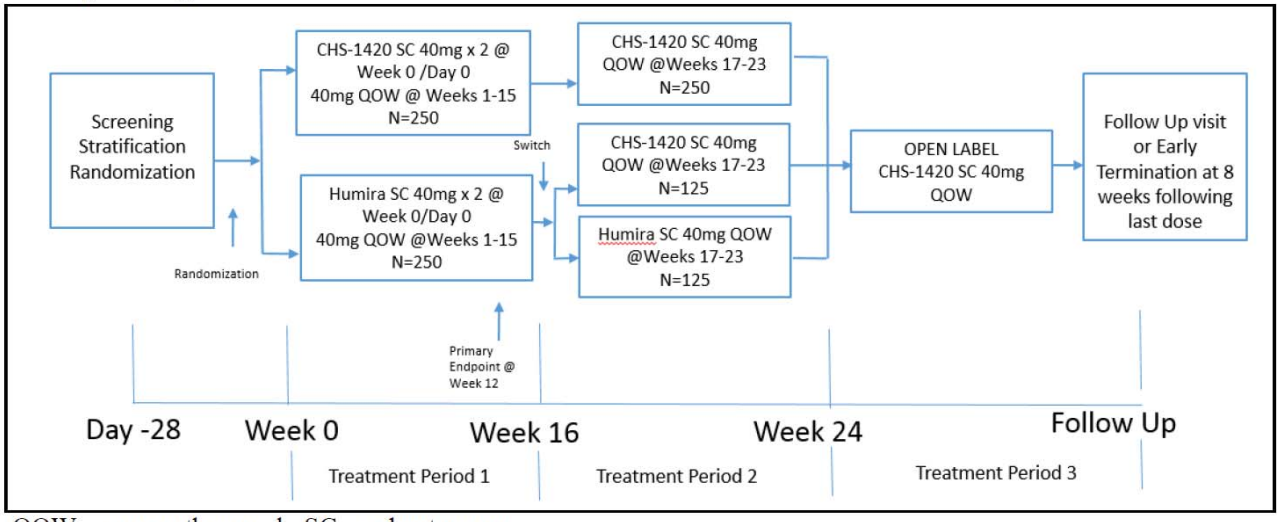
Study Design and Endpoints

Study CHS-1420-02 was a randomized, double-blind, active-control (followed by open-label safety), parallel-group, multicenter comparative clinical study to compare the efficacy and safety of CHS-1420 versus U.S.-Humira in subjects with moderate to severe plaque psoriasis. The study consisted of 23 weeks of administration of blinded study drug over a 24-week period, divided into Treatment Period 1 (16 weeks) and Treatment Period 2 (8 weeks); 23 weeks of open-label CHS-1420 treatment during 24 weeks of Treatment Period 3; and a follow-up visit 56 days (8 weeks) after the last dose of study drug (see Figure 6 for Study Design).

In Treatment period 1, subjects were randomized to either CHS-1420 or U.S.-Humira in a 1:1 ratio and were treated for 15 weeks (2 subcutaneous (SC) injections on Week 0 followed by a single SC injection every other week (QOW) from Week 1 through Week 15). In Treatment period 2, subjects originally randomized to CHS-1420 in Treatment period 1 continued to receive CHS-1420. Subjects originally randomized to U.S.-Humira were randomized to receive CHS-1420 or U.S.-Humira in a 1:1 ratio. In Treatment period 3, all subjects who completed Treatment Periods 1+2 and achieved at least a 50% improvement in PASI (PASI-50) score at Week 24 received 23 weeks of open-label CHS-1420 QOW from Week 25 through Week 47.

Figure 6. Study Design of CHS-1420-02

Study Design:



QOW = every other week; SC = subcutaneous.
Source: Protocol (Appendix 16.1.1)

The study enrolled and randomized 545 subjects, from 97 sites worldwide, age 18 years and older with PASI ≥ 12, Physician's Static Global Assessment (PSGA) ≥ 3 (moderate or severe) and total body surface area (BSA) ≥ 10%. Subjects were not allowed to have any previous exposure to anti-TNF therapies. Subjects were to have been diagnosed at least 6 months before randomization, and were to be considered as a candidate by the Investigator to start anti-TNF therapy for PsO. Subjects with forms of psoriasis other than chronic PsO were excluded from study.

The primary efficacy endpoints considered for the analysis are:

- FDA currently recommended endpoint: Percent change in PASI at Week 16 as recently recommended by the FDA at the BPD Type 4 meeting on October 27,

2020, where the FDA commented "Note that our recommendations for the primary endpoint in a comparative clinical study in subjects with psoriasis have evolved since 2015. We now recommend evaluating the percent change in PASI at Week 16, evaluated using a 90% confidence interval with margins of ± 10%."

- Originally agreed upon endpoint: The 75% improvement in PASI (PASI75) at Week 12 relative to baseline, as the primary efficacy endpoint agreed upon initially with the Agency at the study design stage in 2015.

The key secondary efficacy endpoints are

- PASI-75 at Weeks 2, 4, 6, 8, 10, 16, 20, 24, 32, 40 and 48;
- Percentage changes in PASI from Baseline at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 48;
- 50% improvement in Psoriasis Area and Severity Induced (PASI-50) at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 48;
- 90% improvement in Psoriasis Area and Severity Induced (PASI-90) at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 48;

Selection of Study Population

Inclusion Criteria

1. Male or female adult at least 18 years of age.
2. Diagnosis of chronic PsO at least 6 months prior to Screening.
3. Moderate to severe chronic PsO as defined at Screening by:
   a. PASI score ≥12.
   b. PSGA score ≥3 (based on a scale of 0 to 5).
   c. BSA affected by chronic PsO of ≥10%.
4. Considered a candidate by the Investigator to start anti-TNF therapy for PsO.
5. Able and willing to give written informed consent prior to performance of any study-related procedures.
6. Discontinued the use of any biologics or prohibited treatments (e.g., systemic corticosteroids, ultraviolet [UV] laser treatments, apremilast [Otezla], other phosphodiesterase type 4 [PDE4] inhibitors, and kinase inhibitors) within the 28 days prior to Randomization (Week 0/Day 0).
7. Stopped the use of American Dermatology Association Class 1 to 5 topical corticosteroids within 15 days prior to Randomization (Week 0/Day 0).
8. Women met 1 of the following:
   a. Women of childbearing potential with a negative urine pregnancy test at Screening agreed to use 1 or more approved methods of birth control during the study. Approved methods of birth control were: hormonal contraception, intrauterine device, diaphragm plus spermicide, and condom plus spermicide. Abstinence from heterosexual intercourse

was acceptable only if it was the preferred and usual lifestyle of the subject regardless of study participation; abstinence was practiced for the duration of the study and until 5 months after taking the last dose of study drug.

b. Women who were postmenopausal for at least 2 years (with amenorrhea for at least 1 year/12 consecutive months) or had a hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation prior to signing the ICF.

Exclusion Criteria

1. Forms of psoriasis other than chronic PsO (e.g., pustular erythrodermic, guttate psoriasis).
2. Previous receipt of anti-TNF therapies (and biosimilars to anti-TNF therapies) for any indication at any time, including infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, and pentoxifyllene.
3. Initiation of a drug that was known to cause or exacerbate psoriasis (including, but not limited to, beta-blockers, lithium, and anti-malarials), within the 6 months prior to Randomization (Week 0/Day 0); those who had been on a stable dose for at least 6 months prior to Randomization (Week 0/Day 0) without exacerbation of psoriasis were enrolled and did not need to discontinue these medications.
4. Receipt of an investigational drug or investigational device within the 28 days prior to Randomization (Week 0/Day 0) or a period equal to 5 times the half-life of the investigational agent (whichever was longer).
5. History of alcohol or drug abuse within 2 years prior to Screening.
6. Diagnosis of rheumatic disease, autoimmune disease, connective tissue disease, or immune deficiency disease (e.g., primary Sjögren's syndrome, systemic lupus erythematosus, demyelinating diseases such as multiple sclerosis). Note: PsA was allowed.
7. White blood cell count <3500 cells/mm^3, lymphocyte count <1000 cells/mm^3, platelet count $\leq$125,000 cells/mm^3, serum creatinine $\geq$2 mg/dL (177 µmol/L), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$2 x the upper limit of normal (ULN), or hemoglobin (Hgb) $\leq$8.5 g/dL at Screening.
8. Presence or history of malignancy, except for successfully treated nonmetastatic basal or squamous cell carcinoma of the skin and carcinoma in situ of the cervix.
9. Presence of active or latent TB based on positive blood test (QuantiFERON®-TB Gold test) during Screening or known exposure to a patient with active TB.

Note: QuantiFERON-TB Gold test may have been repeated once using a fresh sample in subjects with an indeterminate result or low positivity defined as QuantiFERON-TB Antigen minus Nil value = 0.35 - 2 IU/mL; if the repeat test result was negative, the subject may have participated in the study.

10. History of positive test results for fungal or other infections (e.g., histoplasmosis, coccidioidomycosis) required by regional guidelines within 3 months prior to Randomization (Week 0/Day 0).
11. Chest x-ray (CXR) obtained within 6 months before Screening suggestive of active or latent TB or another active disease process. If a CXR had not been obtained within the past 6 months, one was obtained during Screening.
12. Major systemic infections, including human immunodeficiency virus (HIV).
13. Unresolved hepatitis B or hepatitis C infection (defined as positive hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HBcAb], or hepatitis C virus [HCV] ribonucleic acid).
14. Presence of any significant comorbid medical condition(s), including, but not limited to:
    a. Uncontrolled diabetes mellitus (Hgb A1c ≥8% within the 3 months prior to Screening or history of diabetic ketoacidosis or hypoglycemic reactions requiring hospitalization within the 12 months prior to Screening).
    b. Uncontrolled hypertension (systolic blood pressure □160 mmHg and diastolic blood pressure >100 mmHg) within the 3 months prior to Screening.
    c. Severe kidney disease requiring hemodialysis or peritoneal dialysis.
    d. Advanced liver disease, such as liver cirrhosis or severe nonalcoholic steatohepatitis.
    e. Severe congestive heart failure or history of ejection fraction ≤30%.
    f. Severe lung disease requiring home oxygen.
    g. Active unstable angina requiring daily treatment with nitrates or other medications.
15. Presence of any other major medical or psychiatric illness that, in the opinion of the Investigator would have put the subject at increased risk or affected the ability to participate in the study.
16. Known or suspected sensitivity or allergic reactions to latex or latex-containing products.
17. Women who were pregnant or nursing.
18. Administration of a live vaccination within 4 weeks prior to Randomization (Week 0/Day 0), or a known need for live vaccination during the study and for 3 months after the last dose of study drug.

Administration of Test Products

Table 21. Study Product Administration

Study Drug	Dose and Mode of Administration	Lot Number
CHS-1420	80 mg on Week 0/Day0 followed by 40 mg QOW starting at Week 1/Day 7 by SC injection	3-FIN-2276 3-FIN-2405 3-FIN-2364

		3-FIN-2406 3-FIN-2556
Humira	80 mg on Week 0/Day0 followed by 40 mg QOW starting at Week 1/Day 7 by SC injection	1030241 1032717 1030239 1029651 1035455 1032718
QOW = every other week; SC = subcutaneous. Source: Study Protocol, Section 4.3 (Appendix 16.1.1); Study Drug Lots (Appendix 16.1.6)		

Administrative structure:

The protocol and informed consent form (ICF) were submitted to and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for each site prior to initiation of the study.

When an adequate amount of data were available for monitoring the safety of subjects over the course of the study and the last subject completed the evaluation at the Week 12 visit, an independent Data Monitoring Committee (DMC) reviewed the accumulating partially unblinded safety and primary efficacy data to determine if the partially unblinded data were adequate to warrant discontinuing the study. The DMC had also reviewed and reported on liver function test abnormalities upon completion of Week 12 of the study, noting that confounding factors present did not allow establishment of the ccurrence of liver injury, and recommending continuation of study with amending the informed consent.

- Procedures and schedule: Refer to Appendix 13.5.4

- Dietary restrictions/instructions: If applicable, list any instructions or restrictions provided in terms of dietary behavior. Comment on whether the dietary restrictions/instructions seem reasonable and acceptable

- Concurrent medications:

  Allowed Medications
  - Low- to mid-potency (American Dermatology Association Class 6 to 7) topical corticosteroids on scalp, face, axillae, groin, and genitalia were allowed except within 24 hours prior to PASI assessment at Screening and study visits.
  - Mild/bland moisturizers/lubricants were allowed at any time except within 24 hours prior to PASI assessment at Screening and study visits.

- Single nonsteroidal anti-inflammatory drug (NSAID) use was not prohibited in this study; however, the dose did not exceed the maximum dose recommended for that NSAID.
- Insulin and hormone replacement therapy.
- All medications required to adequately treat adverse events or concurrent medical conditions at the discretion of the Investigator.

Prohibited Medications

- All TNF-inhibitor biologics (other than study drug, insulin, and hormone replacement therapy) and biosimilars to TNF-inhibitors, including but not limited to: certolizumab pegol, infliximab, golimumab, and etanercept.
- All biologics for PsO or indications other than PsO (including, but not limited to, tocilizumab, anakinra, abatacept, rituximab, and ustekinumab) during the study.
- Any kinase inhibitor for any reason (e.g., tofacitinib citrate) during the study.
- Any PDE4 inhibitor (e.g., apremilast [Otezla]) during the study and within 28 days prior to Randomization (Week 0/Day 0).
- Systemic psoriasis treatments such as oral retinoids, methotrexate, cyclosporine, vitamin A or D analog preparations, dithranol, psoralen plus ultraviolet A (PUVA),
- ultraviolet B (UVB) phototherapy, and laser therapy during the study and within 28 days prior to Randomization (Week 0/Day 0).
- Systemic corticosteroids during the study and within 28 days prior to Randomization (Week 0/Day 0).
- American Dermatology Association Class 1 to 5 topical corticosteroids during the study and within 15 days prior to Randomization (Week 0/Day 0).
- Drugs that could have caused new onset or exacerbation of psoriasis (including, but not limited to, beta-blockers, lithium, and antimalarials) within 6 months prior to Randomization (Week 0/Day 0) and during the study, unless the subject was on a stable dose for at least
- 6 months prior to Randomization (Week 0/Day 0) without exacerbation of psoriasis.
- Live vaccines 4 weeks prior to Randomization, during the study, and for 3 months after the last dose of study drug.

- Treatment compliance: Subjects/caregivers were trained to utilize an eDiary to collect information about the biweekly injections and any possible ISRs. The study staff helped the subject/caregiver register into the eDiary system at the

time of the first dosing visit. At each visit, study staff reviewed the eDiary entries and provided retraining as necessary. Compliance was assessed by the Investigator and study staff based on study drug usage in eDiary record.

- Rescue medication: If rescue medications were planned in the study, describe the schedule, type, and doses permitted. Discuss any restrictions or limitations on the use of rescue medications

Subject completion, discontinuation, or withdrawal:

Subjects were considered completers if the subjects completed 48 weeks of treatment and the Follow-up visit, 56 days (8 weeks) following the last dose in this study.

Subjects who discontinued study drug prior to the end of Treatment Period 1 were encouraged to return for all study visits through Week 16 and for an ET visit 56 days (8 weeks) after the last dose of study drug per the protocol Schedule of Procedures (if applicable). Subjects who discontinued study drug during Treatment Period 2 or 3 were encouraged to return for the Follow-up or ET visit 56 days (8 weeks) after the last dose of study drug (also per the protocol Schedule of Procedures) which included evaluation of safety and immunogenicity. Subjects were withdrawn for the following reasons:

- The subject experienced a serious adverse event (SAE) or medically important adverse event (e.g., serious or opportunistic infection) that precluded further treatment with study drug.
- The subject developed a malignancy while on study.
- The subject required medical treatment excluded by the protocol or that presented a safety risk to the subject.
- The subject was not willing to continue participation in the study (withdrew consent).
- The subject experienced an increase in disease activity that required additional or different therapy.
- The subject developed active TB or a positive response to QuantiFERON-TB Gold test anytime during the study. If the QuantiFERON-TB Gold test yielded low positive results (defined as QuantiFERON-TB Antigen minus Nil value = 0.35 - 2 IU/mL), a repeat test was done. If the repeat test was negative, the subject continued in the study, subject to the clinical judgment of the Investigator).
- The female subject became pregnant.
- The subject was lost to follow up.
- The subject demonstrated a consistent lack of compliance with the provisions of the protocol.

- In the opinion of the Investigator, it was in the best interest of the subject to discontinue participation.
- The Sponsor decided to terminate the study for any reason (e.g., if an unexpected SAE not previously observed with adalimumab occurred).

Statistical Methodologies

The primary efficacy analysis population is the Full Analysis Population (FAP) which includes all randomized subjects who received 1 or more doses of study drug (CHS-1420 or U.S.-Humira). The Per-Protocol (PP) Population is the supportive population which includes those subjects in the FAP who completed at least 12 weeks of treatment and had no protocol violations that may have affected the interpretation of the primary efficacy endpoint, e.g., who received incorrect investigational product in more than two injections through Week 12, who missed more than 2 doses, who received prohibited concomitant medication at any time in the last month prior to Week 12.

For assessing similarity based on percent change in PASI at Week 16, as recommended by the FDA in 2020, we calculate the two sided 90% confidence interval for the difference in mean percent change in PASI from baseline to Week 16 between the two treatment groups in FAP. If the 90% CI falls entirely within the specified margins of ± 10%, we conclude that no clinically meaningful differences between the two products has been demonstrated.

In conducting the primary analysis for the change in PASI, the applicant prespecified LaVange et al (2005)'s Extended Mantel-Haenszel approach to calculate the difference in mean percent change from baseline (CHS-1420 minus U.S.-Humira) and their associated standard errors to account for potential heterogeneity among strata. According to this approach, the test statistics are calculated first by the randomization stratum and subsequently combined using Mantel-Haenszel weights assuming heterogeneity to create an overall estimate of treatment difference across strata (LaVange et al 2005). For handling missing PASI assessments at Week 16 in the primary analysis, the last observation carried forward (LOCF) value were imputed for subjects with post baseline PASI assessment.

The applicant did not conduct additional analysis besides the primary efficacy analysis for the FDA-recommended primary efficacy endpoint. The statistical reviewers conducted the following sensitivity analyses including (1) a GLM model that adjusts for strata (site) using FAP; (2) LaVange et al (2005)'s Extended Mantel-Haenszel approach assuming homogeneity among FAP.

For assessing similarity between CHS-1420 and U.S.-Humira for PASI-75 at Week 12, as agreed upon at the study design, the analysis was based on calculating the 2-sided

90% CI for the difference in the proportions of subjects in the two treatment groups who achieved PASI-75 at Week 12 in FAP, and then comparing the CI with margins of ± 15%. If the 90% CI falls entirely within the interval (-15%, 15%), one concludes that no clinically meaningful differences between the two products have been demonstrated. The applicant used the 95% CI and the statistical reviewers changed it to 90% CI instead, which is the FDA's recommended CI for comparative clinical studies.

The applicant also used LaVange et al (2005)'s Extended Mantel-Haenszel method to analyze the differences in the proportions of subjects between the two treatment arms and their associated standard errors as outlined above.

No formal statistical analyses were performed for the secondary efficacy endpoints and such endpoints were analyzed descriptively, by presenting the 90% CI which is reported for exploratory purpose and thus no multiplicity adjustment was considered for these analyses.

Subgroup analyses for the primary endpoint were conducted by gender (male/female), race (white, non-white), BMI (<30 kg/m2, ≥30 kg/m2), region (US, EU, ROW), antidrug antibody (ADA) status (positive, negative), and neutralizing antibody status (positive, negative). The imputation rules used for the primary efficacy analysis are applied in these subgroup analyses. Note that randomization was stratified by age category (<65 yrs and ≥65 yrs) but this stratification is dropped from the subgroup analysis because only 7% of subjects were ≥65 yrs of age. Descriptive statistics are reported for subgroup analyses.

After development of the original protocol Version 1.0 in February 2015, there was one amendment (Version 2.0) dated July, 2015, to add a 24-week Open Label Extension Study (Treatment Period 3) after a subject successfully has completed the original Double Blind 24 week trial (Treatment Period 1 and 2).

Subject Disposition

Error! Reference source not found. summarizes subject disposition by treatment period and the overall population for the randomized subjects. In total, Study CHS-1420-02 enrolled and randomized 545 subjects, 274 randomized to CHS-1420 and 271 randomized to U.S.-Humira in Period 1 (Week 0-Week 16). For Period 2, the 271 subjects who were assigned to U.S.-Humira in Period 1 were randomized to either continue U.S.-Humira (136 subjects) or switch to CHS-1420 (135 subjects) from Week 17 through Week 23. In Period 3, all subjects who completed Treatment Periods 1+2 and achieved at least 50% improvement in PASI (PASI-50) score at Week 24 received 23 weeks of open-label CHS-1420 from Week 25 through Week 47 (235 in CHS-1420/CHS-1420/CHS-1420, 114 in U.S.-Humira/CHS-1420/CHS-1420, and 125 in U.S.-Humira/U.S.-Humira/CHS-1420). However, one subject (b) (6) who was assigned

to switch to CHS-1420 in Period 2 actually stayed on U.S.-Humira. In this regard, the applicant noted that "At Week 16 visit on (b) (6), site selected IxRS option for repeated visit 8 (Week 12) as the only option available. Site dispense IP kit number 53459 in accordance with IxRX confirmation. Visit number was updated in IxRX to Week 16 and subject instructed to continue using IP kit 53459 until Week 24 to preserve blinding". This subject was included in the planned U.S.-Humira/CHS-1420/CHS-1420 sequence for efficacy analysis, but included in the actual U.S.-Humira/U.S.-Humira/CHS-1420 sequence for safety analysis. Among the 274 subjects assigned to the CHS-1420/CHS-1420/CHS-1420 sequence, one subject (b) (6) was not dosed in after the initial loading dose until Period 3, according to the dataset. An IR was sent to the applicant with a response that the subject had difficulty complying with use of the eDiary although product administration did take place [See Appendix 13.5.3].

All 545 randomized subjects are included in the full analysis population (FAP). Among the 545 randomized subjects, 438 (80.4%) subjects completed the whole study (Period 1 – Period 3), and 107 (19.6%) subjects discontinued at a certain point during the study. Among the 274 subjects who were randomized to CHS-1420 in Period 1, 220 (80.3%) subjects completed the study and 54 (19.7%) subjects discontinued from the study (15 discontinued in Period 1, 24 discontinued in Period 2, and 15 discontinued in Period 3). Among the 271 subjects who were assigned to the U.S.-Humira in Period 1, 218 (80.4%) subjects completed the study and 53 (19.6%) subjects discontinued from the study (14 discontinued in Period 1, 17 discontinued in Period 2, and 22 discontinued in Period 3). The discontinuation rate is comparable between the two treatment sequence groups. Among those assigned to the U.S.-Humira in Period 1, the treatment sequence U.S.-Humira/CHS-1420/CHS-1420 has more subjects discontinued compared to the treatment sequence U.S.-Humira/U.S.-Humira/CHS-1420 (34 subjects vs 19 subjects). The most common reason for discontinuation was "withdrawal of consent" (23 subjects for the sequence with CHS-1420 in period 2 vs. 22 subjects for the sequence with U.S.-Humira in period 2)

Table 22. Overall Subject Disposition (Treatment Period 1 – 3)

Characteristics	CHS-1420 /CHS-1420 /CHS-1420 (N=274) n (%)	U.S.-Humira			Overall (N=545) n (%)
		U.S.-Humira/ CHS-1420/ CHS-1420 (N=135) n (%) #	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N=136) n (%)	Total U.S.-Humira (N=271) n (%)	
Randomized Subjects	274	135	136	271	545
Full Analysis Population	274	135	136	271	545

Overall during study (Period 1- Period 3)					
Completed the study	220 (80.3)	101 (74.8)	117 (86.0)	218 (80.4)	438 (80.4)
Discontinuation of study	54 (19.7)	34 (25.2)	19 (14.0)	53 (19.6)	107 (19.6)
Primary reason for discontinuation of study					
Adverse event	3 (1.1)	2 (1.5)	0	2 (0.7)	5 (0.9)
Withdrawal of consent	23 (8.4)	14 (10.4)	8 (5.9)	22 (8.1)	45 (8.3)
Lost to follow-up	6 (2.2)	1 (0.7)	4 (2.9)	5 (1.8)	11 (2.0)
Disease progression requiring additional therapy	2 (0.7)	1 (0.7)	2 (1.5)	3 (1.1)	5 (0.9)
Subject developed active TB or a positive QuantiFERON-TB Gold test	4 (1.5)	2 (1.5)	1 (0.7)	3 (1.1)	7 (1.3)
Required medical treatment excluded by protocol	1 (0.4)	1 (0.7)	0	1 (0.4)	2 (0.4)
Failure to complete visits or follow-up visits	0	2 (1.5)	1 (0.7)	3 (1.1)	3 (0.6)
Investigator's decision	1 (0.4)	0	0	0	1 (0.2)
Sponsor's decision	4 (1.5)	1 (0.7)	0	1 (0.4)	5 (0.9)
Other	10 (3.6)	10 (7.4)	3 (2.2)	13 (4.8)	23 (4.2)

Note: N = number of subjects randomized was used as the denominator for percentage calculations. TB = tuberculosis.

One subject (b) (6) was assigned to U.S.-Humira/CHS-1420/CHS-1420 actually took U.S.-Humira/U.S.-.Humira/CHS-1420.

Source: Table 8, CHS-1420-02 Clinical Study Report and reviewer analysis.

The discontinuation rates are not unexpected for a study lasting 48 weeks, and are comparable between the group exposed only to CHS-1420 and those having U.S.-Humira exposure. For discontinuation due to adverse events, refer to Section 6.3.2.5.

Error! Reference source not found. summarizes the subject disposition by treatment group in Period 1 (Baseline to Week 16). Among the 545 randomized subjects, 525 (265 CHS-1420 and 260 U.S.-Humira) (96.3%) subjects completed Treatment Period 1. The discontinuation rate is comparable between the two treatment groups. Withdrawal of consent was the main reason for discontinuation in both groups (CHS-1420: 6 (2.2%); U.S.-Humira: 11 (4.1%)).

Table 23. Subject Disposition – Treatment Period 1 (Baseline to Week 16)

Characteristics	CHS-1420 (N=274) n (%)	U.S.-Humira (N=271) n (%)	Total (N=545) n (%)
Completed study treatment	265 (96.7)	260 (95.9)	525 (96.3)
Discontinuation of study treatment	9 (3.3)	11 (4.1)	20 (3.7)
Primary reason for discontinuation of study for subjects who discontinued early from study treatment			
Adverse event	0	0	0
Withdrawal of consent	6 (2.2)	9 (3.3)	15 (2.8)
Lost to follow-up	1 (0.4)	1 (0.4)	2 (0.4)
Investigator's decision	1 (0.4)	0	1 (0.2)
Other	1 (0.4)	1 (0.4)	2 (0.4)

Source: Table 9, CHS-1420-02 Clinical Study Report and reviewer analysis

Table 24 summarizes the PP population through Week 12, which corresponds to the primary time point agreed upon in the original protocol for the PASI 75 endpoint; and the PP population through Week 16, which corresponds to the primary time point as recommended by the FDA for change in the PASI scale. The results of Table 3 show that the number of subjects excluded from the PP populations are relatively small and are comparable for the two treatment arms.

Table 24. Per Protocol Population through Week 12 and Week 16

	CHS-1420 N (%)	U.S.-Humira N (%)	Total N (%)
Subjects Randomized	274	271	545
Total PP Population through Week 12	262 (95.6%)	256 (94.5%)	518 (95.0%)
Total exclusion from PP population	12 (4.4%)	15 (5.5%)	27 (5.0%)
Reason for exclusion from PP population			
Inclusion # 3	1 (0.4%)	0 (0%)	1 (0.2%)
Inclusion # 3-Missed >2 doses thru Week 12	0 (0%)	1 (0.4%)	1 (0.2%)
Inclusion # 8-Received prohibited conmeds MED= METHOTREXATE DATE = 2005	0 (0%)	1 (0.4%)	1 (0.2%)
Missed >2 doses thru Week 12	4 (1.5%)	5 (1.8%)	9 (1.7%)

Missing 12-Week Period 1 with PASI at Week 12	4 (1.5%)	1 (0.4%)	5 (0.9%)
Missing 12-Week Period 1 with PASI at Week 12-Missed >2 doses thru Week 12	2 (0.7%)	5 (1.8%)	7 (1.3%)
Received prohibited conmeds MED= CLOBETASOL PROPIONATE DATE = 2013	0 (0%)	1 (0.4%)	1 (0.2%)
Received prohibited conmeds MED= CORTISONE DATE = 2015-10-28	0 (0%)	1 (0.4%)	1 (0.2%)
Received prohibited conmeds MED= FLUOCINOLONE ACETONIDE DATE = 2010	1 (0.4%)	0 (0%)	1 (0.2%)
Total PP Population through Week 16	259 (94.5%)	251 (92.6%)	510 (93.6%)
Total exclusion from PP population	15 (5.5%)	20 (7.4%)	35 (6.4%)
Reason for exclusion from PP population			
Excluded from PP population by Week 12	12 (4.4%)	15 (5.5%)	27 (5.0%)
Discontinued treatment between Weeks 12 and 16	3 (1.1%)	4 (1.5%)	7 (1.3%)
Missing PASI assessment at Week 16	0 (0%)	1 (0.4%)	1 (0.2%)

Source: Reviewer analysis

Demographics and Baseline Characteristics

Table 25 reports the demographic characteristics for the FAP. The baseline demographics were generally balanced across the treatment groups in Study CHS-1420-02. Among the 545 subjects, the mean age was about 44 years and 92.7% were 65 years and younger. The majority of subjects were male (61%) and white (93%). The distribution of subjects across regions was balanced: 184 (33.8%) subjects were from EU, 150 (27.5%) subjects were from US, and 211 (38.7%) subjects were from ROW.

Table 26 describes the baseline characteristics for the FAP. The baseline characteristics were similar between treatment groups for the FAP. The mean baseline BMI was 29.58 kg/m^2. The mean PASI score was 24.5, with the majority of subjects having moderate (62.0%) or severe (33.9%) disease severity. The mean score for Subjects' Global Assessment (SGA) of psoriasis was 4.1. One hundred and twenty-seven subjects (23.3%) had psoriatic arthritis (PsA), including 66 (24.1%) in the CHS-1420 group and 61 (22.5%) in the U.S.-Humira group.

Table 25. Demographic Characteristics – Full Analysis Population

Characteristics	CHS-1420 (N=274) n (%)	U.S.-Humira			Overall (N=545) n (%)
		U.S.-Humira/ CHS-1420/ CHS-1420 (N=135) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N=136) n (%)	U.S.-Humira Total (N=271) n (%)	
Age (years)					
n	274	135	136	271	545
Mean (SD)	43.7 (12.98)	44.5 (13.52)	43.8 (12.47)	44.1 (12.99)	43.9 (12.98)
Age group - n (%)					
<65 years	256 (93.4)	124 (91.9)	127 (93.4)	251 (92.6)	507 (93.0)
≥65 years	18 (6.6)	11 (8.1)	9 (6.6)	20 (7.4)	38 (7.0)
Gender - n (%)					
Female	82 (29.9)	31 (23.0)	38 (27.9)	69 (25.5)	151 (27.7)
Male	192 (70.1)	104 (77.0)	98 (72.1)	202 (74.5)	394 (72.3)
Ethnicity - n (%)					
Hispanic or Latino	28 (10.2)	17 (12.6)	17 (12.5)	34 (12.5)	62 (11.4)
Not Hispanic or Latino	246 (89.8)	118 (87.4)	119 (87.5)	237 (87.5)	483 (88.6)
Race - n (%)					
White	252 (92.0)	123 (91.1)	130 (95.6)	253 (93.4)	505 (92.7)
Black or African	1 (0.4)	3 (2.2)	1 (0.7)	4 (1.5)	5 (0.9)
Asian	7 (2.6)	2 (1.5)	2 (1.5)	4 (1.5)	11 (2.0)
American Indian or Alaska Native	1 (0.4)	1 (0.7)	0	1 (0.4)	2 (0.4)
Other	13 (4.7)	6 (4.4)	3 (2.2)	9 (3.3)	22 (4.0)
Region - n (%)					
EU	92 (33.6)	46 (34.1)	46 (33.8)	92 (33.9)	184 (33.8)
US	76 (27.7)	37 (27.4)	37 (27.2)	74 (27.3)	150 (27.5)
Rest of World (ROW)	106 (38.7)	52 (38.5)	53 (39.0)	105 (38.7)	211 (38.7)

Source: Table 14, CHS-1420-02 Clinical Study Report and reviewer analysis

Table 26. Baseline Characteristics – Full Analysis Population

Characteristics	CHS-1420 (N=274) n (%)	U.S.-Humira			Overall (N=545) n (%)
		U.S.-Humira/ CHS-1420/ CHS-1420 (N=135) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N=136) n (%)	U.S.-Humira Total (N=271) n (%)	
BMI group - n (%)					
<30 kg/m^2	157 (57.3)	79 (58.5)	79 (58.1)	158 (58.3)	315 (57.8)

≥30 kg/m^2	117 (42.7)	56 (41.5)	57 (41.9)	113 (41.7)	230 (42.2)
BMI (kg/m^2)					
n	274	135	136	271	545
Mean (SD)	29.69 (7.211)	29.49 (6.343)	29.46 (6.184)	29.47 (6.252)	29.58 (6.746)
PASI					
n	274	135	136	271	545
Mean (SD)	24.9 (10.60)	24.4 (9.69)	23.9 (9.75)	24.1 (9.70)	24.5 (10.16)
PSGA - n (%)					
Mild	1 (0.4)	0	0	0	1 (0.2)
Moderate	172 (62.8)	82 (60.7)	84 (61.8)	166 (61.3)	338 (62.0)
Severe	90 (32.8)	45 (33.3)	50 (36.8)	95 (35.1)	185 (33.9)
Very severe	11 (4.0)	8 (5.9)	2 (1.5)	10 (3.7)	21 (3.9)
SGA of psoriasis					
n	273	135	136	271	544
Mean (SD)	4.1 (0.92)	4.1 (0.91)	4.2 (0.83)	4.1 (0.87)	4.1 (0.9)
PsA - n (%)	66 (24.1)	33 (24.4)	28 (20.6)	61 (22.5)	127 (23.3)
hs-CRP for subjects with PsA					
n	63	33	23	56	119
Mean (SD)	12.07 (21.218)	9.69 (13.781)	21.78 (41.602)	14.66 (28.962)	13.29 (25.084)

Note: N = number of subjects in Full Analysis Population was used as the denominator for percentage calculations.
BMI = body mass index; EU = European Union; hs-CRP = highly-sensitive C-reactive protein; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PSGA = Physician's Static Global Assessment; ROW = rest of the world;
SD = standard deviation; SGA = Subject's Global Assessment

Source: Table 14, CHS-1420-02 Clinical Study Report and reviewer analysis

There are no major differences/imbalances across treatment groups which may preclude a demonstration of no clinically meaningful differences between CHS-1420 and U.S.-Humira.

Analysis of Primary Clinical Endpoint(s)

Primary Endpoint

Table 27 presents results of analysis for the recently FDA recommended primary endpoint, percentage change in PASI from baseline to Week 16, by randomization stratum and the overall population, in FAP. Overall, the mean percent change from baseline in PASI at Week 16 was -83.1% for the CHS-1420 group and -82.3% for the U.S.-Humira group, with an estimated treatment difference (weighted) of -0.9%. The 90% CI for treatment differences was (-4.78%, 3.01%), which is fully contained within the FDA recommended margin of -10% to +10%; thus, no clinically meaningful differences between treatment groups for the FDA recommended primary efficacy endpoint is demonstrated.

Table 27. Results of Analysis for the FDA-recommended Primary Endpoint, Percentage Change in PASI from Baseline to Week 16, by Randomization Stratum and the Overall Population, in FAP*

Stratum: BMI by Region	CHS-1420 (N=274)			U.S.-Humira (N=271)			Treatment Difference		
	N'	Mean	SD	N'	Mean	SD	Estimate	SE	Weight
BMI <30 kg/m^2									
EU	55	-94.4	8.63	56	-88.0	20.99	-6.4	3.04	27.7
US	31	-78.8	27.90	30	-75.1	44.02	-3.7	9.47	15.2
ROW	73	-89.6	14.09	71	-89.7	25.91	0.1	3.49	36.0
BMI >30 kg/m^2									
EU	37	-82.6	28.69	36	-85.1	16.12	2.5	5.43	18.2
US	45	-65.2	38.63	44	-64.8	38.41	-0.4	8.17	22.2
ROW	33	-79.0	38.81	33	-83.5	23.97	4.5	7.94	16.5
Overall	**274**	**-83.1**	**27.79**	**270**	**-82.3**	**29.84**	**-0.8**	**2.47**	**NA**
Primary Analysis Results **Estimated treatment difference (Weighted): -0.9%** **Standard error of estimated treatment difference: 2.37%** **90% confidence interval for treatment differences: (-4.78%, 3.01%)**									

Source: Table 16, CHS-1420-02 Clinical Study Report and reviewer analysis
* Extended MH approach, as described in LaVange et.al.2005, is used in the analysis

As a sensitivity analysis for assessing the impact of the modeling assumptions, the statistical reviewers also conducted supportive analyses for the FDA recommended primary endpoint by using a GLM model and extended MH assuming homogeneity in treatment effect across strata in FAP. The results of this sensitivity analysis are given in Table 28 and these are similar to those of the primary efficacy analysis results as reported inTable 27.

Table 28. Supportive Analyses for the FDA Recommended Efficacy Endpoint: Percent Improvement in PASI from Baseline to Week 16

Supportive Analysis	CHS-1420	U.S.-Humira	Difference (weighted)(SE) 90% CI
GLM **LSMean (SD)**	N=274 -83.1 (27.79)	N=270 -82.3 (29.84)	-0.9 (2.36) (-4.77, 3.00)

Extended MH under Homogeneity LSMean (SD)	N=274 -83.1 (27.79)	N=270 -82.3 (29.84)	-0.9 (2.37) (-4.78, 3.00)

Source: Reviewer's analysis

Protocol-specified Primary Efficacy Endpoint

Table 29 summarizes the efficacy results for the primary efficacy endpoint - the percentage of subjects achieving PASI-75 at Week 12 in FAP, agreed upon in the original study protocol.

Overall, the proportion of subjects achieving PASI-75 at Week 12 was 77.0% for the CHS-1420 group and 74.9% for the U.S.-Humira group, with an estimated proportion difference (weighted) of 2.2% for the FAP. The 90% CI for treatment differences was (-3.63%, 8.09%), which is fully contained within the pre-specified range of -15% to 15%; thus, no clinically meaningful differences between CHS-1420 and U.S.-Humira based on PASI 75 at Weeks 12 is demonstrated as well.

Table 29. Results of Analysis for the Protocol-specified Primary Endpoint, PASI 75 at Week 12, by Randomization Stratum and the Overall Population, in FAP *

Stratum (BMI by Region)	CHS-1420 (N=274)			U.S.-Humira (N=271)			Treatment Difference [1]		
	N'	n	p	N'	n	p	Estimate [2]	SE	Weight [3]
BMI <30 kg/m^2									
EU	55	53	96.4	56	45	80.4	16.0	5.93	27.7
US	31	22	71.0	30	21	70.0	1.0	11.88	15.2
ROW	73	61	83.6	72	61	84.7	-1.2	6.11	36.2
BMI ≥30 kg/m^2									
EU	37	26	70.3	36	25	69.4	0.8	10.89	18.2
US	45	25	55.6	44	25	56.8	-1.3	10.64	22.2
ROW	33	24	72.7	33	26	78.8	-6.1	10.69	16.5
Overall	274	211	77.0	271	203	74.9	2.1	3.67	NA
Primary Analysis Results **Estimated treatment difference (weighted): 2.2** **Standard error of estimated treatment difference: 3.6** **90% confidence interval for treatment differences: (-3.63, 8.09) [4]**									

Note: N = number of subjects in Full Analysis Population; N' = number of subjects in specified stratum; n = number of
subjects in stratum achieving PASI-75; p = percentage of subjects in stratum achieving PASI-75.
For this analysis, subjects with missing PASI data at Week 12 were treated as nonresponders.
1. Treatment differences were based on CHS-1420 minus U.S.-Humira.
2. Estimate was estimated percentage difference between treatment groups.
3. Weight (stratum weight) was the product of stratum sample sizes for each treatment divided by the sum of the stratum
sample sizes.
4. If the 90% confidence interval was contained within the range of -15% to 15%, no clinically meaningful differences was demonstrated.
BMI = body mass index; EU = European Union; NA = not available; PASI = Psoriasis Area and Severity Index; PASI-75 = 75% improvement in PASI; ROW = rest of the world; SE = standard error for specified stratum; US = United States.

Source: reviewer analysis

* Extended MH approach, as described in LaVange et.al.2005, is used in the analysis

Supportive analysis using the Mantel Haenszel weight and Sato variance (Sato 1989) showed similar results as the primary efficacy analysis.

Potential Effects of Missing Data

FDA Recommended Primary Endpoint:

The statistical reviewers conducted multiple sensitivity analyses to test the impact of using the LOCF imputation for handling missing data, as specified in the protocol, on the primary efficacy results of the FDA recommended primary endpoint, percent change in PASI from baseline to Week 16. Table 30 shows that a small proportion of subjects (3.3% of CHS-1420 vs. 3.7% of U.S.-Humira) missed PASI assessment at Week 16. The following sensitivity analyses are conducted:

1) PPP analysis: the primary analysis was repeated using the per-protocol population;
2) Observed cases only: the primary analysis was repeated using observed PASI at Week 16.

Table 30 shows that for both sensitivity analyses, the 90% CI of the mean difference still fall within the margin of ± 10%. This confirms the finding from the primary efficacy analysis inTable 29.

Table 30. Sensitivity Analysis for Handling Missing data for the FDA Recommended Efficacy Endpoint, Percent Change in PASI from Baseline to Week 16

	CHS-1420 Mean (STD)	U.S.- Humira Mean (STD)	Mean Difference (weighted)(SE) 90% CI
Missing data rate at Week 16	9 (3.3%)	10 (3.7%)	
Sensitivity Analysis:			
PP Population Analysis	N=259 -86.1 (23.15)	N=251 -85.8 (22.03)	-0.3 (1.91) (-3.47, 2.81)
Observed Cases Only	N=265 -85.4 (24.30)	N=261 -84.0 (26.21)	-1.3 (2.12) (-4.83, 2.16)

Protocol-specified Primary Efficacy Endpoint:

In order to test the robustness of the primary efficacy analysis for using non-responder imputation for handling missing data in the analysis of the PASI 75 score, the applicant conducted the following 3 sensitivity analyses:

1) LOCF analysis: missing PASI-75 assessment at Week 12 was imputed using LOCF for subjects with postbaseline PASI-75 assessment, and imputed as non-responders for subjects with no postbaseline PASI score;
2) PPP analysis: the primary analysis was repeated using the PP Population;
3) Observed case only analysis: the primary analysis was repeated using only observed PASI-75 at Week 12.

In addition, the statistical reviewers conducted two more worst case imputations:

4) Worst case imputation 1: among the 7 subjects in CHS-1420 who missed PASI assessment at Week 12, non-responder was imputed for all 7 subjects; among the 5 subjects in U.S.-Humira who missed PASI assessment at Week 12, responder was imputed for all 5 subjects. This is an extreme case on one end;
5) Worst case imputation 2: among the 7 subjects in CHS-1420 who missed PASI assessment at Week 12, responder was imputed for all 7 subjects; among the 5 subjects in U.S.-Humira who missed PASI assessment at Week 12, non-responder was imputed for all 5 subjects. This is an extreme case on the other end.

Table 31 shows the result of various sensitivity analyses for PASI-75 at Week 12. There is a small missing data rate: 7 (2.6%) in CHS-1420 and 5 (1.8%) in U.S.-Humira. For all of the five sensitivity analyses, the 90% CI of the proportion difference in PASI-75 at Week 12 between the two treatment groups falls within the margin of ± 15%, including the two worst case imputations. Hence, this confirms the study finding from the primary efficacy analysis in Table 27.

Table 31. Sensitivity Analysis for Handling Missing Data for the Protocol-specified Primary Efficacy Endpoint: PASI-75 at Week 12

	CHS-1420 (FAP: N=274) (PPP: N=262)	**U.S.-Humira (FAP: N=271) (PPP: N=256)**	**Proportion Difference (weighted) 90% CI**
Missing data rate at Week 12	7 (2.6%)	5 (1.8%)	
Sensitivity Analysis:			
LOCF imputation	213 (77.7%)	204 (75.3%)	2.6 (-3.22, 8.40)
PP Population Analysis*	209 (79.8%)	196 (76.6%)	3.3 (-2.51, 9.18)
Observed Cases Only	211 (79.0%)	203 (76.3%)	2.7 (-3.14, 8.45)
Worst case imputation 1: Non-responder in CHS-1420 group + responder in U.S.-Humira	211 (77.0%)	208 (76.8%)	0.4 (-5.4, 6.2)
Worst case imputation 2: Responder in CHS-1420 + non-responder in U.S.-Humira	218 (79.6%)	203 (74.9%)	4.8 (-1.0. 10.5)

Source: Reviewer analysis
*The denominator for PPP analysis is the number of subjects in PPP. For all the other sensitivity analysis, the denominator is the number of subjects in FAP.

Assay Sensitivity and Constancy

Study CHS-1420-02 was a comparative clinical study of CHS-1420 and U.S.-Humira and it did not include a placebo arm. One Phase II placebo-controlled trial of Humira has been published (Gordon (2006)), and the Humira label includes the results from the two pivotal Phase III placebo-controlled trials of Humira (BLA125057 Study Ps-I and Study Ps-II). Each of these studies presented the percent improvement in PASI at either

Week 12 or 16 as a secondary endpoint. The key design criteria and results for the Humira studies in label and publication are presented in Table 32. The Gordon study had less restrictive inclusion criteria (BSA ≥ 5, no requirement on PASI), but Study Ps-I and Ps-II had similar inclusion criteria to Study CHS-1420-02 (BSA ≥ 10, PASI ≥ 12, and PSGA ≥ Moderate). The percent improvement in PASI on the U.S.-Humira arm in Study CHS-1420-02 is generally consistent with the results from the previous Humira studies at Week 12-16. The proportion of subjects achieving PASI-75 at Week 12 and Week 16 in CHS-1420-02 is also consistent with the previous Humira studies. Because of the low placebo response rate in the previous studies and the consistency of response across studies, the assumption of assay sensitivity appears reasonable for Study CHS-1420-02.

Table 32. Characteristics and Results of Published Humira Studies on Psoriasis and of Study CHS-1420-02

	Gordon (2006)	**BLA125057 Study Ps-I [Menter (2008)]**	**BLA125057 Study Ps-II [Saurat (2008)]**	**Study CHS-1420-02**
Selected inclusion criteria	BSA ≥ 5	BSA ≥ 10 PASI ≥ 12 PSGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 PSGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 PSGA ≥ Mod
Region/Country	US, Canada	US, Europe, Canada	US, Canada	US, Europe, ROW
Baseline PASI Mean *(Humira)*	PASI = 16.7	PASI = 19.0	PASI = 21.0	PASI = 24.5
% Imp. in PASI ***Humira***	(Week 12) 70	(Week 12) 76	(Week 16) 81	(Week 16) 82
Placebo	14	15	22	--
PASI-75 ***Humira***	(Week 12) 53% (n=50)	(Week 16) 71% (n=814)	(Week 16) 78% (n=99)	(Week 12) 75% (n= 271) (Week 16) 77% (n=271)
Placebo	4% (n=52)	7% (n=398)	19% (n=48)	--

Source: Reviewer analysis

Analysis of Secondary Clinical Endpoint(s)

The key secondary efficacy endpoints are PASI response endpoints (PASI-50, PASI-75, PASI-90) at various timepoints (Week 12, 16, 20, and 24). The PASI response rates in Period 1 (Week 12 and Week 16) by treatment among the FAP are reported in Table 33. LOCF imputation is used for handling missing PASI assessments. The response rates are generally similar for the two arms.

Table 33. Key Secondary Efficacy Endpoints PASI-50, PASI-75, PASI-90 in Treatment Period 1 (Week 12 and Week 16)

	CHS-1420 N=274	U.S.-Humira N=271	Treatment difference (90% CI)#
Week 12			
PASI-50	242 (88.3%)	247 (91.1%)	-2.8 (-7.1, 1.5)
PASI-75	211 (77.0%)	203 (74.9%)	-2.1 (-3.9, 8.1)
PASI-90	145 (52.9%)	142 (52.4%)	0.5 (-6.5, 7.6)
Week 16			
PASI-50	247 (90.1%)	241 (88.9%)	1.2 (-3.1, 5.5)
PASI-75	221 (80.7%)	209 (77.1%)	3.5 (-2.2, 9.3)
PASI-90	161 (58.8%)	165 (60.9%)	-2.1 (-9.3, 4.8)

The 90% CI for the treatment difference between treatment is for exploratory purpose.
Source: Reviewer analysis

Table 34 presents the PASI response rates for PASI-50, PASI-75, and PASI-90 in Treatment Period 2 (Week 20, 24) by treatment sequence among the FAP. The response rates are generally similar among the three treatment sequences.

Table 34. Key Secondary Efficacy Endpoints PASI-50, PASI-75, PASI-90 in Treatment Period 2 (Week 20 and 24)

	CHS-1420 (N=259)	U.S.-Humira		Treatment Difference (90% CI) [a]	Treatment Difference (90% CI) [b]
		U.S.-Humira/ CHS-1420 (N=128)	U.S.-Humira/ U.S.-Humira (N=129)		
Week 20					
PASI-50	234 (90.3%)	118 (92.2%)	123 (95.3%)	-5.0 (-9.3, -0.7)	-3.2 (-8.1, 1.8)
PASI-75	210 (81.1%)	104 (81.3%)	110 (85.3%)	-4.2 (-10.7,2.3)	-4.0 (-11.7, 3.6)

PASI-90	167 (64.5%)	90 (70.3%)	80 (62.0%)	2.5 (-6.1, 11.0)	8.3 (-1.4, 18.0)
Week 24					
PASI-50	238 (91.9%)	116 (90.6%)	126 (97.7%)	-5.8 (-9.3, -2.2)	-7.1 (-11.8, -2.3)
PASI-75	217 (83.8%)	103 (80.5%)	114 (88.4%)	-4.6 (-10.6,1.4)	-7.9 (-15.3, -0.5)
PASI-90	182 (70.3%)	87 (68.0%)	86 (66.7%)	3.6 (-4.7, 11.9)	1.3 (-8.3,10.9)

a. Treatment difference and 90% CI for CHS-1420/CHS-1420 minus U.S.-Humira/U.S.-Humira, for exploratory purpose.
b. Treatment difference and 90% CI for U.S.-Humira/CHS-1420 minus U.S.-Humira/U.S.-Humira, for exploratory purpose.

Source: Reviewer analysis

Table 35 summarizes the percentage of subjects achieving PASI-50, PASI-75, and PASI-90 over time by treatment for the Open-Label Extension Population in Treatment Period 3 (Week 32, 40, and 48). The response rates are also generally similar among the three treatment sequences.

Table 35. Key Secondary Efficacy Endpoints PASI-50, PASI-75, PASI-90 in Treatment Period 3 (Week 32, 40, and 48)

Time Point	CHS-1420/ CHS-1420/ CHS-1420 (N=235)			U.S.-Humira/ CHS-1420/ CHS-1420 (N=114)			U.S.-Humira/ U.S.-Humira/ CHS-1420 (N=125)			Overall (N=474)		
Parameter	**N'**	**n**	**p**	**N'**	**n**	**p**	**N'**	**n**	**p**	**N'**	**n**	**p**
Week 32												
PASI-50	229	225	98.3	111	109	98.2	123	120	97.6	463	454	98.1
PASI-75	229	214	93.4	111	103	92.8	123	107	87.0	463	424	91.6
PASI-90	229	178	77.7	111	85	76.6	123	84	68.3	463	347	74.9
Week 40												
PASI-50	224	218	97.3	111	103	92.6	122	113	92.6	457	434	95.0
PASI-75	224	209	93.3	111	96	86.5	122	104	85.2	457	409	89.5
PASI-90	224	173	77.2	111	82	73.9	122	84	68.9	457	339	74.2
Week 48												
PASI-50	206	198	96.1	93	90	96.8	104	97	93.3	403	385	95.5
PASI-75	206	186	90.3	93	83	89.2	104	88	84.6	403	357	88.6
PASI-90	206	155	75.2	93	68	73.1	104	62	59.6	403	285	70.7

Note: N = number of subjects in Open-Label Extension Population; N' = number of subjects with data at specified study week; n = number of subjects achieving PASI-50, PASI-75, and PASI-90 respectively; p = percentage of subjects achieving PASI-50, PASI-75, and PASI-90, respectively.
Only subjects with PASI response assessment at a Study Week were included for analysis for that study week.
PASI = Psoriasis Area and Severity Index; PASI-50 = 50% improvement in PASI; PASI-75 = 75% improvement in PASI; PASI-90 = 90% improvement in PASI.

Source: reviewer analysis

Table 36 presents the percentage change in PASI from baseline over time among the FAP in Treatment Period 1. In general, both CHS-1420 and U.S.-Humira demonstrate similar gradually increasing mean percent change in PASI score from baseline, beginning in Week 2 and incrementally improving every 2 weeks through Week 16.

Table 36. Key Secondary Efficacy Endpoint Percent Change from Baseline in PASI Over Time in Treatment Period 1

Time Point	CHS-1420 (N=274)			U.S.-Humira (N=271)			Difference in Means	
	N'	Mean	SD	N'	Mean	SD	Estimate	Wald 90% CI #
Week 2	271	-27.8	23.20	264	-26.2	23.44	-1.7	(-4.99, 1.64)
Week 4	273	-51.2	29.16	268	-52.9	24.26	1.7	(-2.23, 5.30)
Week 6	268	-65.5	28.02	264	-68.5	23.95	3.0	(-1.14, 6.21)
Week 8	257	-73.1	27.73	257	-75.7	21.79	2.6	(-0.78, 6.31)
Week 10	266	-78.9	26.26	264	-80.4	22.68	1.4	(-2.24, 4.45)
Week 12	267	-82.7	24.85	266	-82.6	24.43	-0.2	(-3.85, 2.99)
Week 16	265	-85.4	24.30	261	-84.0	26.21	-1.4	(-4.81, 2.14)
Note: N = number of subjects in Full Analysis Population; N' = number of subjects with data at specified week.								

90% CI for the mean difference between two treatment groups is for exploratory purpose.
Source: Reviewer analysis

Table 37 presents the percentage change in PASI over time for the Open-Label Extension Population in Treatment Period 3. The percent change in PASI over time was similar across treatment groups at all time points for the Open-Label Extension Population in Treatment Period 3.

Table 37. Key Secondary Efficacy Endpoint Percent Change from Baseline in PASI Over Time in Treatment Period 2

Time Point	CHS-1420/CHS-1420 (N=259)			U.S.-Humira/ CHS-1420 (N=128)			U.S.-Humira/ U.S.-Humira (N=129)		
	N'	Mean	SD	N'	Mean	SD	N'	Mean	SD
Week 20	253	-87.0	22.59	127	-85.6	27.89	128	-88.7	17.33
Week 24	251	-89.8	18.43	125	-86.3	26.65	129	-89.5	15.90

Source: Table 27, Clinical Study Report, CHS-1420-02 CSR and reviewer analysis

Additional Analyses

Table 38 presents the subgroup analyses for the percentage of subjects achieving PASI75 at Week 12 by treatment among the FAP in Treatment Period 1. Overall, there were no meaningful differences between treatment groups in the percentage of subjects achieving PASI75 at Week 12 by the various subgroups of subjects analyzed. The impact of BMI, gender, race, and region was similar for subjects treated with CHS-1420 and U.S.-Humira.

In general, a lower percentage of subjects with high BMI achieved PASI75, compared to subjects with low BMI, in both the CHS-1420 and U.S.-Humira groups. For the U.S. subgroup, the percentage of subjects achieving PASI75 at Week 12 was lower than those in Europe and ROW, in both the CHS-1420 and U.S.-Humira groups.

Table 38. Subgroup Analysis for the Protocol-specified Primary Endpoint, PASI 75 at Week 12

Subgroup	CHS-1420 (N=274)			U.S.-Humira (N=271)		
	N'	n	p	N'	n	p
BMI group						
< 30 kg/m^2	159	137	86.2	158	128	80.0
≥ 30 kg/m^2	115	76	66.1	113	76	67.3
Gender						
Female	82	64	78.1	69	49	71.0
Male	192	149	77.6	202	155	76.7
Race						
White	252	197	78.2	253	191	75.5
Non-white	22	16	72.7	18	13	72.2
Region						
US	76	48	63.2	74	46	62.2
EU	92	80	87.0	92	71	77.2
ROW	106	85	80.2	105	87	82.9

Note: N = number of subjects in Full Analysis Population; N' = number of subjects in treatment group within subgroup; n = number of subjects in stratum achieving PASI75; p = percentage of subjects in stratum achieving PASI75. BMI = body mass index; CI = confidence interval; EU = European Union; PASI = Psoriasis Area and Severity Index; PASI75 = 75% improvement in PASI; ROW = rest of the world; U.S. = United States.
Subjects with missing PASI75 at Week 12 were treated as non responders.
Treatment differences were based on CHS-1420 minus U.S.-Humira.

Source: Reviewer analysis

Table 39 reports the percent change from baseline at Week 16 among subgroups: BMI, gender, race, and region. In summary, there were no meaningful differences between treatment groups in the percent change of PASI at Week 16 from baseline by the various subgroups of subjects analyzed. The impact of BMI, gender, race, and region was similar for CHS-1420 and U.S.-Humira.

Table 39. Subgroup Analysis for the FDA Recommended Primary Efficacy Endpoint: Percent Change from Baseline in PASI at Week 16

Subgroup	CHS-1420 (N=274)		U.S.-Humira (N=271)	
	N'	Mean (Std Dev)	N'	Mean (Std Dev)
BMI group				
< 30 kg/m^2	159	-89.2 (17.2)	158	-86.3 (29.1)
≥ 30 kg/m^2	115	-74.8 (36.3)	113	-76.7 (30.1)
Gender				
Female	82	-80.0 (35.5)	69	-73.8 (42.3)
Male	192	-84.5 (23.7)	202	-85.2 (23.7)
Race				
White	252	-83.2 (28.2)	253	-83.2 (28.2)
Non-white	22	-81.8 (23.8)	18	-69.2 (46.1)
Region				
US	76	-70.7 (35.1)	74	-68.9 (40.8)
EU	92	-89.6 (20.1)	92	-86.9 (19.2)
ROW	106	-86.3 (24.9)	105	-87.7 (25.4)

Source: Reviewer analysis

6.2.2. **OTHER STUDIES: CHS-1420-01, -03, -04, -05, and -07**

The Applicant has included four PK studies (CHS-1420-01, -03, -05, and -07) and one study involving CHS-1420 autoinjector in this BLA submission.

CHS-1420-03, entitled "*A Randomized, Double-Blind, Single-Dose, Parallel-Group Study to Assess the Pharmacokinetic Similarity of CHS-1420 DP and Humira® (US) in Healthy Male and Female Subjects*", is the pivotal PK study. Refer to Section 5 for details of the comparative PK and immunogenicity review of this study, and Section 6.3 for brief review of the safety data.

CHS-1420-01, entitled "*A Randomized, Double-Blind, Single-Dose, Parallel-Group Study to Assess the Pharmacokinetic Similarity of CHS-1420 DP and Humira® in Healthy Male and Female Subjects*", is a single-dose PK study testing an earlier formulation of CHS-1420 not proposed for marketing. Its comparative data are not relevant to support the CHS-1420 formulation to be marketed.

CHS-1420-05, entitled "*A Randomized, Open-Label, Single-Dose, Parallel-Group Study to Assess the Pharmacokinetic Bioequivalence of CHS-1420 DP in a Prefilled Syringe vs. CHS-1420 DP in an Auto Injector in Healthy Male and Female Subjects*", is an open-label, single-dose, PK study testing PFS and AI presentations of CHS-1420 and is not relevant to the current request for licensure of CHS-1420. Safety data are briefly reviewed to confirm that those results did not preclude or conflict with conclusions based on Studies CHS-1420-02 and -03.

CHS-1420-07, entitled "*A Randomized, Single-Blind, Single-Dose, Parallel-Group Study to Assess the Pharmacokinetic Bioequivalence of CHS-1420 and Humira® (EU) in Healthy Male and Female Subjects*", is a single-blind, single-dose PK study using the EU version of Humira as comparator. Its comparative data are not relevant to the current request for licensure of CHS-1420. Safety data for CHS-1420 only (not in comparison to EU-Humira) are briefly reviewed to confirm that those results did not preclude or conflict with conclusions based on Studies CHS-1420-02 and -03.

CHS-1420-04, entitled "*A Study to Assess the Dosing Robustness of the CHS-1420 Autoinjector in Subjects with Rheumatoid Arthritis*", is not relevant to the current BLA which requests licensure of the PFS presentation. Since the PFS and AI presentations of CHS-1420 contain the same formulation, the safety data of this study are briefly reviewed.

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6.3. Review of Safety Data

To characterize safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary study used to evaluate safety was the comparative clinical study CHS-1420-02, as it provided controlled and blinded comparisons between U.S.-Humira and CHS-1420 in patients with PsO for 24 weeks. Additionally, the safety of longer term use of CHS-1420 was assessed in Treatment Period 3 in this study.

Safety data from the autoinjector study on use by RA patients and caregivers (CHS-1420-04) and single-dose PK studies (CHS-1420-01, -03, -05 and -07) in healthy volunteers were briefly reviewed to confirm that those results did not preclude or conflict with conclusions based on the primary safety assessment.

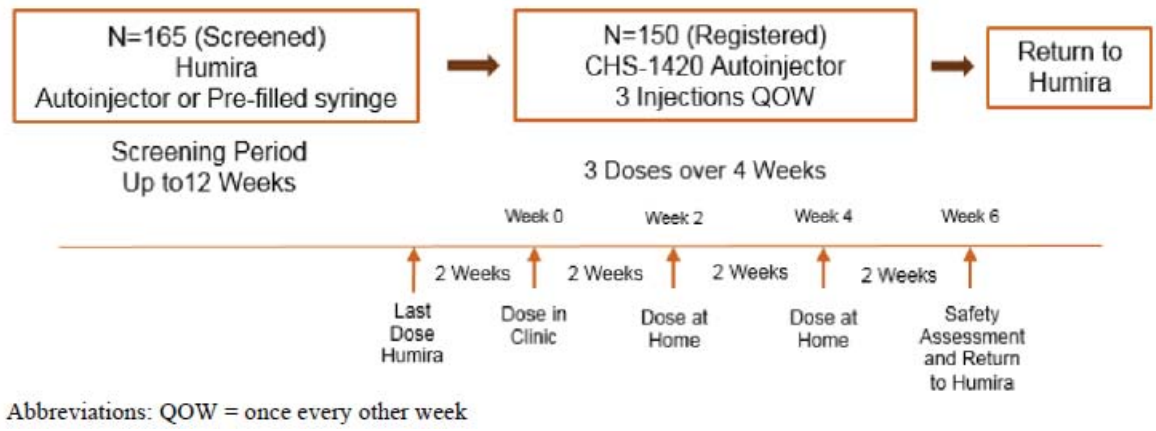
6.3.1. Methods

6.3.1.1 Clinical Studies Used to Evaluate Safety

The six clinical studies submitted in this BLA have been listed under Table 4 in Section 2.2. The primary study used to evaluate safety is the comparative clinical study CHS-1420-02, entitled "*A Double-Blind, Randomized, Parallel-Group, Active-Control Study to Compare the Efficacy and Safety of CHS-1420 Versus Humira® in Subjects with Chronic Plaque Psoriasis (PsOsim)*", which provided controlled and blinded comparisons between U.S.-Humira and CHS-1420 in patients with PsO for 24 weeks, and safety data from longer term use of CHS-1420 for an additional 24 weeks. Refer to Section 6.2 for details on design of this study.

Safety data from the autoinjector study on use by RA patients and caregivers (CHS-1420-04) and from the single-dose PK studies (CHS-1420-01, -03, -05 and -07) in healthy volunteers have been briefly reviewed to confirm that those results did not preclude or conflict with conclusions based on the primary safety assessment.

Study CHS-1420-04 was an open-label study on patients already being treated with U.S.-Humira (AI or PFS), to be enrolled for use of CHS-1420 40 mg SC via AI qow administered by self or caregiver over 4 weeks, with the following design:



Since the CHS-1420 product used in the single-dose studies CHS-1420-03, -05, and -07 is the formulation to-be-marketed in the U.S., the safety data from these three studies will be presented as combined. These single-dose studies have similar basic design: randomized, single-dose, parallel-group studies in healthy subjects to assess PK with comparison of relative bioavailability after SC administration of a single dose of 40 mg. They also have the following differences –

- CHS-1420-03 - double-blind study comparing CHS-1420 to U.S.-Humira
- CHS-1420-05 - open-label study comparing CHS-1420 PFS to CHS-1420 AI
- CHS-1420-07 - single-blind study comparing CHS-1420 to Humira (EU)

The safety population in all of the above studies is defined as including all subjects who received one or more doses of study drug. Note that comparisons between CHS-1420 to EU-Humira were not used to support the determination whether CHS-1420 is biosimilar to U.S.-Humira.

Exposure

Refer to Table 4, in Section 2.2 for the number of subjects enrolled into each treatment arm in the clinical studies for CHS-1420 and the number of subjects who completed the studies.

- The overall safety database of CHS-1420 clinical studies using the to-be-marketed formulation of CHS-1420 (CHS-1420-02, CHS-1420-03, CHS-1420-04, CHS-1420-05, CHS-1420-07) consists of 1104 subjects exposed to CHS-1420, 374 subjects to U.S.-Humira, and 108 subjects were exposed to EU-Humira.

Table 40. Number of Subjects Exposed to Study Drug

Study Type Study Number(s)	Number of Subjects Exposed to Study		
	CHS-1420	U.S.-Humira	EU-Humira

Repeat dose in subjects with chronic PsO CHS-1420-02	526 *	271	Not applicable
Repeat dose in subjects with RA CHS-1420-04	141	Not applicable	Not applicable
Single dose in healthy subjects CHS-1420-03, CHS-1420-05, CHS-1420-07	437	103	108
Total	1104	374	108

EU = European Union; PsO = plaque psoriasis; RA = rheumatoid arthritis; US = United States.
* Includes 274 subjects exposed to CHS-1420 in Treatment Period 1, 126 additional subjects exposed to CHS-1420 in Treatment Period 2, and 126 additional subjects exposed to CHS-1420 in Treatment Period 3.
Source: Clinical Study Reports for CHS-1420-02 (Table 30, Table 31, Table 33), CHS-1420-04 (Table 11.3), and Integrated Table 14.3.3.5.

The product exposure and compliance in these five clinical studies are shown in the following Tables.

Table 41. Drug Exposure and Compliance (CHS-1420-02, Treatment Period 1 + 2 + 3, Safety Population)

	CHS-1420/ CHS-1420/ CHS-1420 (N = 274)	**U.S.-Humira CHS-1420/ CHS-1420 (N = 134)**	**U.S.-Humira/ U.S.-Humira/ CHS-1420 (N = 137)**
Duration on study drug in weeks [a]			
Mean (SD)	42.6 (11.33)	41.7 (11.74)	44.2 (9.80)
Median	48.0	48.0	48.0
Min, max	4, 52	1, 53	2, 50
Proportion of subjects who ended study treatment within time interval n (%) [c]			
> 0 to 4 weeks	1 (0.4)	3 (2.2)	1 (0.7)
> 4 to 8 weeks	5 (1.8)	1 (0.7)	2 (1.5)
> 8 to 12 weeks	7 (2.6)	2 (1.5)	1 (0.7)
> 12 to 16 weeks	4 (1.5)	3 (2.2)	3 (2.2)
> 16 to 24 weeks	23 (8.4)	11 (8.2)	5 (3.6)
> 24 to 32 weeks	10 (3.6)	6 (4.5)	2 (1.5)
> 32 to 40 weeks	5 (1.8)	7 (5.2)	7 (5.1)
> 40 to 48 weeks	209 (76.3)	98 (73.1)	110 (80.3)
> 48 weeks	10 (3.6)	3 (2.2)	6 (4.4)
Number of injections			

Mean (SD)	22.6 (5.81)	22.1 (6.00)	23.5 (5.25)
Median	25.0	25.0	26.0
Min, max	3, 28	2, 28	3, 28
Compliance (%) [b]			
Mean (SD)	96.7 (9.01)	96.8 (7.46)	97.6 (7.94)
Median	100.0	100.0	100.0
Min, max	17, 117	48, 104	36, 113

Max = maximum; Min = minimum; N = number of subjects in the Safety Population; SD = standard deviation.
[a] Duration on study drug in weeks = integration ([last injection date–first injection date + 7]/7).
[b] Compliance (%) = 100 (number of days injection administered)/(1 + integration [(last injection date–first injection date + 7)/14]).
[c] Rows are mutually exclusive.

Table 42. Study Drug Exposure and Compliance (CHS-1420-04, Safety Population)

	CHS-1420 (40 mg) N = 141 n (%)
Administration of Week 0 Injections	
Number of Subjects with Injections	141 (100.0)
Injections by Subject	133 (94.3)
Injections by Caregiver	8 (5.7)
Administration of Week 2 Injections	
Number of Subjects with Injections	135 (95.7)
Injections by Subject	127 (90.1)
Injections by Caregiver	8 (5.7)
Administration of Week 4 Injections	
Number of Subjects with Injections	136 (96.5) [a]
Injections by Subject	128 (90.8)
Injections by Caregiver	9 (6.4)
Number of Subjects Receiving 1, 2, or 3 Injections	
3 Injections	133 (94.3)
2 Injections	6 (4.3)
1 Injection	2 (1.4)

Note: Post-baseline injections were assigned to Week 2 or Week 4 based on injection date relative to baseline injection date.
N = Number of subjects in the Safety Population; n = number of subjects in the sample.
[a]One subject had two injections that were assigned to Week 4.
Source: CHS-1420-04 CSR Post-text Table 14.3.5.1.

Table 43. Actual Amount of Study Drug Administered by Treatment (Pooled Single-Dose Studies CHS-1420-03, -05, and -07, Safety Population)

Parameter Statistic	CHS-1420 (N = 437)	U.S.-Humira (N = 103)	"Humira" Total (N = 211) [a]	Overall Total (N = 648)
Actual Amount Administered (mg)				
Mean (SD)	38.52 (0.670)	38.13 (1.135)	38.38 (0.910)	38.47 (0.759)
Median	38.54	38.28	38.51	38.51
Min, Max	34.4, 40.5	27.9, 39.2	27.9, 39.9	27.9, 40.5

EU = European Union; Max = maximum; Min = minimum; N = Number of subjects in the Safety Population; SD = standard deviation; US = United States.

[a] The comparison of focus is between CHS-1420 and U.S.Humira; data for "Humira" Total are provided for informational purposes only. U.S.-Humira was used in CHS-1420-03 and EU-Humira was used in CHS-1420-07; both studies met the pre-specified PK criteria. Neither U.S.-Humira nor EU-Humira were used in CHS-1420-05.

Source: Integrated Table 14.1.3.2

The product exposure database and compliance from Study CHS-1420-02 is adequate for evaluation of comparative safety between CHS-1420 and U.S.-Humira. The size of the database would be able to allow for a demonstration of no clinically meaningful differences between them. The safety results from PK studies in healthy subjects were also reviewed. Note that comparisons between CHS-1420 to EU-Humira were not used to support the determination whether CHS-1420 is biosimilar to U.S.-Humira.

6.3.1.2 Categorization of Adverse Events

CHS-1420-02. In the comparative clinical study in plaque psoriasis (CHS-1420-02), which provided the primary support for comparative safety, he Applicant used coding to system organ class (SOC) and preferred term with MedDRA (version 17.1). Adverse events were processed via reporting, observation, and eDiary, to include injection site assessments, vital signs, physical examination, ECG, and laboratory testing as well as monitoring for tuberculosis. The focus has been on treatment-emergent adverse events (TEAEs), which were those adverse events that started after the subject received the first dose of study drug.

All adverse events, including observed or suspected problems, complaints, or symptoms, were to be recorded on the appropriate eCRF. Documentation must have been supported by an entry in the subject's source document. Each adverse event was to be evaluated for duration, severity, and causal relationship with the study drug or other factors.

Sites accessed the electronic data capture (EDC) system and entered data into the eCRF. Specifically designed computer– generated checks (as well as manual edit checks) were used to identify data entry errors or other data inconsistencies. Data were

reviewed on an ongoing basis. The central laboratory for this study, (b) (4) performed all study-related safety labortoratory tests. The duration of adverse events was established via follow-up to resolution, with their treatment noted in the eCFR.

Severity grading of adverse events in CHS-1420-02:

- Grade 1: Mild – An event that is usually transient in nature and generally not interfering with normal activities.
- Grade 2: Moderate – An event that is sufficiently discomforting to interfere with normal activities.
- Grade 3: Severe – An event that is incapacitating with inability to work or perform normal daily activity
- Grade 4: Life threatening consequences – urgent intervention indicated
- Grade 5: Death

The assessment of causality included temporal relationship, confounders such as baseline condition, concomitant treatments, intercurrent illnesses, reversibility, rechallenge, investigator evaluation, etc.

For safety analyses, the approach was for adverse events to be summarized and listed. No inferential statistical analyses of the safety data were planned. All safety summaries and listings were generated using the Safety Population based upon treatment received for the treatment period of interest.

The Applicant's categorization of adverse events and safety data analyses are standard procedures and considered reasonable in support of comparisons between CHS-1420 with U.S.-Humira for similarity and no clinically meaningful differences.

CHS-1420-03, -04, -05, and -07. The categorization and analyses of adverse events are similar to those for CHS-1420-02. Like CHS1420-02, CHS-1420-04 uses MedDRA version 17.0, while CHS-1420-03, -05 and -07 use version 19.0. All studies used the same grading system for severity of adverse events like that in CHS-1420-02. These four studies have been briefly reviewed to confirm that their safety data do not preclude or conflict with conclusions based on the primary safety assessment.

6.3.1.3 Safety Analyses

The Safety Analysis Set for each study was defined as those participants who received at least one dose of study medication. Patient safety data were analyzed according to the treatment actually received.

The safety analyses submitted by the Applicant were from the individual studies and in the integrated analyses of safety, the single-dose human volunteer PK studies were pooled (except CHS-1420-01, which used an earlier formulation of CHS-1420). The

differences in study population and conduct of the studies made pooling with the other clinical studies (CHS-1420-02 and -04) inappropriate.

6.3.2. Major Safety Results

6.3.2.1 Relevant Characteristics of the Population Evaluated for Safety

For CHS-1420-02, the population demographics has been discussed in Section 6.2. Refer to Tables 4 and 5 in Section 6.2.1.

The population characteristics of the other four studies, CHS-1420-04, -03, -05, and -07 are shown in the following Table:

	CHS-1420-04	**CHS-1420-03**		**CHS-1420-05**		**CHS-1420-07**	
Study product	CHS-1420 AI	CHS-1420	U.S.-Humira	CHS-1420 AI	CHS-1420 PFS	CHS-1420	EU-Humira
Study subjects	RA patients	Healthy volunteers					
N	141	107	103	111	111	108	108
Age	Median 55	Mean 34	Mean 36	Mean 34	Mean 36	Mean 39	Mean 33
Sex F%/M%	78/22	36/65	35/65	41/60	41/60	41/59	41/59
Race (%)							
• White	91	38	35	60	48	88	87
• Black	5	44	47	34	46	7	8
• Asian	1	18	16	1	3	1	1
• Other	3	0	3	5	4	4	4

Source: modified from CSR Table 11.1 of CHS-120-04, Table 7 of CHS-1420-03, Table 5 of CHS-1420-05 and Table 5 of CHS-1420-07

The study arms for the three PK studies in healthy volunteers (CHS-1420-03, -05 and -07) are balanced with respect to age, sex, and race, and would allow data pooling among them. CHS-1420-04 is a study for the use of CHS-1420 AI in RA patients but has no comparative component; its safety data would have to be assessed separately.

6.3.2.2 Other Product-Specific Safety Concerns

The reference product, U.S.-Humira, is associate with a number of adverse reactions listed in the Warnings and Precautions section of labeling. These include serious Infections, malignancies, hypersensitivity Reactions, hepatitis B virus reactivation, neurologic reactions, hematological reactions, heart failure, and autoimmunity.

The Applicant has provided analyses for potential product-specific adverse effects of CHS-1420 as summarized below:

Hypersensitivity

- There were no anaphylaxis cases reported in the clinical studies.
- In CHS-1420-02, the proportion of subjects who had at least 1 hypersensitivity TEAE was no more than 4.4% in any treatment group or treatment period
- In CHS-1420-04 (CHS-1420 AI administration only), the proportion of subjects who had at least 1 hypersensitivity was 0.7%.
- For the Pooled Studies (CHS1420-03, -05, and -07), results of the search for hypersensitivity indicate that the incidence of hypersensitivity is slightly higher with U.S.-Humira (8.7%) than with CHS-1420 (4.3%).

Immunogenicity

- CHS-1420-02, the repeat-dose study in subjects with chronic PsO, confirmed the immunogenicity similarity and supports the conclusion of no clinically meaningful differences between CHS-1420 and U.S.-Humira, with incidence, time-course, and magnitude (ADA titer) of ADA and Nab similar between CHS-1420 and U.S.-Humira groups.
- CHS-1420-03 confirmed similar immunogenicity (incidence, time-course, and magnitude [ADA titer]) after a single dose of CHS-1420 or U.S.-Humira in healthy subjects.

Hepatic disorder

- A comprehensive search for events related to hepatic disorders was performed for each study in the CHS-1420 clinical program to identify any terms for possible drug-related hepatic events.
- In CHS-1420-02, the incidence rates for reported hepatic disorder are comparable between CHS-1420 and U.S.-Humira through treatment periods (approximately 1%). These were primarily liver enzyme elevations, and none met Hy's Law criteria. The enzyme elevations were further explored with IR to the applicant (see Appendix 13.5.1) and they resolved with the return to within normal limits despite continued treatment and presence of concomitant confounding factors.
- In CHS-1420-04 routine laboratory tests were not performed after baseline.
- In the Pooled Studies CHS-1420-03, -05, and -07, there were no drug-related hepatic disorders recorded.

Serious infections and tuberculosis

- In CHS-1420-02 the incidence rates for reported serious infections are comparable between CHS-1420 and U.S.-Humira through treatment periods (up to 1%).
- In CHS-1420-04, there were 2 SAEs of infections and infestations (gastroenteritis and acute bronchitis) which were not considered related to the study product (only CHS-1420 AI in this study)

- In the Pooled Studies (CHS-1420-03, -05, and -07), there was 1 (1.0%) SAE of influenza in the U.S.-Humira group and no SAE infections in the CHS-1420 group.
- In CHS1420-02, one subject, (b) (6) (Humira/Humira/CHS-1420 group), experienced a re-activation of TB during Treatment Period 2 before use of CHS-1420.
- There were no positive TB test results in either CHS-1420-04 or the Pooled Studies (CHS1420-03, -05, and -07).

Cardiac failure

- In CHS-1420-02, none of the cardiac failure SMQ TEAEs were experienced by >1% of subjects in any of the treatment groups during any of the treatment periods.
- In CHS-1420-04, no TEAEs were identified by the SMQ search for cardiac failure.
- In the Pooled Studies (CHS-1420-03, -05, and -07), one TEAE for cardiac failure was identified by the SMQ search. The event was peripheral swelling in a subject receiving CHS-1420.

Neoplasms

- There were 7 TEAEs of neoplasm in 6 subjects in the CHS-1420 clinical program (one in CHS-1420-05 and the remainder in CHS-1420-02), 5 of these events were reported in subjects who had received at least 1 dose of CHS-1420, while the 2 remaining events occurred in subjects who received only U.S.-Humira.
- The case of glioblastoma multiforme (Subject (b) (6) in CHS-1420-02) was the only neoplasm considered an SAE. Skin papilloma was the only event reported in more than 1 subject.
- These data are shown below in Table 44.

Table 44. Neoplasms Reported During the CHS-1420 Clinical Program (Safety Population)

Study Number	Treatment Group	Treatment Period	Preferred Term
CHS-1420-02	Humira*	1	Skin papilloma
CHS-1420-02	Humira/Humira	2	Haemangioma of breast
CHS-1420-02	CHS-1420/CHS-1420/CHS-1420	3	Basal Cell Carcinoma and Keratoacanthoma
CHS-1420-02	Humira/CHS-1420/CHS-1420	3	Glioblastoma multiforme
CHS-1420-02	Humira/Humira/CHS-1420	3	Skin papilloma
CHS-1420-05	CHS-1420 DP PFS	Not applicable	Skin papilloma

*In CHS-1420-02, U.S.-Humira was used as comparator
Source: BLA 761216 Module 2.7.4 Summary of Clinical Safety, Table 41.

Injection site reactions

- In the CHS-1420 clinical program, the incidence of ISRs to CHS-1420 as recorded on the AE case report forms (AE CRFs) was similar to that for U.S.-Humira, and no new safety signals were identified.
- In CHS-1420-02, the ISR in Treatment Periods 1, 2, and 3 are shown in the following Tables.

Table 45. Injection Site Reactions Reported on Adverse Event Case Report Forms (CHS-1420-02, Treatment Period 1, Safety Population)

ISR Reported on AE Forms	CHS-1420 (N = 274)	U.S.-Humira (N = 271)
Subjects with at Least One Event		
Any ISR	11 (4.0)	10 (3.7)
Erythema/redness	6 (2.2)	6 (2.2)
Induration/swelling	0	3 (1.1)
Pain/tenderness	0	3 (1.1)
Pruritus/itching	1 (0.4)	3 (1.1)
Hematoma/ecchymosis/bruising	5 (1.8)	4 (1.5)
Other	0	1 (0.4)

Note: N = Number of subjects in the Safety Population; n (%) = number and % of subjects with events starting on or after the day of first dose of study medication of Treatment Period 1 and before first dose of study medication of Treatment Period 2. ISR = injection site reaction.
All ISRs reported from the day of first dose through the day prior to the first dose of study drug in Treatment Period 2 are reported in this summary.
Source: CHS-1420-02 CSR Post-text Table 14.3.1.9.5.

Table 46. Injection Site Reactions Reported on Adverse Event Case Report Forms (CHS-1420-02, Treatment Period 2, Safety Population)

ISR Reported on AE Forms	CHS-1420/ CHS-1420 (N = 255) n (%)	U.S.-Humira/ CHS-1420 (N = 126) n (%)	U.S.-Humira/ U.S.-Humira (N = 130) n (%)
Subjects with at Least One Event			
Any ISR	2 (0.8)	0	2 (1.5)
Erythema/redness	1 (0.4)	0	0
Induration/swelling	0	0	1 (0.8)
Pain/tenderness	0	0	1 (0.8)
Pruritus/itching	1 (0.4)	0	1 (0.8)
Hematoma/ecchymosis/bruising	1 (0.4)	0	1 (0.8)
Other	0	0	1 (0.8)

Note: N = Number of subjects in the Safety Population; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 2 and before first dose of study drug of Treatment Period 3. All ISRs reported from the day of first dose of Treatment Period 2 and prior to the first dose of study drug in Treatment Period 3 are reported in this summary.
ISR = injection site reaction.
Source: CHS-1420-CSR Post-text Table 14.3.1.9.6.

Table 47. Injection Site Reactions Reported on Adverse Event Case Report Forms (CHS-1420-02, Treatment Period 3, Open Label Extension Population)

ISR Reported on AE Forms	CHS-1420/ CHS-1420/ CHS-1420 (N = 235) n (%)	U.S.-Humira/ CHS-1420/ CHS-1420 (N = 113) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N = 126) n (%)	Overall (N = 474) n (%)
Subjects with at Least One Event				
Any ISR	0	0	1 (0.8)	1 (0.2)
Erythema/redness	0	0	1 (0.8)	1 (0.2)
Induration/swelling	0	0	0	0
Pain/tenderness	0	0	1 (0.8)	1 (0.2)
Pruritus/itching	0	0	0	0
Hematoma/ecchymosis/bruising	0	0	0	0
Other	0	0	1 (0.8)	1 (0.2)

Note: N = number of subjects treated in the Safety Population; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 3. All ISRs reported on or after first dose of Treatment Period 3 are reported in this summary.
ISR = injection site reaction.

Table 48. Injection Site Reactions Reported on Adverse Event Case Report Forms (CHS-1420-02, Treatment Periods 1 + 2 + 3, Safety Population)

ISR Reported on AE Forms	CHS-1420/ CHS-1420/ CHS-1420 (N = 274) n (%)	U.S.-Humira/ CHS-1420/ CHS-1420 (N = 134) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N = 137) n (%)
Subjects with at Least One Event			
Any ISR	12 (4.4)	5 (3.7)	6 (4.4)
Erythema/redness	7 (2.6)	1 (0.7)	5 (3.6)
Induration/swelling	0	0	3 (2.2)
Pain/tenderness	0	0	3 (2.2)
Pruritus/itching	2 (0.7)	1 (0.7)	3 (2.2)
Hematoma/ecchymosis/bruising	5 (1.8)	4 (3.0)	1 (0.7)
Other	0	0	1 (0.7)

Note: N = Number of subjects in the Safety Population; n (%) = number and % of subjects with events starting on or after the day of first dose of study medication of Treatment Period 1 through study termination. All injection site reactions reported from the day of first dose in Treatment Period 1 through study termination are reported in this summary. ISR = injection site reaction
Source: CHS-1420-02 CSR Post-text Table 14.3.1.9.12.

- In CHS-1420-04, there were 5 TEAEs of ISR: 2 reports of injection site erythema and 1 report each of injection site bruising, injection site pain and injection site pruritus.
- In the Pooled Studies (CHS-1420-03, CHS-1420-05, CHS-1420-07), there were 20 (4.6%) subjects who experienced a TEAE of injection site erythema in the CHS-1420 group compared to 1 (1.0%) subject in U.S.-Humira; however, there were 3 (0.7%) subjects in CHS-1420 and 6 (5.8%) subjects in U.S.- Humira who experienced TEAE of injection site rash. All other ISRs occurred in < 2% of subjects in the CHS-1420 or U.S.-Humira group.

Table 49. Treatment-emergent Adverse Events of Injection Site Reactions (Pooled Studies CHS-1420-03, -05, and -07, Safety Population)

System Organ Class Preferred Term	CHS-1420 (N = 437) n (%)	U.S.-Humira (N = 103) n (%)	"Humira" Total (N = 211) [a] n (%)	Overall Total (N = 648) n (%)
Subjects with at Least One Event				
General disorders and administration site conditions	53 (12.1)	9 (8.7)	29 (13.7)	82 (12.7)
Injection site erythema	20 (4.6)	1 (1.0)	15 (7.1)	35 (5.4)
Injection site rash	3 (0.7)	6 (5.8)	7 (3.3)	10 (1.5)
Injection site pruritus	5 (1.1)	0	3 (1.4)	8 (1.2)
Injection site haemorrhage	5 (1.1)	0	1 (0.5)	6 (0.9)
Injection site bruising	5 (1.1)	0	0	5 (0.8)
Injection site pain	3 (0.7)	0	2 (0.9)	5 (0.8)
Injection site reaction	2 (0.5)	1 (1.0)	1 (0.5)	3 (0.5)
Injection site oedema	2 (0.5)	0	0	2 (0.3)
Injection site induration	1 (0.2)	(1.1)	5 (1.0)	6 (0.6)
Injection site inflammation	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Injection site swelling	1 (0.2)	1 (0.4)	2 (0.4)	3 (0.3)
Injection site papule	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.1)

Studies Included: CHS-1420-03, CHS-1420-05, CHS-1420-07. EU-Humira data (CHS-1420-07) excluded from Table
N = Number of subjects in the Safety Population; U.S. = United States.
[a]The comparison of focus is between CHS-1420 and U.S.-Humira; data for EU-Humira excluded and "Humira" Total are provided for informational purposes only. U.S.-Humira was used in CHS-1420-03 and EU-Humira was used in CHS-1420-07; both studies met prespecified PK criteria. Neither U.S.-Humira nor EU-Humira were used in CHS-1420-05.Source: Integrated Table 14.3.2.6.

In the clinical development program for CHS-1420, adverse events for Hepatitis B virus reactivation, demyelinating conditions or hematologic disorders have not been reported. Although these adverse reactions are listed under Warnings and Precautions in current U.S.-Humira labeling, and (b) (4) no specific discussions to address them have been made in this BLA.

6.3.2.3 Deaths

Two deaths occurred in the CHS-120 development program.

- In CHS-1420-02, one subject who received CHS-1420/CHS-1420/CHS-1420 died. Subject (b) (6) experienced suspected thermal shock after jumping into water during Treatment Period 3. The event was described as not related to study drug.
- In CHS-1420-03, one subject who received U.S.-Humira died during the study. This subject (Subject (b) (6)) had a TESAE of "completed suicide by hanging" that was considered by the Investigator to be not related to the study drug.

Both deaths do not appear to be related to the investigational product.

6.3.2.4 Treatment Emergent Adverse Events

Refer to Section 6.1 "Statistical and Clinical Executive Summary and Recommendations for a brief account of the TEAE data which will not be repeated here. Details of TEAE Tables will be provided in Appendix 13.5.2.

From the standpoint of comparing CHS-1420 and U.S.-Humira product safety, the TEAE data from the clinical trials provide evidence in support of biosimilarity and no clinically meaningful differences between these products.

Serious Adverse Events (SAEs)

CHS-1420-02

- Treatment Period 1 (Subjects Received Either CHS-1420 or U.S.-Humira)
  During Treatment Period 1, 4 (1.5%) subjects in the CHS-1420 group and 6 (2.2%) subjects in the U.S.-Humira group experienced at least 1 SAE. No SAEs were experienced by more than 1 subject in either treatment group. There were no study drug-related SAEs.

Table 50. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (CHS-1420-02, Treatment Period 1, Safety Population

System Organ Class Preferred Term	CHS-1420 (N = 274) n (%)	U.S.-Humira (N = 271) n (%)
Subjects with at Least One Event		
Any TESAE	4 (1.5)	6 (2.2)

Cardiac disorders	1 (0.4)	0
• Acute myocardial infarction	1 (0.4)	0
Gastrointestinal disorders	0	1 (0.4)
• Diarrhea	0	1 (0.4)
Infections and infestations	0	3 (1.1)
• Gastroenteritis	0	1 (0.4)
• Pneumonia	0	1 (0.4)
• Sinusitis	0	1 (0.4)
Injury, poisoning, and procedural complications	0	1 (0.4)
• Foot fracture	0	1 (0.4)
Metabolism and nutrition disorders	0	1 (0.4)
• Dehydration	0	1 (0.4)
• Diabetic ketoacidosis	0	1 (0.4)
Musculoskeletal and connective tissue disorders	2 (0.7)	0
• Psoriatic arthropathy	1 (0.4)	0
• Rotator cuff syndrome	1 (0.4)	0
Respiratory, thoracic, and mediastinal disorders	0	1 (0.4)
• Chronic and obstructive pulmonary disease	0	1 (0.4)
Skin and subcutaneous tissue disorders	1 (0.4)	0
• Psoriasis*	1 (0.4)	0

N = number of subjects treated in the treatment period; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 1 and before first dose of study drug of Treatment Period 2; TESAE = treatment-emergent serious adverse event.

*Subject (b) (6), a 41-year-old black female, developed SAE, AE leading to study discontinuation [Verbatim Term: Psoriasis (Skin moderate itching, worsening of psoriasis)]: she reported being hospitalized for ultraviolet treatment for worsening of her psoriasis 113 days after starting CHS-1420

- Treatment Period 2 (Subjects Received Either CHS-1420 or U.S.-Humira, With Switching Group [Humira/CHS-1420])

  During Treatment Period 2, the number of subjects with SAEs was similar across the 3 treatment groups (i.e., the CHS-1420/CHS-1420, U.S.-Humira/U.S.-Humira, and U.S.-Humira/CHS-1420 groups). One (0.8%) subject in the U.S.-Humira/U.S.-Humira group experienced an SAE considered to be drug-related during Treatment Period 2 (tuberculosis, Subject (b) (6).

Table 51. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (CHS-1420-02, Treatment Period 2, Safety Population)

System Organ Class Preferred Term	CHS-1420/ CHS-1420 (N = 255) n (%)	U.S.-Humira/ CHS-1420 (N = 126) n (%)	U.S.-Humira/ U.S.-Humira (N = 130) n (%)
Subjects with at Least One Event			
Any TESAE	4 (1.6)	3 (2.4)	1 (0.8)
Gastrointestinal disorders	2 (0.8)	1 (0.8)	0
• Anal fistula	0	1 (0.8)	0
• Gastritis	1 (0.4)	0	0
• Inguinal hernia	1 (0.4)	0	0
Infections and infestations	0	2 (1.6)	1 (0.8)
• Bronchitis	0	1 (0.8)	0
• Lobar pneumonia	0	1 (0.8)	0
• Tuberculosis	0	0	1 (0.8)
Injury, poisoning, and procedural complications	1 (0.4)	0	0
• Limb injury	1 (0.4)	0	0
Metabolism and nutrition disorders	1 (0.4)	0	0
• Obesity	1 (0.4)	0	0
Renal and urinary disorders	0	1 (0.8)	0
• Calculus ureteric	0	1 (0.8)	0

N = number of subjects treated in the treatment period; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 2 and before first dose of study drug of Treatment Period 3; TESAE = treatment-emergent serious adverse event.

Source: CHS-1420-02 CSR Post-text Table 14.3.1.5.2.

- Treatment Period 1 + 2
  Results observed in Treatment Periods 1 + 2, with its longer duration of exposure, were consistent with the results observed in Treatment Period 1.

- Treatment Period 3 (All Subjects Received CHS-1420 Open-Label)
  During Treatment Period 3, the number of subjects with SAEs was similar among treatment groups (i.e., CHS-1420/CHS-1420/CHS-1420, U.S.-Humira/CHS-1420/CHS-1420, and U.S.-Humira/U.S.-Humira/CHS-1420 groups). No SAEs were experienced by more than 1 subject in any group, and overall, 4 (0.8%) subjects experienced at least 1 SAE, with 1 (0.2%) subject in the U.S.-Humira/CHS-1420/CHS-1420 group experiencing an SAE considered to be product-related (pneumonia, Subject (b) (6)).

Table 52. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (CHS-1420-02, Treatment Period 3, Open-label Extension Population)

System Organ Class Preferred Term	CHS-1420/ CHS-1420/ CHS-1420 (N = 235) n (%)	U.S.-Humira/ CHS-1420/ CHS-1420 (N = 113) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N = 126) n (%)	Overall (N = 474) n (%)
Subjects with at Least One Event				
Any TESAE	1 (0.4)	3 (2.7)	0	4 (0.8)
Congenital, familial, and genetic disorders	0	1 (0.9)	0	1 (0.2)
• Congenital cystic kidney	0	1 (0.9)	0	1 (0.2)
Infections and infestations	0	1 (0.9)	0	1 (0.2)
• Pneumonia	0	1 (0.9)	0	1 (0.2)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	1 (0.9)	0	1 (0.2)
• Glioblastoma multiforme	0	1 (0.9)	0	1 (0.2)
Renal and urinary disorders	0	1 (0.9)	0	1 (0.2)
• Renal failure chronic	0	1 (0.9)	0	1 (0.2)
Vascular disorders	1 (0.4)	0	0	1 (0.2)
• Shock	1 (0.4)	0	0.	1 (0.2)

N = number of subjects treated in the treatment period; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 3; TESAE = treatment-emergent serious adverse event.
Source: CHS-1420-02 CSR Post-text Table 14.3.1.5.4.

- Treatment Period 1 + 2 + 3
  During Treatment Period 1 + 2 + 3, the number of subjects with SAEs was similar among treatment groups (i.e., CHS-1420/CHS-1420/CHS-1420, U.S.-Humira/CHS-1420/CHS-1420, and U.S.-Humira/U.S.-Humira/CHS-1420 groups). Overall, 9 (3.3%) subjects in the CHS-1420/CHS-1420/CHS-1420 group, 9 (6.7%) subjects in the U.S.-Humira/CHS-1420/CHS-1420 group, and 2 (1.5%) subjects in the U.S.-Humira/U.S.-Humira/CHS-1420 group experienced at least 1 SAE. No SAEs were experienced by more than 1 subject in any of the treatment groups.

In the Infections and infestations SOC, more infections were reported in the U.S.-Humira/CHS-1420/CHS-1420 group (3.7%) than in the U.S.-Humira/U.S.-Humira/CHS-1420 (0.7%) and CHS-1420/CHS-1420/CHS-1420 (0%) groups.

Table 53. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (CHS-1420-02, Treatment Periods 1 + 2 + 3, Safety Population)

System Organ Class Preferred Term	CHS-1420/ CHS-1420/ CHS-1420 (N = 274) n (%)	U.S.-Humira/ CHS-1420/ CHS-1420 (N = 134) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N = 137) n (%)
Subjects with at Least One Event			
Any TESAE	9 (3.3)	9 (6.7)	2 (1.5)
Cardiac disorders	1 (0.4)	0	0
• Acute myocardial infarction	1 (0.4)	0	0
Congenital, familial, and genetic disorders	0	1 (0.7)	0
• Congenital cystic kidney disease	0	1 (0.7)	0
Gastrointestinal disorders	2 (0.7)	1 (0.7)	1 (0.7)
• Anal fistula	0	1 (0.7)	0
• Diarrhea	0	0	1 (0.7)
• Gastritis	1 (0.4)	0	0
• Inguinal hernia	1 (0.4)	0	0
Infections and infestations	0	5 (3.7)	1 (0.7)
• Bronchitis	0	1 (0.7)	0
• Gastroenteritis	0	1 (0.7)	0
• Lobar pneumonia	0	1 (0.7)	0
• Pneumonia	0	1 (0.7)	1 (0.7)
• Sinusitis	0	1 (0.7)	0
• Tuberculosis	0	0	1 (0.7)
Injury, poisoning, and procedural			
• Foot fracture	0	1 (0.7)	0
• Limb injury	1 (0.4)	0	0
Metabolism and nutrition disorders	1 (0.4)	1 (0.7)	0
• Dehydration	0	1 (0.7)	0

• Diabetic ketoacidosis	0	1 (0.7)	0
• Obesity	1 (0.4)	0	0
Musculoskeletal and connective tissue			
• Psoriatic arthropathy	1 (0.4)	0	0
• Rotator cuff syndrome	1 (0.4)	0	0
Neoplasms benign, malignant, and			
• Glioblastoma multiforme	0	1 (0.7)	0
Renal and urinary disorders	0	2 (1.5)	0
• Calculus ureteric	0	1 (0.7)	0
• Renal failure chronic	0	1 (0.7)	0
Respiratory, thoracic, and mediastinal			
• Chronic obstructive pulmonary	0	1 (0.7)	0
Skin and subcutaneous disorders	1 (0.4)	0	0
• Psoriasis	1 (0.4)	0	0
Vascular disorders	1 (0.4)	0	0
• Shock	1 (0.4)	0	0

N = number of subjects treated in the treatment period; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 1 through study termination;

TESAE = treatment-emergent serious adverse event.

Source: CHS-1420-02 CSR Post-text Table 14.3.1.5.30.

CHS-1420-04

There were 3 SAEs, and none was determined to be related to study product.

- One subject (Subject (b) (6)) had a transient ischaemic attack. This subject recovered.
- One subject (Subject (b) (6)) had gastroenteritis of moderate severity. This subject recovered.
- One subject (Subject (b) (6)) had multiple SAEs of bronchitis, hypokalaemia, hypomagnesaemia, and acute respiratory failure considered to be severe. This subject recovered.

Pooled Studies - CHS-1420-03, CHS-1420-05, CHS-1420-07

For the pooled Studies, there were 4 subjects in the Safety Population with SAEs; none of the SAEs occurred in more than 1 subject.

- In the CHS-1420 group, 1 subject experienced renal colic determined to be unrelated to study drug (Subject (b) (6) [CHS-1420-03]), and 1 subject had generalized rash, determined to be related to study drug (Subject (b) (6) [CHS-1420-03]).

- In the U.S.-Humira group, there was 1 report of "completed suicide" determined to be unrelated to study drug (Subject (b) (6) [CHS-1420-03]), and 1 subject experienced influenza determined to be related to study drug (Subject (b) (6) [CHS-1420-03]).

Overall Conclusion on TSAEs and Serious Adverse Events
The TSAE and SAE data from the comparative clinical study between CHS-1420 and U.S.-Humira in psoriasis patients (CHS-1420-02), the comparative use study between CHS-1420 PFS versus CHS-1420 AI in CHS-1420-04 and the single-dose PK studies (CHS-1420-03, -05, and -07) support similarity in safety between CHS-1420 and U.S.-Humira and have not demonstrated meaningful differences between them.

6.3.2.5 Dropouts and/or Discontinuations

CHS-1420-02
The protocol for CHS-1420-2 has several provisions for discontinuation due to adverse events, including:

- The subject experiences a serious adverse event (SAE) or medically important AE (e.g., serious or opportunistic infection) that would preclude further treatment with study drug;
- The subject develops a malignancy while on study;
- The subject requires medical treatment excluded by the protocol or that could present a safety risk to the subject;
- The subject experiences an increase in disease activity that requires additional or different therapy;
- The subject develops active TB or a positive response to QuantiFERON-TB Gold test anytime during the study. If the QuantiFERON-TB Gold test yields low positive results (defined as QuantiFERON TB Antigen minus Nil value = 0.35 - 2 IU/mL), a repeat test should be done. If the repeat test is negative, the patient can continue on the study, subject to the clinical judgment of the Investigator);
- The female subject becomes pregnant;

These criteria, together with review by Data Monitoring appear reasonable to ensure safety.

There were no differences between treatment groups during Treatment Periods 1, 2, or 3 in percentage of subjects with TEAEs leading to discontinuations.

- Treatment Period 1 (Subjects Received Either CHS-1420 or U.S.-Humira)
  Overall, there was no single specific type of TEAE that caused discontinuation of study product in the CHS-1420 group during Treatment Period 1: 4 (1.5%) subjects in the CHS-1420 group and 2 (0.7%) subjects in the Humira (US) group discontinued the study product due to a TEAE.

In the CHS-1420 group, events that led to discontinuation were hypersensitivity (Subject [redacted], ALT increased (Subject [redacted], AST increased (Subject [redacted], bilirubin conjugated increased (Subject [redacted] blood alkaline phosphatase increased (Subject [redacted] blood CPK increased (Subject [redacted], and psoriasis worsening (Subject [redacted] (1 [0.4%] subject each).

In the U.S.-Humira group, events that led to discontinuation were injection site reaction (Subject [redacted] and psoriasis worsening (Subject [redacted] (1 [0.4%] subject each).

In view of more liver enzyme elevations reported for product discontinuation in subjects treated with CHS-1420, this was further explored with an Information Request to Coherus for greater details. Coherus has provided satisfactory response with information on confounding factors and returning enzyme levels in subjects who continued treatment with CHS-1420 (See Appendix 13.5.1 on the IR)

- Treatment Period 2 (Subjects Received Either CHS-1420 or U.S.-Humira, With Switching Group [U.S.-Humira/CHS-1420])
  A single TEAE (positive QuantiFERON-TB Gold test) in a subject caused discontinuation in the CHS-1420/CHS-1420 treatment group (Subject [redacted] In addition, 2 (1.6%) subjects in the U.S.-Humira/CHS-1420 group, and 1 (0.8%) subject in the U.S.-Humira/U.S.-Humira group discontinued due to TEAE. In the U.S.-Humira/CHS-1420 group, events that led to discontinuation were interferon gamma release assay positive (positive QuantiFERON-TB Gold test) (Subject [redacted] and exacerbation of psoriasis (Subject [redacted] (1 [0.8%] subject each). In the U.S.-Humira/U.S.-Humira group, the event that led to discontinuation was tuberculosis (Subject [redacted]

- Treatment Period 1 + 2
  The results on product discontinuation observed in Treatment Periods 1 + 2 are consistent with the those observed in Treatment Period 1.

- Treatment Period 3 (All Subjects Received CHS-1420)
  During Treatment Period 3, 7 (1.5%) subjects in the Open-label Extension Population discontinued the study product due to a TEAE. The most common TEAE leading to study drug discontinuation was interferon gamma release assay positive (positive QuantiFERON-TB Gold test), occurring in 3 (0.6%]) subjects overall (Subjects [redacted]). No other TEAEs leading to discontinuation of the study product during Treatment Period 3 were experienced by more than 1 subject in any of the treatment groups.

- Treatment Period 1 + 2 + 3

There were 8 (2.9%) subjects in the CHS-1420/CHS-1420/CHS-1420 group, 7 (5.2%) subjects in the U.S.-Humira/CHS-1420/CHS-1420 group, and 2 (1.5%) subjects in the U.S.-Humira/U.S.-Humira/CHS-1420 group who discontinued study product due to TEAE.

The most common TEAE leading to discontinuation was interferon gamma release assay positive (QuantiFERON-TB Gold test), occurring in 3 (1.1%) subjects in the CHS-1420/CHS-1420/CHS-1420 group, 2 (1.5%) subjects in the U.S.-Humira/CHS-1420/CHS-1420 group, and no subjects in the U.S.-Humira/U.S.-Humira/CHS-1420 group. None of these subjects had tuberculosis reported as TEAE. There was 1 subject who had a positive QuantiFERON-TB Gold test (not reported as a TEAE) and was discontinued due to clinical diagnosis of tuberculosis reactivation (Subject (b) (6), U.S.-Humira/U.S.-Humira/CHS-1420, Treatment Period 3). Another (Subject (b) (6), CHS-1420/CHS-1420/CHS-1420) discontinued the study in Treatment Period 2 after a positive QuantiFERON-TB Gold test, but TEAE was not reported.

The second most common TEAE leading to study drug discontinuation was worsening of psoriasis (1 [0.4%] subject in the CHS-1420/CHS-1420/CHS-1420 group, 2 [1.5%] subjects in the U.S.-Humira/CHS-1420/CHS-1420 group and no subjects in the Humira/Humira/CHS-1420 group).

No other TEAEs leading to discontinuation of the study product during Treatment Periods 1 + 2 + 3 were experienced by more than 1 subject in any of the treatment groups.

For discontinuations in CHS-1420-02 with reasons other than adverse events, refer to Table 22 and comments in Section 6.2.1.

CHS-1420-04

The criteria for discontinuation/withdrawal in CHS-1420-04 are similar to those for CHS-1420-02. During CHS-1420-04, 3 subjects discontinued due to TEAE.

One subject discontinued the study due to a moderate SAE of gastroenteritis considered to be unrelated to the study product. This subject had received 2 doses of study product prior to discontinuation (Subject (b) (6)).

Once subject discontinued the study due to a mild TEAE of urinary tract infection considered to be related to the study product. This subject had received 2 doses of study product prior to discontinuation (Subject (b) (6)).

One subject discontinued due to severe SAEs of bronchitis, hypokalaemia, hypomagnesemia, and acute respiratory failure considered to be not related to study

product by the Investigator. This subject had received 2 doses of study product before discontinuation but completed the study (Subject (b) (6)).

Pooled PK Studies CHS-1420-03, -05, and -07
Since these are single-dose studies, discontinuation from study refers to discontinuing follow-up, as investigational product has been administered.

In CHS-1420 treatment group, 1 subject experienced an SAE of generalized rash considered by the Investigator to be severe and related to study product (Subject (b) (6) in CHS-1420-03). Concomitant medication was given and the TEAE was resolved; however, this subject discontinued from the study due to the TEAE.

In U.S.-Humira treatment group, 1 subject committed suicide and died by hanging during the study that was considered by the Investigator to be not related to study product (Subject (b) (6) in CHS-1420-03). This subject was listed as discontinued from the study due to the TEAE.

Overall Conclusion on Discontinuations due to Adverse Events
The data on discontinuations due to adverse events from the comparative trial between CHS-1420 and U.S.-Humira in psoriasis patients (CHS-1420-02) and the single-dose PK study (CHS-1420-03) support similarity in safety between CHS-1420 and U.S.-Humira and have not demonstrated clinically meaningful difference between them. The results from studies CHS-1420-04, -05, and -07 did not preclude or conflict with those conclusions.

6.3.3. **Additional Safety Evaluations**

There are no other safety issues or uncertainties not yet resolved.

As to the results of the single transition - comparative assessment of patients randomized to undergo a single transition from U.S.-Humira to CHS1420 versus those randomized to stay on U.S.-Humira, this transition occurred between treatment period 1 and treatment period 2 for the U.S.-Humira/CHS1420 versus U.S.-Humira/U.S.-Humira arms. The safety data of these arms are similar in treatment period 2 (see above).

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6.4. Clinical Conclusions on Immunogenicity

Refer to Section 5.4. I agree with conclusions reached by the Clinical Pharmacology team. This is summarized below.

The immunogenicity of CHS-1420 was shown to be comparable to that of U.S.-Humira after a single dose in healthy subjects and after multiple doses in patients with chronic plaque psoriasis.

- In the single-dose healthy human study (CHS-1420-03), the overall incidence of anti-drug antibody (ADA) formation over the course of the study in healthy subjects was 82% and 83% in the CHS-1420 and U.S.-Humira groups, respectively. The overall incidence of neutralizing antibodies (nAb) formation over the course of the study in healthy subjects was 60% and 65% for CHS-1420 and U.S.-Humira, respectively.
- In the study on chronic plaque psoriasis patients (CHS1420-02), some patients in the U.S.-Humira arm were switched treatment arms following Period 1. After multiple 40 mg SC doses in treatment period 1 only, the incidence of ADAs was similar between CHS-1420 and U.S.-Humira patients (90% and 94%, respectively). The incidence of nAb formation was also similar (33% and 34%, respectively) following treatment period 1. The incidence of ADAs and NAbs was similar between subjects who continued treatment with CHS-1420 or U.S.-Humira in period 2 compared to subjects who switched from U.S.-Humira to CHS-1420 in period 2. The open-label period 3 allowed the remaining subjects treated with U.S.-Humira to also switch to CHS-1420, thus allowing all subjects to receive CHS-1420. All study subjects across the spectrum had very similar levels of treatment-emergent ADAs by the end of period 3. Overall, incidence of ADAs was similar between all CHS-1420 and U.S.-Humira groups. Switching to CHS-1420 from U.S.-Humira did not result in increased ADAs
- In single-dose PK Study CHS-1420-03, systemic drug exposure (AUC) was lower in ADA-positive subjects compared to ADA-negative subjects for both CHS-1420 and U.S.-Humira. Similarly, NAb-positive subjects had lower systemic exposure than NAb-negative subjects in both treatment groups. The magnitude of lowered exposure was similar between the CHS-1420 and U.S.-Humira treatment groups.
- In the psoriasis study (CHS-1420-02), the presence of ADAs was associated with decreased C_{trough} in all treatment groups and sequences in the study. Serum drug trough was further lowered in NAb+ patients. The magnitude that serum trough concentrations were lowered for ADA+ and NAb+ patients was similar between CHS-1420 and U.S.-Humira. Overall, the trough concentrations between the subgroups of each treatment arm are considered similar for each week through week 15.

- In psoriasis study (CHS-1420-02), the protocol-specified primary efficacy endpoint was 75% improvement in PASI (PASI-75) at week 12 relative to baseline. Decreased efficacy was observed by week 12 in NAb+ patients. However, this decreas was observed in both CHS-1420 and U.S.-Humira treatment arms to a similar degree. Some patients randomized to U.S.-Humira in treatment period 1 were switched to CHS-1420 in treatment period 2, but they did not have lower efficacy than those who remained on either CHS-1420 or U.S.-Humira for the entire 24-week treatment. At week 24, there was similar treatment effects in all treatment arms.
- Also, in the psoriasis study (CHS1420-02), the incidence of treatment-emergent adverse events (TEAEs) was similar in ADA-negative, ADA-positive and NAb-positive subjects in the treatment groups for Periods 1 and 2. The incidence of hypersensitivity and injection site reactions (ISRs) was low and similar in ADA-negative, ADA-positive, and NAb-positive subjects in both treatment groups in treatment periods 1 and 2. Overall, no impact of immunogenicity on safety was observed.

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6.5. Extrapolation

The Applicant submitted data and information in support of a demonstration that CHS-1420 is highly similar to U.S.-Humira notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between CHS-1420 and U.S.-Humira in terms of safety, purity and potency in patients with plaque psoriasis (Study CHS-1420-02). No extrapolation is needed for the indication of plaque psoriasis.

In addition to the plaque psoriasis indication, the Applicant is seeking licensure of CHS-1420 for the following indication(s) for which U.S.-Humira has been previously licensed and for which CHS-1420 has not been directly studied:

- Rheumatoid Arthritis (adults)
- Juvenile Idiopathic Arthritis (age 2 and above)
- Psoriatic Arthritis (adults)
- Ankylosing Spondylitis (adults)
- Crohn's Disease (age 6 and above)
- Ulcerative Colitis (adults)

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of CHS-1420 as a biosimilar for each such indication for which licensure is sought and for which U.S.-Humira has been previously approved. This Applicant's justification was evaluated and considered adequate, as summarized below in subsections 6.5.1 and 6.5.2.

Therefore, the totality of the evidence provided by the Applicant supports licensure of CHS-1420 for each of the following indication(s) for which U.S.-Humira has been previously licensed and for which the Applicant is seeking licensure of CHS-1420:

- Rheumatoid Arthritis (adults)
- Juvenile Idiopathic Arthritis (age 2 and above)
- Psoriatic Arthritis (adults)
- Ankylosing Spondylitis (adults)
- Crohn's Disease (age 6 and above)
- Ulcerative Colitis (adults)
- Plaque Psoriasis (adults)

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6.5.1. DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE

In addition to the plaque psoriasis indication, the Applicant is seeking licensure of CHS-1420 for the following indication(s) under the purview of DRTM for which U.S.-Humira has been previously licensed and for which CHS-1420 has not been directly studied:

- Rheumatoid Arthritis (RA): reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

- Juvenile Idiopathic Arthritis (JIA): reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.

- Psoriatic Arthritis (PsA): reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

- Ankylosing Spondylitis (AS): reducing signs and symptoms in adult patients with active AS.

The Applicant provided a justification for extrapolation of data and information submitted in the application to support licensure of CHS-1420 as a biosimilar for each of the above indications for which licensure is sought and for which U.S.-Humira has been previously licensed.

First, as summarized by the CDTL executive summary above, the Applicant submitted data and information in support of a demonstration that CHS-1420 is highly similar to U.S.-Humira notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between CHS-1420 and U.S.-Humira in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in patients with plaque psoriasis (Study CHS-1420-02).

Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of CHS-1420 for the treatment of RA, JIA in patients 2 years of age and older, PsA, and AS, include:

- Similar PK was demonstrated between CHS-1420 and U.S.-Humira as discussed in the section on Clinical Pharmacology. Importantly, CHS-1420 was demonstrated to be highly similar to U.S.-Humira, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between CHS-1420 and U.S.-Humira in the rheumatology indications sought for licensure. Thus, a similar PK profile would be expected between CHS-1420 and US- Humira in patients across all the rheumatology indications being sought for licensure.

- In general, immunogenicity of U.S.-Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used[6]. As stated elsewhere in this document, the Agency has concluded that there are sufficient data to support similar immunogenicity between CHS-1420 and U.S.-Humira with repeat dosing in patients with PsO, and between CHS-1420 and U.S.-Humira, after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between CHS-1420 and U.S.-Humira in patients with RA, JIA, PsA, and AS.

- The Applicant demonstrated that there are no clinically meaningful differences between CHS-1420 and U.S.-Humira in patients with PsO, and between CHS-1420 and U.S.-Humira following single doses in healthy subjects. Additionally, in controlled clinical studies of U.S.-Humira submitted to support its approval, as

[6] FDA-approved U.S.-Humira labeling

described in the approved labeling, the types of adverse events and their rates were similar across indications. The foregoing, coupled with the demonstration of analytical and PK similarity between CHS-1420 and U.S.-Humira, support the conclusion that a similar safety profile would be expected between CHS-1420 and U.S.-Humira in patients with RA, JIA, PsA, and AS.

- The Applicant addressed each of the known and potential mechanisms of action of U.S.-Humira and submitted data to support the conclusion that CHS-1420 and U.S.-licensed Humira have the same mechanisms for each of the sought indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Therefore, based on the above considerations, DRTM has concluded that the Applicant has provided adequate data and information to support licensure of CHS-1420 for each of the following rheumatologic indications for which U.S.-Humira has been previously licensed and for which the Applicant is seeking licensure of CHS-1420: RA, JIA in patients 2 years of age and older, PsA, and AS.

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6.5.2. DIVISION OF GASTROENTEROLOGY

Executive Summary: Consistent with the principles of the FDA Guidance - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)[7], the Division of Gastroenterology (DG) concludes that the Applicant has provided sufficient scientific justification to support extrapolation of data submitted in the application to support licensure of CHS-1420 as a biosimilar, under section 351(k) of the PHS Act, for the non-studied indications of Crohn's disease (CD) in patients 6 years and above, and ulcerative colitis (UC) in adults. The scientific justification based on the mechanism of action, pharmacokinetics, immunogenicity and safety supporting this conclusion are summarized in the following paragraphs.

Mechanism of Action: The mechanisms of action of adalimumab that are relevant to chronic plaque psoriasis (PsO; the studied clinical study population) are also relevant to inflammatory bowel disease (IBD) (i.e., CD and UC). The Applicant provided data to support that CHS-1420 has the same known and potential mechanisms of action as U.S.-Humira, which supports extrapolation to indications not directly studied in the CHS-1420 clinical program. Adalimumab belongs to the pharmacologic class of tumor

[7] Guidance for Industry – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

necrosis factor alpha (TNF-α) blockers. Adalimumab neutralizes the biological activity of TNF-α by binding with high affinity to the soluble (s) (sTNF-α) and transmembrane (tm) (tmTNF-α) forms of TNF-α and inhibits binding of TNF-α with its receptors. Similar to the studied indication (PsO), TNF-α plays a central role in the pathogenesis of IBD. TNF-α inhibition is important in treating the disease, as evidenced by the efficacy of approved TNF-α inhibitors in the treatment of IBD. In addition, the efficacy of adalimumab in the treatment of IBD is thought to involve reverse signaling via binding to tmTNF-α, and other plausible mechanisms of action involving the Fc region of the antibody.[8,9] Table 54 summarizes the known and potential mechanisms of action of US-licensed Humira. Binding to sTNF-α and tmTNF-α involves the fragment antigen-binding (Fab) region of the antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

Table 54. Known and Potential Mechanisms of Action of U.S.-Humira

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

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

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors

The biological activities of CHS-1420 and U.S.-Humira were evaluated by a comprehensive set of comparative functional and binding assays. The product quality reviewers concluded that the comparative analytical assessment was acceptable. Data for TNF-α binding and neutralization, the primary function of adalimumab, as well as other mechanisms of action, such as reverse signaling, antibody dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of regulatory macrophages support the determination that CHS-1420 and U.S.-Humira are

[8] Oikonomopoulos A, et al., Current Drug Targets 2013; 14:1421-32
[9] Tracey D, et al., Pharmacology & Therapeutics 2008; 117:244–79

highly similar. These data support the conclusion that CHS-1420 and U.S.-Humira utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK): Study CHS-1420-03 was a randomized, double-blind, parallel group, single dose, PK similarity study conducted in healthy adult male and female subjects. The clinical pharmacology reviewers concluded that the data from study CHS-1420-03 support a demonstration of PK similarity of CHS-1420 to U.S.-Humira in healthy subjects (refer to Section 5 Clinical Pharmacology Evaluation and Recommendations). Available data on U.S.-Humira do not indicate any major differences in PK based on disease state. Therefore, it is reasonable to conclude that PK for CHS-1420 is expected to be similar between patients with PsO (the studied population) and those with IBD. In addition, it should be noted that the PK of adalimumab products is also influenced by immunogenicity. Specifically, the clearance of adalimumab has been shown to be higher in patients who developed anti-drug-antibodies (ADA). Immunogenicity considerations are discussed further below.

Immunogenicity: In the CHS-1420 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (PsO and healthy subjects). Immunogenicity was found to be similar when comparing CHS-1420 and U.S.-Humira in the PK similarity study CHS-1420-03 in healthy subjects, and in the comparative clinical study CHS-1420-02 conducted in patients with PsO. Specifically, the rates of binding and neutralizing anti-drug antibodies were found to be similar between CHS-1420 and U.S.-Humira in these studies. These results support a demonstration of no clinically meaningful differences between CHS-1420 and U.S.-Humira.

In the clinical study CHS-1420-02, patients who received U.S.-Humira were re-randomized to either continue on U.S.-Humira or switch to CHS-1420. This occurred at the transition between Treatment Period 1 and Treatment Period 2 for the US-Humira/CHS-1420/CHS-1420 group, and between Treatment Period 2 and Treatment Period 3 for the US-Humira/US-Humira/CHS-1420 group. The single transition was used to specifically assess potential risks with regard to the safety and immunogenicity as a result of switching from U.S.-Humira to CHS-1420. There were no meaningful differences in the rates of binding and neutralizing antidrug antibodies in those subjects that underwent a single transition from U.S.-Humira to CHS-1420, compared to those that remained on their randomized treatment (U.S.-Humira or CHS-1420). Therefore, it is reasonable to conclude that immunogenicity in patients with IBD receiving CHS-1420 would be similar to that observed in patients with IBD receiving U.S.-Humira.

Safety: The safety of CHS-1420 compared to U.S.-Humira was assessed in comparative clinical study (CHS-1420-02) conducted in patients with PsO, and supported by a single dose, PK similarity study (CHS-1420-03) conducted in healthy subjects. Safety assessments in the two clinical studies included adverse events (AEs), physical

examinations, vital signs, electrocardiograms (ECGs), clinical laboratory testing, and immunogenicity assessments. As described in Section 6.3. – Review of Safety Data, the data overall support a similar safety profile between the CHS-1420 and U.S.-Humira, and there were no meaningful differences in the frequency of TEAEs, SAEs, and events leading to discontinuation of study drug. In addition, as previously noted, a single transition from U.S.-Humira to CHS-1420 was assessed as part of the study CHS-1420-02. No meaningful differences in the incidence of adverse events, including hypersensitivity, were observed in patients with PsO that underwent a single transition from U.S.-Humira to CHS-1420, compared to those that remained on their randomized treatment (CHS-1420 or U.S.-Humira). In controlled clinical studies of US-licensed Humira, as described in the approved labeling, the types of adverse events and their rates were similar across indications. Since the safety profile of CHS-1420 has been shown to be similar to that of U.S.-Humira in patients with PsO, and considering their similar product quality attributes, PK, and immunogenicity, the safety profile in the IBD population is unlikely to be different from that observed in patients with PsO.

Extrapolation to pediatric IBD indications: The following rationale supports extrapolation to the pediatric CD and UC indications.

- The mechanisms by which adalimumab exerts its therapeutic effect are expected to be the same in adults and in pediatric CD and UC patients. Together with the demonstrated structural and functional similarity between CHS-1420 and U.S.-Humira, the mechanisms of action of CHS-1420 are not expected to be different from that of U.S.-Humira in pediatric CD and UC, to the extent that the mechanisms are known or can be reasonably determined.
- Adalimumab concentrations are similar in adult and pediatric CD and UC patients (Humira USPI, 2021). Together with the demonstrated PK similarity (CHS-1420 vs. U.S.-Humira) in healthy volunteers, and in patients with PsO, the PK of adalimumab following CHS-1420 are not expected to be different to that of U.S.-Humira in pediatric CD and UC patients.
- Immunogenicity rates of U.S.-Humira were comparable between adult and pediatric CD and UC patients (Humira USPI, 2021). Together with the comparable immunogenicity in healthy volunteers (CHS-1420 vs. U.S.-Humira) and in PsO patients, the immunogenicity of CHS-1420 is not expected to be different from that of U.S.-Humira in pediatric CD and UC patients.
- The safety profile of U.S.-Humira was comparable in adult vs. pediatric CD and UC patients (Humira USPI, 2021). Together with the demonstrated comparable safety profile of CHS-1420 vs. U.S.-Humira in adult PsO patients, the safety of CHS-1420 is not expected to be different from that of U.S.-Humira in pediatric CD and UC patients.

Note that while the applicant has submitted acceptable extrapolation justification for pediatric UC patients 5 years of age to 17 years, FDA has determined that U.S.-Humira

is eligible for orphan drug exclusivity for pediatric UC, ages 5-17 years. FDA therefore cannot license CHS-1420 for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028.

Regulatory Recommendations: DG concludes that sufficient scientific justification was provided to support licensure of CHS-1420 for the following indications:

- For the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.
- For the treatment of moderately to severely active ulcerative colitis in adult patients.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, adalimumab-aqvh, was found to be accepted by the Agency (DMAMES memo dated August 25, 2021).

7.2. Proprietary Name

The proposed proprietary name for CHS-1420 is conditionally approved as Yusimry. This name has been reviewed by DMEPA, who concluded the name was acceptable (letter granting proprietary name dated March 25, 2021).

7.3. Other Labeling Recommendations

Yusimry is a proposed biosimilar to U.S.-Humira. The Applicant is proposing the following dosage form and strength:

- Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe

The proposed Yusimry prescribing information incorporated relevant data and information from the U.S.-Humira prescribing information, with appropriate

modifications. The Applicant is seeking licensure for the following indications for which U.S.-Humira has been previously approved: rheumatoid arthritis, juvenile idiopathic arthritis (age 2 and above), psoriatic arthritis, ankylosing spondylitis, Crohn's disease (age 6 and above), ulcerative colitis, and plaque psoriasis.

The Applicant is not seeking licensure for the following indications for which U.S.-Humira has been previously approved: hidradenitis suppurativa, and uveitis. The Applicant's proposed labeling does not include these indications and certain information relating to them. For the ulcerative colitis indication, ages 5 to 17 are not included due to unexpired exclusivity of U.S.-Humira .

The Applicant is proposing that the dosage and administration information relating to the JIA indication be limited to patients weighing more than 30 kg and to include a statement in the labeling that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 30 kg. Similarly for the Crohn's disease indication, there is no dosage form of the product allowing weight-based dosing for patients weighing below 40 kg, and labeling is to also state this.

It has been determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), and is consistent with labeling guidance recommendations and CDER/OND best labeling practices and policies, is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The Applicant has agreed to changes requested by the Division to improve readability, clarity, and accuracy of the prescribing information. The final agreed-to labeling is consistent with that of the reference product and will be included in the Approval Letter.

Authors:

Hon-Sum Ko Clinical Reviewer	Hon-Sum Ko Acting Clinical Team Leader & CDTL

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and

independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Appendix 13.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:

Hon-Sum Ko
Clinical Reviewer

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Acting Clinical Team Leader & CDTL

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

Author:

Hon-Sum Ko
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10. Pediatrics

Coherus submitted iPSP for CHS-1420 to IND 119540 and this was reviewed by PeRC on November 17, 2020. PeRC concured with the Applicant's plan to request deferral of PREA obligations for the UC indication in ages 5-17 (Reference product not approved for this age group) and provide assessments via extrapolation for JIA ages 2-17 and CD ages 6-17 (Reference product exclusivity for JIA ages 2-<4 and CD ages 6-17 due to expire in September 2021), as well as waiver requests (full waivers for RA, AS, PsA and PsO; partial waivers for JIA ages 0-<2, CD 0-<6 and UC 0-<5) outlined in the iPSP. In addition, (b) (4) .

The Reference product, U.S.-Humira, was approved for UC ages 5-17 in February,

2021. FDA informed Coherus that the firm had the option of submitting pediatric assessment for UC ages 5-17 via extrapolation, but could not include this as indication due to unexpired exclusivity.

Coherus has included assessment via extrapolation for JIA ages 2-17 and CD ages 6-17 in the original BLA. In a submission dated July 7, 2021 (received July 12, 2021), Coherus also provided assessment via extrapolation for UC ages 5-17 (b) (4) Refer to Section 6.5 for review of the assessments.

The current adalimumab-aqvh 40 mg/0.8 mL PFS, is not designed to allow for accurate administration of doses less than 40 mg, which impacts patients who weigh less than 40 kg for CD, and 30 kg for JIA. For accurate weight-based dosing, age-appropriate formulations (presentations) would be needed. Therefore, a PREA PMR is required to develop presentations that can be used to accurately administer Yusimry (adalimumab-aqvh) to patients weighing 10 kg to less than 40 kg.

PeRC discussed this application on October 25, 2021 and concurred with the Division's recommendations for PREA waiver, deferral, and PMR.

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11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

There are no PMC(s); however, this BLA has a PMR under PREA to develop formulation/presentation for pediatric dosing.

The current Yusimry presentation is not designed to allow for accurate administration of

doses less than 40 mg, which impacts JIA patients who weigh less than 30 kg and Crohn's disease patients who weigh less than 40 kg. For accurate weight-based dosing, age-appropriate formulations (presentations) are required by PREA. Therefore, a PREA PMR is recommended for the development of formulations (presentations) that can be used to administer Yusimry in JIA patients who weigh less than 30 kg and Crohn's disease patients who weigh less than 40 kg. This will be stated in the Approval Letter:

> *PMR 4184-1: Develop presentations that can be used to accurately administer Yusimry (adalimumab-aqvh) to pediatric patients weighing 10 kg to less than 40 kg.*
>
> *Final Report Submission Date: December 31, 2023.*

Authors:

Hon-Sum Ko Clinical Reviewer	Hon-Sum Ko Acting Clinical Team Leader & CDTL

12. Division Director/Signatory Comments

I concur with the team's assessment of the data and information submitted in this BLA. I also concur with the team's recommendation to approve Yusimry as biosimilar biological product to U.S.-Humira for the following indications for which U.S.-Humira has been previously licensed:

- Rheumatoid Arthritis (RA): reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- Juvenile Idiopathic Arthritis (JIA): reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.
- Psoriatic Arthritis (PsA): reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- Ankylosing Spondylitis (AS): reducing signs and symptoms in adult patients with active AS.
- Crohn's Disease (CD): treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

- Ulcerative Colitis (UC): treatment of moderately to severely active ulcerative colitis in adult patients.
  Limitations of Use: Effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers.

- Plaque Psoriasis (Ps): treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

A PREA PMR will be required for the development of an age-appropriate presentation. There will be no PMCs.

No additional data or REMS are required for this BLA.

Author:
Nikolay Nikolov, M.D.
Director, Division of Rheumatology and Transplant Medicine

13. Appendices

13.1. References

Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, Heffernan M, Miller B, Hamlin R, Lim L, Zhong J, Hoffman R, Okun MM. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006;55(4):598-606.

LaVange LM, Durham TA, Koch GG. Randomization-based nonparametric methods for the analysis of multicentre trials. Stat Methods Med Res. 2005;14(3):281-301.

Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, Strober BE, Kaul M, Gu Y, Okun M, Papp K.J. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. Am Acad Dermatol. 2008;58(1):106-15.

Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A; CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158(3):558-66.

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13.2. Financial Disclosure

Although six clinical studies have been submitted, only two of them are considered here, as the others involve CHS-1420 presentation (autoinjector) not proposed for marketing under current BLA (CHS-1420-04 and -05) or formulations not supportive of establishing biosimilarity (CHS-1420-01 and -07). The financial disclosure information for two of the studies is presented below.

Covered Clinical Study (CHS-1420-02):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 97*		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*Source: List and Description of Investigators and Other Important Participants in the Study pp 5-14, under the Table entitled "List and Description of Investigators" - Link: \\CDSESUB1\evsprod\BLA761216\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5351-stud-rep-contr\chs-1420-02\1614-invest-list.pdf

Covered Clinical Study (CHS-1420-03):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3*		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*Source: List and Description of Investigators page 1, under the Table entitled "List and Description of Investigators" - Link: \\CDSESUB1\evsprod\BLA761216\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\chs-1420-03\1614-invest-list.pdf

Authors:

Hon-Sum Ko
Clinical Reviewer

Hon-Sum Ko
Acting Clinical Team Leader & CDTL

13.3. Nonclinical Appendices

13.3.1. Nonclinical Pharmacology

In Vivo Pharmacology

The potential effects of CHS-1420 (Process C) compared to U.S.-Humira on central nervous system (CNS), cardiovascular (CV) system, and respiratory system were

assessed in a 1-month repeat-dose toxicity study in male and female cynomolgus monkeys, comparing 5 SC doses CHS-1420 (30 and 100 mg/kg/week) and U.S.-Humira (30 mg/kg/week) (Study# 20026996-1420-004). No drug-related effect on CNS (clinical signs), CV (ECG parameters, blood pressure, rhythm, and ECG waveform morphology), or respiratory system (respiration rate) was noted.

13.3.2. Nonclinical Pharmacokinetics

In a single dose PK study, cynomolgus monkeys (3/sex/group) received one dose (1 mg/kg) of CHS-1420 (Process C) or U.S.-Humira via the SC route, the intended route of administration (ROA) for the commercial product (Study# 20043567). The study design is considered appropriate. The serum concentration-time profiles of CHS-1420 or U.S.-Humira in monkeys over 240 hrs postdose were similar (**Figure 7**, excerpted from the Applicant's submission). There were no apparent sex -related differences in exposures for CHS-1420 or U.S.-Humira. PK profiles were comparable in terms of C_{max} (99% to 120% of that for U.S.-Humira) and AUC_{0-t} (100% to 117% of that for U.S.-Humira) (**Table 55**, excerpted from the Applicant's submission). There was a slightly longer time to maximal serum concentration (T_{max}) for CHS-1420 compared to U.S.-Humira (i.e., median T_{max} of 88 hr vs. 72 hr). There was a notable decline in some animal's serum drug concentrations in both CHS-1420 and U.S.-Humira -treated groups at 240 hr postdose. No immunogenicity assessment was conducted.

Figure 7. Mean (± SD) Serum Concentration Profiles in Male and Female Monkeys after a Single Subcutaneous Dose of CHS-1420 (Process C) or U.S.-Humira

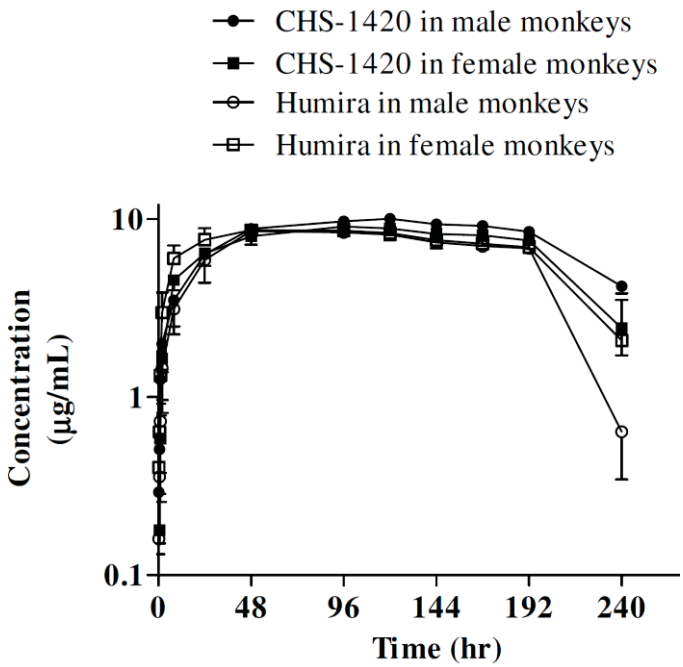

Table 55. Summary of PK parameters after a Single Subcutaneous Dose of CHS-1420 (Process C) or U.S.-Humira in Monkeys

Test Article	Gender	Animal ID	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (µg/mL)	T_{last} (hr)	AUC_{last} (hr*µg/mL)	$AUC_{0\text{-}168}$ (hr*µg/mL)	$AUC_{0\text{-}\infty}$ (hr*µg/mL)	AUC Extrap(%)	V_z/F (mL/kg)	CL/F (mL/hr/kg)
CHS	F	N	2	3	3	3	3	3	2	2	2	2
		Mean	473.45	80.00	9.26	192.00	1495.96	1307.80	6058.0	70.41	103.82	0.21
		SD	NR	27.71	1.51	0.00	179.40	150.49	NR	NR	NR	NR
		CV%	NR	34.6	16.3	0.0	12.0	11.5	NR	NR	NR	NR
CHS	M	N	2	3	3	3	3	3	2	2	2	2
		Mean	251.95	96.00	10.37	192.00	1628.29	1416.25	4897.97	63.73	74.02	0.20
		SD	NR	41.57	1.24	0.00	268.10	265.12	NR	NR	NR	NR
		CV%	NR	43.30	12.00	0.0	16.50	18.70	NR	NR	NR	NR
HUM	F	N	3	3	3	3	3	3	3	3	3	3
		Mean	360.06	56.00	9.39	192.00	1494.00	1323.41	5209.89	68.59	99.02	0.22
		SD	141.93	36.66	0.89	0.00	181.43	160.67	1880.53	11.49	7.78	0.10
		CV%	39.4	65.5	9.5	0.0	12.1	12.1	36.1	16.8	7.9	45.5
HUM	M	N	3	3	3	3	3	3	3	3	3	3
		Mean	328.19	88.00	8.67	192.00	1393.64	1226.60	4583.14	69.49	103.23	0.22
		SD	46.56	36.66	0.51	0.00	90.30	76.60	330.18	2.86	11.16	0.02
		CV%	14.2	41.7	5.9	0.0	6.5	6.2	7.2	4.1	10.8	9.1

CHS: CHS-1420; HUM: U.S.-Humira; NR: Not reported (n < 3/group)

13.3.3. General Toxicology

A one-month repeat-dose general toxicity study in cynomolgus monkeys was conducted to compare the toxicity and TK profiles of CHS-1420 (Process C, 30 and 100 mg/kg/week) and U.S.-Humira (30 mg/kg/week) via the SC route (Study# 20026996-1420-004). The study design is considered appropriate. Drug-related findings were noted in lymph nodes and spleen (PD -related effects) in both CHS-1420 and U.S.-Humira -treated groups with similar incidence and severity. No new toxicity finding was noted in CHS-1420 -treated groups after 4 weeks of treatment. The TK profiles of CHS-1420 and U.S.-Humira were also considered to be similar. ADA was detected in some CHS-1420 and U.S.-Humira -treated animals and correlated with decreased systemic exposure in 2 U.S.-Humira (30 mg/kg) and 1 CHS-1420 (30 mg/kg) -treated animals.

Single-Dose Toxicity/Toxicokinetics

In the single dose PK study, cynomolgus monkeys (3/sex/group) received one SC dose (1 mg/kg) of CHS-1420 (Process C) or U.S.-Humira. No toxicity assessment was condcuted. The comparability of PK profile is disccused in Section 13.3.2 above.

Repeat-Dose Toxicity/Toxicokinetics

A one-month repeat-dose general toxicity study in cynomolgus monkeys (3/sex/group) was conducted comparing 5 SC doses of 30 and 100 mg/kg/week CHS-1420 (Process

C) and 30 mg/kg/week U.S.-Humira. This pivotal GLP-compliant study was reviewed previously under IND 119540 *(DARRTS Reference IDs: 3425569, 3967872, and 3981426)*. The study included histopathological examinations of a complete panel of organs and tissues. Decreased lymphoid cellularity in lymph nodes and spleen (CD20+) and decreased spleen weights in the three test article groups were considered to be PD effects. The toxicity of CHS-1420 and U.S.-Humira were considered to be similar, and no new toxicity finding was noted for CHS-1420 after 4 weeks of treatment. The TK profiles of CHS-1420 and U.S.-Humira were also considered to be similar except for females on Day 29 where exposure to 30 mg/kg CHS-1420 was about +50% higher compared to 30 mg/kg U.S.-Humira, likely due to limited number of animals with large variation. ADA was detected in both CHS-1420 and U.S.-Humira -treated groups. The presence of ADA correlated with decreased systemic exposure for adalimumab in 2 animals treated with 30 mg/kg U.S.-Humira and 1 animal treated with 30 mg/kg CHS-1420.

One-month Subcutaneous Repeat-Dose Toxicity Study in Monkeys

Study title/ number: A 1-month Subcutaneous Toxicity Study in Cynomolgus Monkeys with CHS-1420 and Adalimumab with a 6-week Recovery Period (Study# 20026996-1420-004)

Key Study Findings

- Cynomolgus monkeys received a total of 5 weekly SC doses of 0 mg/kg (vehicle), 30 mg/kg U.S.-Humira, 30 mg/kg CHS-1420, or 100 mg/kg CHS-1420.
- Histopathological findings included mild to marked decreased follicular lymphoid cellularity (B-cell regions) in lymph nodes and spleen. Immunohistochemical analysis revealed reduced CD20+ lymphocytes in splenic lymphoid follicles of animals receiving CHS-1420 and U.S.-Humira. The spleen findings were associated with decreased spleen weights and were considered PD effects. Overall, there were no toxicologically significant differences in the histopathological findings between CHS-1420 and U.S.-Humira groups and no new histopathological findings for CHS-1420 groups.
- Systemic exposure to CHS-1420 was approximately dose proportional between 30 and 100 mg/kg and an approximate 2- to 3-fold accumulation was observed for both CHS-1420 and U.S.-Humira groups from Day 1 to Day 29. T_{max} was comparable between CHS-1420 and U.S.-Humira groups on Days 1 and Day 29.
- The mean AUC_{0-168} values for 30 mg/kg CHS-1420 were considered similar to 30 mg/kg U.S.-Humira (95% to 109% of that for U.S.-Humira for both sexes on Day 1 and for males Day 29). Similarly, the mean C_{max} values for 30 mg/kg CHS-1420 were considered similar to 30 mg/kg U.S.-Humira (95% to 107% of that for U.S.-Humira for both sexes on Day 1 and for males Day 29). For females on Day 29, exposure to 30 mg/kg CHS-1420 was +43% (AUC) to +50% (C_{max}) higher

compared to 30 mg/kg U.S.-Humira, although the standard deviation is relatively large in females receiving 30 mg/kg CHS-1420.

- In total, 1 control animal, 2 animals treated with 30 mg/kg U.S.-Humira, 4 animals treated with 30 mg/kg CHS-1420 tested positive for CHS-1420- and U.S.-Humira-specific ADA, and 2 animals treated with 100 mg/kg CHS-1420 tested positive for CHS-1420-specific ADA. The presence of ADA was associated with decreased systemic exposure in 2 animals treated with 30 mg/kg U.S.-Humira and 1 animal treated with 30 mg/kg CHS-1420.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle) mg/kg, 30 and 100 mg/kg CHS-1420 (Process C), 30 mg/kg U.S.-Humira, QW for one month (5 doses) on Days 1, 8, 15, 22, and 29
Route of administration:	SC injection
Formulation/Vehicle:	CHS-1420 GMP 1 and Humira Diluent: (b) (4)
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	3/sex/group for main study
Age:	2.2 to 3.6 years of age at initiation of dosing
Satellite groups/ unique design:	2/sex/group for recovery
Deviation from study protocol affecting interpretation of results:	None

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Transient red, mucoid, and/or watery feces was observed in animals dosed with CHS-1420 and U.S.-Humira. The number of animals and severity of observations were similar between the 30 mg/kg U.S.-Humira and 100 mg/kg CHS-1420 groups, with a slightly lower incidence and severity in the 30 mg/kg CHS-1420 group.

Injection sites	Very slight to severe palpable subcutaneous masses at injection sites identified in all groups with a higher incidence and severity in the 30 mg/kg CHS-1420-treated animals; transient and clinically monitorable.
Body Weights	None
Feed Consumption	None
Ophthalmoscopy	None
ECG and blood pressure	None
Respiration rate	None
Hematology and Coagulation	None
Clinical Chemistry	None
Urinalysis	None
Gross Pathology	None
Organ Weights	Decreased absolute and relative spleen weight in animals dosed with CHS-1420 and U.S.-Humira, not dose-dependent for CHS-1420.
Histopathology Adequate battery: Yes	• Histopathological findings were similar in U.S.-Humira and CHS-1420 -treated animals and were expected PD effects, including decreased follicular lymphoid cellularity (B-cell regions) in lymph nodes and spleen. • Immunohistochemical analysis revealed reduced CD20+ lymphocytes in splenic lymphoid follicles of animals receiving U.S.-Humira and CHS-1420 (both doses).

General toxicology; additional studies
No genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or additional toxicity studies were conducted per ICH S6(R1) Guidance (June, 2011) and FDA guidance for industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April, 2015).

Authors:

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Carol Galvis, PhD
Nonclinical Supervisor/Team leader

13.4. Clinical Pharmacology Appendices

13.4.1. Summary of Bioanalytical Method Validation and Performance

For the comparative clinical Study CHS-1420-02 and PK similarity Study CHS-1420-03, serum CHS-1420 and U.S.-Humira was quantified using a validated anti-idiotype antibody sandwich enzyme-linked immunosorbent assay (ELISA). The development

and validation of method TM-DPI-0010 was conducted by [redacted] (b) (4) [redacted] Assay validation demonstrated that the assay was precise and accurate for the purpose of quantification of CHS-1420 and U.S.-Humira in human serum. The serum samples collected during Study CHS-1420-02 and CHS-1420-03 were analyzed using the validated procedure and 220/240 (91.%) and 218/234 (93%) of runs, respectively, passed the method acceptance criteria. Incurred sample reanalysis was performed in both studies and results were also acceptable.

Pharmacokinetics

Bioanalytical method validation report name, amendments, and hyperlinks	VALIDATION OF AN ENZYME LINKED IMMUNOSORBENT ASSAY (ELISA) FOR THE QUANTITATION OF CHS-1420 AND HUMIRA IN HUMAN SERUM DPI-16-179-VR01-AMEND01
Method description	[redacted] (b) (4) [redacted] test method TM-DPI-0010 used to quantitate CHS-1420 and Humira in human serum in clinical studies CHS-1420-02 and CHS-1420-03 is an anti-idiotype antibody sandwich enzyme-linked immunosorbent assay (ELISA). Prepared calibration standards, quality control samples and human samples are diluted to a minimal required dilution of 1:50 prior to loading onto assay plates pre-coated with an anti-idiotypic human monoclonal anti-adalimumab (Humira) antibody HCA203 (clone AbD18654_hIgG1, Bio-Rad). The plates are incubated to allow the Humira or CHS-1420 present in the sample to bind to the anti-idiotype antibody on the plate and subsequently are washed to remove unbound material. Then, a horseradish peroxidase conjugated second anti-idiotypic human monoclonal anti-adalimumab (Humira) antibody HCA204P (clone AbD18655_hIgG1, Bio-Rad) is added to the plate as the detection antibody for captured Humira or CHS-1420. After further incubation and washing, 3,3',5,5'-tetramethylbenzidine substrate is added to the plates and the reaction is stopped by adding 1N sulfuric acid. Plates are read at 450 nm (for detection) and 650 nm (for background). The corrected (650 nm subtracted from 450 nm) OD values obtained from the calibration standards are fitted to a 5-parameter logistic (5-PL) fit equation with $1/y^2$ weighting to calculate the Humira or CHS-1420 concentrations in the samples.
Materials used for calibration curve & concentration	CHS 1420 Lot# 3-FIN-2518 Stock: 47.2 mg/mL Calibration Curve Concentrations: 2560 ng/mL (Anchor) 1280 ng/mL (ULOQ) 640 ng/mL 320 ng/mL 160 ng/mL 80.0 ng/mL

	40.0 ng/mL 20.0 ng/mL 10.0. ng/mL (LLOQ) 5.00 ng/mL (Anchor)
Validated assay range	10.0 ng/mL to 1280 ng/mL
Material used for QCs & concentration	CHS-1420* and U.S.-Humira* 10.0 ng/mL (LLOQ) 30.0 ng/mL (LQC) 300 ng/mL (MQC) 960 ng/mL (HQC) 1280 ng/mL (ULOQ) *Refer to Source and Lot of Reagents section below for individual lot information
Minimum required dilutions (MRDs)	1:50
Source & lot of reagents (LBA)	**Capture Antibody** Human Anti-Idiotypic Adalimumab Monoclonal Antibody (b) (4) HCA203 (clone AbD18654_hIgG1) Batch # 1609 Batch #1611 **Detection Antibody** Human Anti-Idiotypic Adalimumab Monoclonal Antibody (b) (4) HCA204P (clone AbD18655_hIgG1) Batch # INN1608 **Biological Matrix** Pooled normal human serum (b) (4) HMSRM Lot# BRH1211270 **Reference Standards** CHS 1420 Lot# 3-FIN-2406 47.8 mg/mL CHS 1420 Lot# 3-FIN-2518 47.2 mg/mL CHS 1420 Lot# 3-FIN-2717 47.6 mg/mL CHS 1420 Lot# 3-FIN-3370 46.0 mg/mL U.S.-Humira Lot# 1030241 47.8 mg/mL U.S.-Humira Lot# 1039180 48.4 mg/mL U.S.-Humira Lot# 1064053 47.0 mg/mL EU-Humira Lot# 62159XD11 48.0 mg/mL EU-Humira Lot# 62154XD04 46.9 mg/mL

	EU-Humira Lot# 63166XD01 47.9 mg/mL Humira Lot# 1110162 48.2 mg/mL		
Regression model & weighting	Five-parameter logistic (5-PL) model with 1/y2 weighting		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ (10.0 ng/mL) to ULOQ (1280 ng/mL)	8	Table 2, report DPI-16-179-VR01-AMEND01
	Cumulative accuracy (%bias) from LLOQ (10.0 ng/mL) to ULOQ (1280 ng/mL) CHS-1420 (U.S.-Humira not used as calibrator)	-1.9 to 5.5%	Table 2, report DPI-16-179-VR01-AMEND01
	Cumulative precision (%CV) from LLOQ (10 ng/mL) to ULOQ (1280 ng/mL) CHS-1420 (U.S.-Humira not used as calibrator)	≤ 6.6%	Table 2, report DPI-16-179-VR01-AMEND01
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs Prepared with: (CHS-1420 lot 3-FIN-2518, 3-FIN-2406 and U.S.-Humira lot 1030241 and 1039180)		
	CHS-1420	13.1 to 3.3%RE	**Error! Reference source not found.**
	U.S.-Humira	0.4 to 3.7%RE	**Error! Reference source not found.**
	CHS-1420 and U.S.-Humira Combined	-5.3 to 1.6%RE	Table 4, report DPI-16-179-VR01-AMEND01
	QCs Prepared with: (CHS-1420 lot 3-FIN-2717 and U.S.-Humira lot 1064053, 63166XD01, 62154XD04, 62159XD11) * *Supplemental P&A performed with additional lots of CHS-1420 and U.S.-Humira		
	CHS-1420	-21.3 to -4.9%RE	**Error! Reference source not found.**

	U.S.-Humira	-13.3 to -1.5%RE	**Error! Reference source not found.**
	CHS-1420 and U.S.-Humira Combined	-12.3 to 3.9%RE	Table 6, report DPI-16-179-VR01-AMEND01
	Inter-batch %CV QCs Prepared with: (CHS-1420 lot 3-FIN-2518, 3-FIN-2406 and U.S.-Humira lot 1030241 and 1039180)		
	CHS-1420	≤ 17.0% CV	**Error! Reference source not found.**
	U.S.-Humira	≤ 19.0 % CV	**Error! Reference source not found.**
	CHS-1420 and U.S.-Humira Combined	≤ 15.6 % CV	Table 4, report DPI-16-179-VR01-AMEND01
	QCs Prepared with: (CHS-1420 lot 3-FIN-2717 and U.S.-Humira lot 1064053, 63166XD01, 62154XD04, 62159XD11) * *Supplemental P&A performed with additional lots of CHS-1420 and U.S.-Humira		
	CHS-1420	≤ 7.4% CV	**Error! Reference source not found.**
	U.S.-Humira	≤ 12.7 % CV	**Error! Reference source not found.**
	CHS-1420 and U.S.-Humira Combined	≤ 11.9 % CV	Table 6, report DPI-16-179-VR01-AMEND01
	Total Error (TE) QCs Prepared with: (CHS-1420 lot 3-FIN-2518, 3-FIN-2406 and U.S.-Humira lot 1030241 and 1039180)		
	CHS-1420	≤ 25.6%	**Error! Reference source not found.**

	U.S.-Humira	≤ 22.5%	**Error! Reference source not found.**
	CHS-1420 and U.S.-Humira Combined	≤ 18.4%	Table 4, report DPI-16-179-VR01-AMEND01
	QCs Prepared with: (CHS-1420 lot 3-FIN-2717 and U.S.-Humira lot 1064053, 63166XD01, 62154XD04, 62159XD11) * *Supplemental P&A performed with additional lots of CHS-1420 and U.S.-Humira		
	CHS-1420	≤ 28.7%	**Error! Reference source not found.**
	U.S.-Humira	≤ 23.6 %	**Error! Reference source not found.**
	CHS-1420 and U.S.-Humira Combined	≤ 22.0 %	Table 6, report DPI-16-179-VR01-AMEND01
Selectivity & matrix effect	**10 serum lots from normal human subjects spiked with CHS-1420 or U.S.-Humira** U.S.-Humira lot 1030241: LLOQ (10 ng/mL): -1.8 to 35.0 %RE (-1.8 to 9.0% RE in 9/10 lots) HQC (960 ng/mL): -3.6 to 19.8 %RE in 10/10 lots Potential LLOQ (20 ng/mL): -4.0 to 38.5 %RE (-4.0 to 15.0% RE in 9/10 lots) CHS-1420 lot 3-FIN-2518: LLOQ (10 ng/mL): -15.4 to 24.0 %RE (-15.4 to 9.0% RE in 9/10 lots) HQC (960 ng/mL): -4.3 to 28.1 %RE (-4.3 to 18.8% RE in 8/10 lots) Potential LLOQ (20 ng/mL): -8.5 to 6.5 %RE in 10/10 lots CHS-1420 lot 3-FIN-2406: LLOQ (10 ng/mL): -7.9 to 32.0 %RE (-7.9 to 10.0% RE in 8/10 lots) HQC (960 ng/mL): -13.4 to 10.4 %RE in 10/10 lots		Table 7, report DPI-16-179-VR01-AMEND01

	10 serum lots from psoriasis subjects spiked with CHS-1420 or U.S.-Humira U.S.-Humira lot 1030241: LLOQ (10 ng/mL): -24.1 to NC* %RE (-24.1 to -6.6% RE in 9/10 lots) HQC (960 ng/mL): -93.4 to 2.3 %RE (-7.9 to 2.3% RE in 9/10 lots) *NC = not calculable as sample was BLQ CHS-1420 lot 3-FIN-2518: LLOQ (10 ng/mL): -21.2 to NC* %RE (-21.2 to 17.0% RE in 9/10 lots) HQC (960 ng/mL): -97.1 to 1.7 %RE (-8.6 to 1.7% RE in 9/10 lots) *NC = not calculable as sample was BLQ CHS-1420 lot 3-FIN-2406: LLOQ (10 ng/mL): -7.0 to 25.0 %RE in 10/10 lots HQC (960 ng/mL): 1.5 to 16.7 %RE in 10/10 lots	Table 9, report DPI-16-179-VR01-AMEND01
Interference & specificity	10/10 unspiked samples from normal human subjects were below limit of quantitation (BLQ) 10/10 unspiked samples from psoriatic human subjects were BLQ 4/4 unspiked lipemic samples from normal human subjects were BLQ 4/4 unspiked hemolyzed samples from normal human subjects were BLQ	Tables 7,8,9 , report DPI-16-179-VR01-AMEND01
Hemolysis effect	**4 serum lots spiked with CHS-1420 or U.S.-Humira** U.S.-Humira lot 1030241: LLOQ (10 ng/mL): -10.6 to 21.0% RE in 4/4 lots HQC (960 ng/mL): -12.6 to 13.5% RE in 4/4 lots CHS-1420 lot 3-FIN-2518: LLOQ (10 ng/mL): -12.6 to -5.7% RE in 4/4 lots HQC (960 ng/mL): -7.1 to 10.4% RE in 4/4 lots CHS-1420 lot 3-FIN-2406: LLOQ (10 ng/mL): -17.4 to -5.6% RE in 4/4 lots HQC (960 ng/mL): -4.8 to 12.5% RE in 4/4 lots	Table 8, report DPI-16-179-VR01-AMEND01

Lipemic effect	**4 serum lots spiked with CHS-1420 or U.S.-Humira** U.S.-Humira lot 1030241: LLOQ (10 ng/mL): -7.8 to 14.0% RE in 4/4 lots HQC (960 ng/mL): -2.8 to 7.3% RE in 4/4 lots CHS-1420 lot 3-FIN-2518: LLOQ (10 ng/mL): -28.2 to 16% (9.0 to 16.0% RE in 3/4 lots) HQC (960 ng/mL): 1.3 to 6.3% RE in 4/4 lots CHS-1420 lot 3-FIN-2406: LLOQ (10 ng/mL): -28.6 to 24.0%RE (5.0 to 24.0% RE in 3/4 lots) HQC (960 ng/mL): -12.3 to 0.9% RE in 4/4 lots	Table 8, report DPI-16-179-VR01-AMEND01
Dilution linearity & hook effect	Highest concentration tested: 2.5 mg/mL – No hook effect (prozone) observed 5 Dilutions tested (1:10, 1:20, 1:40, at 10 mg/mL; 1: 2500, and 1:5000 at 2.5 mg/mL) Range of Observed bias: -10.0 to 13.0% RE	Table 10, report DPI-16-179-VR01-AMEND01
Bench-top/process stability	Up to 96 hours for both CHS-1420 and U.S.-Humira at ambient temperature	Table 11, report DPI-16-179-VR01-AMEND01
	Up to 96 hours for both CHS-1420 and U.S.-Humira at 2-8°C	Table 12, report DPI-16-179-VR01-AMEND01
Freeze-Thaw stability	Freeze-thaw stability demonstrated for up to 10 cycles for both U.S.-Humira and CHS-1420	Table 13, report DPI-16-179-VR01-AMEND01
Long-term storage	CHS-1420 and U.S.-Humira: Up to 537 days at -70°C CHS-1420 LQC (30 ng/mL) was tested and confirmed stability after 648 days at -70°C	Table 15, report DPI-16-179-VR01-AMEND01

	CHS-1420 and U.S.-Humira: Up to 239 days at -20°C	Table 14, report DPI-16-179-VR01-AMEND01
Parallelism	Not done	–
Carry over	Not done. Not applicable for the method platform	–
Method performance in study CHS-1420-03 (b) (4) Reference DPI-16-181) Study report DPI-16-181-SR01 and DPI-16-181-SR01-ADDENDUM01		
Assay passing rate	218/234 Runs: 93% passing rate (including incurred sample reanalysis (ISR))	Table 1, report DPI-16-181-SR01
Standard curve performance	• Cumulative bias range: -2.5 to 4.0% (excluding anchor points) • Cumulative precision: ≤ 7.6% CV (excluding anchor points)	Table 2, report DPI-16-181-SR01
QC performance	• Cumulative bias range: -5.3 to -0.1% • Cumulative precision: ≤ 9.4% CV • TE: ≤ -5.3%	Table 3, report DPI-16-181-SR01
Method reproducibility	Incurred sample reanalysis was performed in 10.2% of study samples and 90.4 % of samples met the pre-specified criteria	Section 17 and Table 6, report DPI-16-181-SR01
Study sample analysis/ stability	The duration between the date of the earliest collection and the date of the latest analysis was 400 days. Samples were stored at -70°C. Frozen storage stability has been established for 537 days at -70°C for both CHS-1420 and U.S.-Humira and all samples, QCs and standards were tested within that time period. The maximum freeze thaw for study samples was 6 cycles (10 cycles established during validation). No sample exceeded 96 hours at ambient or 2-8°C temperatures.	
Method performance in study CHS-1420-02 (b) (4) Reference DPI-18-025) Study report DPI-18-025-SR01 and DPI-18-025-SR01-ADDENDUM01		
Assay passing rate	220 of 240 total runs (91.7%) (including incurred sample reanalysis (ISR))	Table 1, report DPI-18-025-SR01
Standard curve performance	• Cumulative bias range: -2.7 to 9.4% • Cumulative precision: ≤ 8.0% CV	Table 2, report DPI-18-025-SR01
QC performance	• Cumulative bias range: 0.0 to 7.3% • Cumulative precision: ≤ 12.7% CV • TE: ≤ 7.3%	Table 3, report DPI-18-025-SR01
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of study samples and 92.3% of samples met the pre-specified criteria	Section 16 and Table 6, report DPI-18-025-SR01

Study sample analysis/ stabilit	The maximum sample storage duration was 1092 days at -70°C. Long term stability at -70°C has been demonstrated for 537 days at -70°C for both CHS-1420 and U.S.-Humira and for CHS-1420 for 648 days. Further stability assessments are ongoing. The standards were stored for no more than 103 days from preparation until use, while the QCs were stored no more than 122 days from preparation until use. The maximum freeze thaw for study samples was 5 cycles (10 cycles established during validation). No sample exceeded 96 hours at ambient or 2-8°C temperatures.

Source: Addendum to Summary of Biopharmaceutic Studies and Associated Analytical Methods. Link: \\cdsesub1\evsprod\BLA761216\0004\m2\27-clin-sum\summary-biopharm.docx

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13.5. Clinical Appendices

13.5.1. Information Requests on CHS1420-02 re: Protocol Deviations and Liver Enzyme Elevations

Protocol Deviations

The study report for CHS-1420-02 included ambiguous information on major protocol deviations. Also, as FDA had requested primary analysis for efficacy to be based on Week-16 data, protocol deviations up to that time was not provided (only up to Week-12, Coherus' original primary endpoint time).

On February 2, 2021, FDA requested Coherus's explanation on the ambiguous protocol deviations and information on deviations by Week-16:

1. In Study CHS-1420-02, you provide the major protocol deviations through Week 12 (Table 14.1.1.2.2).
   a. As the primary endpoint is to be analyzed at Week 16, provide the major protocol deviations through Week 16.
   b. Clarify the "IP" protocol deviation(s) for each subject with details of the violation, and amend the "DVTERM" in the DV and ADDV datasets accordingly, using verbatim name of the deviation criterion (SDTMIG v3.3, Section 6.2.4).

Coherus responded to the request on February 16:

The BLA 761216 describes the major protocol deviations through Week 12 and not Week 16 because the pre-specified primary endpoint of Study CHS-1420-02 was the percentage of subjects achieving PASI-75 at Week 12.
Per agreement during BPD Type 4 meeting held on 27 Oct 2020, an evaluation of percent change in PASI at Week16 was added as post-hoc analysis.
The request for additional information on major protocol deviations through Week 16 is addressed as follow:
a. The major protocol deviations through Week 16 are provided in the revised Table 14.1.1.2.2 (Table 14_1_1_2_2_IR) and corresponding Listing 16_2_2_2_IR.
b. "IP" protocol deviations for each subjects, including details of the violations, is provided in Listing 16_2_2_2_Ira through Week 16. In addition, DVTERM is amended in the updated DV and ADDV datasets (.xpt format) for each subjects (dv.xpt and addv.xpt).

Coherus' response was considered adequate.

Liver Enzyme Elevations
On July 29, 2021, FDA requested Coherus to explain the abnormal laboratory findings, especially liver function test abnormalities in CHS-1420-02, and to provide information on confounding factors, if any, in the subjects with elevated ALT and ALT.

Coherus provided details of liver enzyme abnormalities in responses to Information Requests, which were received by FDA on August 5 (eCTD #0014) and August 25, 2021 (eCTD #0017).

The following Table details the liver enzyme abnormalities and confounding factors in the study subjects.

Liver Function Test Abnormalities in CHS-1420-02

Treatment Period	USUBJID*	Treatment Sequence§	Treatment	Study Day	ALT (U/L) [≥ 3xULN]	AST (U/L) [≥ 3xULN]	ALP (U/L) [≥ 2.5xULN]	Bilirubin (µmol/L) [≥ 1.5xULN]	Confounder (Provide details)
Period 1	CHS-1420- 02- (b) (6)	H/H/C	H	57	130				**Treatment period of increased LFT**: Humira; **Baseline LFTs**: Normal; **Increased LFTs**: ALT increase in week 8 (Humira); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: ADA positive at week 8 (same time as increased ALT). **Sponsor Assessment:** This was a single elevation that was transient and resolved while study drug was being administered.
Period 1	CHS-1420- 02- (b) (6)	C/C/C	C	29	201				**Treatment period of Increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT increase in week 4 (CHS- 1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: No other confounders. **Sponsor Assessment:** This subject had a short, transient increase in liver enzymes that resolved on study drug.
Period 1	CHS-1420- 02- (b) (6)	C/C/C	C	84	176				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT increase in week 8 (CHS- 1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: EtOH and/or NSAID use. **Sponsor Assessment:** There is a temporal relationship between the elevation of LFTs, discontinuing study drug and return of LFTs to the normal range. However, the event is confounded by possible alcohol and/or NSAID use.

Period 1	CHS-1420- 02- (b) (6)	C/C/C	C	91	193	110			**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT and AST increase in week 12 (CHS-1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: EtOH and/or NSAID use. **Sponsor Assessment:** There is a temporal relationship between the elevation of LFTs, discontinuing study drug and return of LFTs to the normal range. However, the event is confounded by possible alcohol and/or NSAID use.
Period 1	CHS-1420- 02- (b) (6)	H/C/C	H	62	129	103			**Treatment period of increased LFT**: Humira; **Baseline LFTs**: ALT increased; **Increased LFTs**: ALT and AST increase in week 8 (Humira); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: Elevated LFTs at baseline. **Sponsor Assessment**: The LFT increased with study drug administration and normalized over >1 month when study drug was discontinued. However, the event is confounded by the subject's baseline ALT increase.
Period 1	CHS-1420- 02- (b) (6)	H/C/C	H	113	231	104			**Treatment period of increased LFT**: Humira; **Baseline LFTs**: ALT increased; **Increased LFTs**: ALT and AST increase in week 16 (Humira), **Medical Hx**: No confounders, **Con Meds**: No confounders, **Other**: elevated LFTs at baseline and reported gastroenteritis at the time of the event. **Sponsor Assessment:** The LFT increased with study drug administration and normalized over >1 month when study drug was discontinued. However, the event is confounded by the subject's baseline ALT increase and reported gastroenteritis.

Period 1	CHS-1420- 02-(b) (6)	C/C/C	C	29	240				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT increase in week 4 (CHS- 1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: No other confounders. **Sponsor Assessment:** This was a single elevation that was transient and the LFTs normalized with continued administration of study drug.
Period 1	CHS-1420- 02-(b) (6)	C/C/C	C	115	169				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT increase in week 16 (CHS- 1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: EtOH use. **Sponsor Assessment:** The subject had an increase in LFTs beginning in day 60 that decreased after study drug stopped. However, the event is confounded by the subject's reported regular EtOH use (1-7 times per week).
Period 1	CHS-1420- 02-(b) (6)	C/C/C	C	92	124	120			**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: ALT increased; **Increased LFTs**: ALT increase during unscheduled visit between Week 12-16 (CHS-1420), CK increase; **Medical Hx**: Obesity; **Con Meds**: No confounders; **Other**: Intense exercise, elevated LFTs at baseline. **Sponsor Assessment:** The subject had elevated LFTs at baseline and a medical history significant for obesity. In addition, the subject was noted to have exercised intensely prior to the event which could account for the CK increase and ALT increase and acts as a confounder.
Period 1	CHS-1420- 02-(b) (6)	C/C/C	C	114	141	193			**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: ALT and AST increased; **Increased LFTs**: ALT and AST increase in week 16 (CHS-1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: Elevated LFTs at baseline. **Sponsor Assessment:** This subject had an increase in ALT/AST at the Day 0 visit that waxed and waned throughout the clinical study suggesting pre-existing liver injury.

Period 1	CHS-1420- 02-(b) (6)	H/C/C	H	97	325				**Treatment period of increased LFT**: Humira; **Baseline LFTs**: Normal; **Increased LFTs**: ALT increase in week 12 (Humira); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: No other confounders. **Sponsor Assessment:** This subject had a significant, but transient increase in liver function tests that resolved while study drug was continued.
Period 1	CHS-1420- 02-(b) (6)	H/C/C	H	111	147				**Treatment period of increased LFT**: Humira; **Baseline LFTs**: Normal; **Increased LFTs**: ALT increase in week 16 (Humira); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: No other confounders. **Sponsor Assessment:** This subject had a significant, but transient increase in liver function tests that resolved while study drug was continued.
Period 1	CHS-1420- 02-(b) (6)	C/C/C	C	57	123				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT and AST increase in week 8 (CHS-1420); **Medical Hx**: Obesity, DM2; **Con Meds**: No confounders; **Other**: Fatty liver infiltration reported at day 100. **Sponsor Assessment:** The increase in LFTs occurred while the subject was receiving CHS-1420 and returned to normal over several weeks after the study drug was discontinued. However, this event is confounded by the subject's concurrent fatty liver and multiple comorbid medical conditions.

Period 1	CHS-1420- 02- (b) (6)	C/C/C	C	72	204				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT and AST increase in unscheduled visiting between week 8-12 (CHS-1420); **Medical Hx**: Obesity, DM2; **Con Meds**: No confounders; **Other**: Fatty liver infiltration reported at day 100. **Sponsor Assessment:** The increase in LFTs occurred while the subject was receiving CHS- 1420 and returned to normal over several weeks after the study drug was discontinued. However, this event is confounded by the subject's concurrent fatty liver and multiple comorbid medical conditions.
Period 1	CHS-1420- 02- (b) (6)	C/C/C	C	57	409	148			**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT and AST increase in week 8 (CHS-1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: Fatty liver infiltration reported at day 78. **Sponsor Assessment:** The subject had an increase in LFTs with the administration of study drug that resolved when study drug was discontinued. However, this event is confounded by the subject's concurrent fatty liver.
Period 1	CHS-1420- 02- (b) (6)	C/C/C	C	65	235				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT and AST increase in week 8 (CHS-1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: Fatty liver infiltration reported at day 78. **Sponsor Assessment:** The subject had an increase in LFTs with the administration of study drug that resolved when study drug was discontinued. However, this event is confounded by the subject's concurrent fatty liver.
Period 2	No liver function abnormality reported in Period 2								

Period 3	CHS-1420- 02- (b) (6)	H/H/C	C	308	128	190			**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal, CK increased; **Increased LFTs**: ALT and AST increase in week 55 (CHS-1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: No other confounders. **Sponsor Assessment:** The subject was noted to have an increase in LFTs and CK increase 62 days after the last dose of study drug. Given the onset latency of the event from the last dose of study drug, a causal relationship is unlikely.
Period 3	CHS-1420- 02- (b) (6)	H/C/C	C	280	356	144			**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal; **Increased LFTs**: ALT and AST increase in week 40 (CHS-1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other:** Gastroenteritis. **Sponsor Assessment:** The subject was noted to have an increase in LFTs 6 days after the previous dose. However, the event is confounded by the subject's reported gastroenteritis.
Period 3	CHS-1420- 02- (b) (6)	H/H/C	C	339	142	114			**Treatment period of increased LFT**: Humira; **Baseline LFTs**: ALT increased; **Increased LFTs**: ALT and AST increase in week 4 (Humira); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other:** Intense exercise, elevated LFTs at baseline. **Sponsor Assessment:** This subject had an increase in ALT at the screen visit. The acute increase in AST to >3 × ULN is concurrent with the elevation in CK, which is thought to be due to exercise, a more likely etiology than study drug.

Period 3	CHS-1420- 02- (b) (6)	C/C/C	C	282	152				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: Normal, LDH increased; **Increased LFTs**: ALT increase in week 40 (CHS-1420); **Medical Hx**: No confounders; **Con Meds**: No confounders; **Other**: No other confounders. **Sponsor Assessment:** This was a single elevation that was transient and resolved while study drug was being administered.
Period 3	CHS-1420- 02- (b) (6)	C/C/C	C	227	156	106			**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: ALT and AST increased; **Increased LFTs**: ALT and AST increase in week 32 (CHS-1420); **Medical Hx**: Obesity; **Con Meds**: No confounders; **Other**: EtOH use, elevated LFTs at baseline. **Sponsor Assessment:** An acute elevation of ALT >3 × ULN occurred at Week 32 after administration of study drug and continued through Week 41. ALT decreased to mildly elevated levels by study end. Although increased LFTs are likely due to regular alcohol intake and obesity, study drug may have been contributory.

Period 3	CHS-1420- 02-UA658016	C/C/C	C	275	135				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: ALT and AST increased; **Increased LFTs**: ALT and AST increase in week 40 (CHS-1420); **Medical Hx**: Obesity; **Con Meds**: No confounders; **Other**: EtOH use, elevated LFTs at baseline. **Sponsor Assessment:** An acute elevation of ALT >3 × ULN occurred at Week 32 after administration of study drug and continued through Week 41. ALT decreased to mildly elevated levels by study end. Although increased LFTs are likely due to regular alcohol intake and obesity, study drug may have been contributory.
Period 3	CHS-1420- 02-(b) (6)	H/H/C	C	225	196	102			**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: ALT and AST increased; **Increased LFTs**: ALT increase in week 32 (CHS-1420); **Medical Hx**: Obesity; **Con Meds**: No confounders; **Other**: Elevated LFTs at baseline. **Sponsor Assessment:** This subject had elevated ALT and AST at the screening visit and throughout the study due to excessive drinking and obesity. An acute elevation of ALT/AST >3 × ULN at the Week 32 visit (6 days post study drug) suggests a temporal relationship associated with study drug administration and it was withheld until ALT/AST had decreased. At re-initiation of study drug approximately 7 weeks later, the subject's ALT/AST values assumed the earlier elevated fluctuations. Although study drug may have contributed to acute ALT/AST increase, excessive drinking history and obesity provided a backdrop of pre-existing liver inflammation.

Period 3	CHS-1420- 02-(b) (6)	H/H/C	C	234	159				**Treatment period of increased LFT**: CHS-1420; **Baseline LFTs**: ALT and AST increased; **Increased LFTs**: ALT increase in unscheduled visiting between week 32-40 (CHS-1420); **Medical Hx**: Obesity; **Con Meds**: No confounders; **Other**: Elevated LFTs at baseline. **Sponsor Assessment:** This subject had elevated ALT and AST at the screening visit and throughout the study due to excessive drinking and obesity. An acute elevation of ALT/AST >3 × ULN at the Week 32 visit (6 days post study drug) suggests a temporal relationship associated with study drug administration and it was withheld until ALT/AST had decreased. At re-initiation of study drug approximately 7 weeks later, the subject's ALT/AST values assumed the earlier elevated fluctuations. Although study drug may have contributed to acute ALT/AST increase, excessive drinking history and obesity provided a backdrop of pre-existing liver inflammation.

*USUBJID=unique subject identifier §C=CHS-1420, H=Humira
ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase, bilirubin=total bilirubin; ULN= upper limits of normal
Source: Coherus's August 5, 2021 Response to Information Request Table "Liver Function Test Abnormalities in CHS-1420-02". Link: \\cdsesub1\evsprod\BLA761216\0014\m1\us\clinical-info-amend.pdf

As discussed in Section 6.3 of this review, there were confounding factors for the liver enzyme elevations in most patients, and the abnormalities resolved despite continuation of use of investigational product. There were no cases of SAE associated with the enzyme elevations and no occurrence of Hy's law. The elevations are consistent with those in other clinical development programs shown in the U.S.-Humira label. Thus, this issue is considered resolved.

13.5.2. TEAE Tables of Clinical Studies

TEAE Tables will be presented in a similar manner as in Section 6.3 of this BMER, with Tables for the Treatment Periods of Study CHS-1420-02, followed by those of CHS-1420-04, and then the pooled data of single-dose healthy volunteer PK studies: CHS-1420-03, -05, and -07. The prime focus will be on the comparative studies between CHS-1420 and U.S.-Humira, i.e., CHS-1420-02 and CHS-1420-03. The other studies

are used to confirm that their safety data do not preclude or conflict with conclusions based on the primary safety assessment.

Two sets of TEAE Tables will be included here: Tables on common adverse events (occurrence ≥2% in any treatment group), and Tables on "drug-related" adverse events, the latter being events considered by the Investigator as being associated with use of investigational product(s) in the study.

Common TEAEs (Occurrence ≥2% in any Treatment Arm)

CHS-1420-02

Treatment Period 1

Table 56. Summary of Treatment-emergent Adverse Events (≥2% Subjects in Either Treatment Group) by System Organ Class and Preferred Term (CHS-1420-02, Treatment Period 1, Safety Population)

System Organ Class / Preferred Term	CHS-1420 (N = 274) n (%)	U.S.- Humira (N = 271) n (%)
Subjects with at Least One Event		
Any TEAE	134 (48.9)	122 (45.0)
General disorders and administration site conditions	18 (6.6)	17 (6.3)
• Injection site reaction	11 (4.0)	10 (3.7)
Infections and infestations	82 (29.9)	76 (28.0)
• Influenza	6 (2.2)	6 (2.2)
• Nasopharyngitis	24 (8.8)	24 (8.9)
• Upper respiratory tract infection	17 (6.2)	14 (5.2)
• Urinary tract infection	7 (2.6)	5 (1.8)
Investigations	24 (8.8)	13 (4.8)
• Alanine aminotransferase increased	6 (2.2)	2 (0.7)
• Blood creatine phosphokinase increased	5 (1.8)	7 (2.6)
Musculoskeletal and connective tissue disorders	20 (7.3)	15 (5.5)
• Arthralgia	6 (2.2)	2 (0.7)
• Back pain	2 (0.7)	6 (2.2)
Nervous system disorders	14 (5.1)	19 (7.0)
• Headache	7 (2.6)	10 (3.7)
Respiratory, thoracic, and mediastinal disorders	15 (5.5)	10 (3.7)

• Cough	6 (2.2)	0
• Oropharyngeal pain	6 (2.2)	4 (1.5)
Skin and subcutaneous tissue disorders	18 (6.6)	18 (6.6)
• Psoriasis	3 (1.1)	8 (3.0)

N = number of subjects treated in the treatment period was used as the denominator for percentage calculations; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 1 and before first dose of study drug of Treatment Period 2; TEAE = treatment-emergent adverse event.
Source: CHS-1420-02 CSR Post-text Table 14.3.1.2.1.

Treatment Period 2

Table 57. Summary of Treatment-emergent Adverse Events (≥2% Subjects in Any Treatment Group) by System Organ Class and Preferred Term (CHS-1420-02, Treatment Period 2, Safety Population)

System Organ Class / Preferred Term	CHS-1420/ CHS-1420 (N = 255) n (%)	U.S.-Humira/ CHS-1420 (N = 126) n (%)	U.S.-Humira/ U.S.-Humira (N = 130) n (%)
Subjects with at Least One Event			
Any TEAE	54 (21.2)	26 (20.6)	22 (16.9)
Gastrointestinal disorders	7 (2.7)	4 (3.2)	2 (1.5)
• Nausea	0	3 (2.4)	0
Infections and infestations	24 (9.4)	7 (5.6)	8 (6.2)
• Nasopharyngitis	5 (2.0)	1 (0.8)	0
• Upper respiratory infection	7 (2.7)	0	1 (0.8)

N = number of subjects treated in the treatment period; n (%) =number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 2 and before first dose of study drug of Treatment Period 3; TEAE = treatment-emergent adverse event.
Source: CHS-1420-02 CSR Post-text Table 14.3.1.2.2.

Treatment Period 3

Table 58. Summary of Treatment-emergent Adverse Events (≥ 2% Subjects in Any Treatment Group) by System Organ Class and Preferred Term (CHS-1420-02, Treatment Period 3, Open-label Extension Population)

System Organ Class / Preferred Term	CHS-1420/ CHS-1420/ CHS-1420 (N = 235) n (%)	U.S.-Humira/ CHS-1420/ CHS-1420 (N = 113) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N = 126) n (%)

Subjects with at Least One Event			
Any TEAE	99 (42.1)	48 (42.5)	50 (39.7)
Infections and infestations	52 (22.1)	21 (18.6)	23 (18.3)
• Influenza	2 (0.9)	1 (0.9)	4 (3.2)
• Nasopharyngitis	11 (4.7)	7 (6.2)	5 (4.0)
• Upper respiratory infection	8 (3.4)	1 (0.9)	4 (3.2)
Investigations	17 (7.2)	8 (7.1)	14 (11.1)
• Alanine aminotransferase increased	3 (1.3)	4 (3.5)	5 (4.0)
• Aspartate aminotransferase increased	2 (0.9)	2 (1.8)	6 (4.8)
• Blood creatine phosphokinase increased	3 (1.3)	1 (0.9)	5 (4.0)
• Interferon - γ release assay positive	7 (3.0)	3 (2.7)	0
Musculoskeletal and connective tissue disorders	15 (6.4)	9 (8.0)	6 (4.8)
• Back pain	2 (0.9)	3 (2.7)	1 (0.8)
Nervous system disorders	11 (4.7)	1 (0.9)	3 (2.4)
• Headache	8 (3.4)	0	3 (2.4)
Skin and subcutaneous tissue disorders	13 (5.5)	5 (4.4)	9 (7.1)
• Psoriasis	6 (2.6)	4 (3.5)	6 (4.8)

N = number of subjects treated in the treatment period; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 3; TEAE = treatment-emergent adverse event.
Source: CHS-1420-02 CSR Post-text Table 14.3.1.2.4.

Treatment Periods 1+ 2 +3

Table 59. Summary of Treatment-emergent Adverse Events (>2% Subjects in Any Treatment Group) by System Organ Class and Preferred Term (CHS-1420-02, Treatment Periods 1 + 2 + 3, Safety Population)

System Organ Class Preferred Term	CHS-1420/ CHS-1420/ CHS-1420 (N = 274) n (%)	U.S.-Humira/ CHS-1420/ CHS-1420 (N = 134) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N = 137) n (%)
Subjects with at Least One Event			
Any TEAE	172 (62.8)	85 (63.4)	89 (65.0)
Gastrointestinal disorders	21 (7.7)	17 (12.7)	13 (9.5)
• Abdominal pain	3 (1.1)	3 (2.2)	2 (1.5)
• Diarrhea	4 (1.5)	3 (2.2)	3 (2.2)

• Nausea	1 (0.4)	4 (3.0)	0
• Vomiting	1 (0.4)	2 (1.5)	3 (2.2)
General disorders and administration site conditions	26 (9.5)	15 (11.2)	12 (8.8)
• Injection site reaction	12 (4.4)	5 (3.7)	6 (4.4)
Infections and infestations	113 (41.2)	50 (37.3)	57 (41.6)
• Bronchitis	7 (2.6)	3 (2.2)	3 (2.2)
• Gastroenteritis	2 (0.7)	4 (3.0)	1 (0.7)
• Influenza	9 (3.3)	5 (3.7)	7 (5.1)
• Nasopharyngitis	35 (12.8)	17 (12.7)	17 (12.4)
• Pharyngitis	6 (2.2)	4 (3.0)	1 (0.7)
• Pneumonia	1 (0.4)	1 (0.7)	3 (2.2)
• Respiratory tract infection viral	5 (1.8)	5 (3.7)	4 (2.9)
• Rhinitis	6 (2.2)	2 (1.5)	4 (2.9)
• Sinusitis	5 (1.8)	5 (3.7)	1 (0.7)
• Upper respiratory tract infection	23 (8.4)	6 (4.5)	13 (9.5)
• Urinary tract infection	11 (4.0)	3 (2.2)	5 (3.6)
Investigations	44 (16.1)	16 (11.9)	21 (15.3)
• Alanine aminotransferase increased	10 (3.6)	5 (3.7)	6 (4.4)
• Aspartate aminotransferase increased	8 (2.9)	3 (2.2)	7 (5.1)
• Blood creatine phosphokinase increased	12 (4.4)	5 (3.7)	8 (5.8)
• Hepatic enzyme increased	4 (1.5)	0	4 (2.9)
• Interferon-γ release assay positive	8 (2.9)	4 (3.0)	0
Metabolism and nutrition disorders	6 (2.2)	3 (2.2)	5 (3.6)
• Hyperglycemia	0	1 (0.7)	3 (2.2)
Musculoskeletal and connective tissue disorders	33 (12.0)	15 (11.2)	16 (11.7)
• Arthralgia	10 (3.6)	2 (1.5)	2 (1.5)
• Back pain	4 (1.5)	5 (3.7)	5 (3.6)
• Pain in extremity	0	2 (1.5)	4 (2.9)
Nervous system disorders	24 (8.8)	14 (10.4)	12 (8.8)
• Headache	14 (5.1)	7 (5.2)	8 (5.8)
Respiratory, thoracic, and mediastinal disorders	19 (6.9)	11 (8.2)	6 (4.4)

• Cough	8 (2.9)	1 (0.7)	0
• Oropharyngeal pain	7 (2.6)	3 (2.2)	4 (2.9)
Skin and subcutaneous tissue disorders	32 (11.7)	14 (10.4)	16 (11.7)
• Pruritus	7 (2.6)	2 (1.5)	3 (2.2)
• Psoriasis	10 (3.6)	8 (6.0)	10 (7.3)
Vascular disorder	8 (2.9)	1 (0.7)	4 (2.9)
• Hypertension	6 (2.2)	0	3 (2.2)

N = number of subjects treated in the treatment period; n (%) = number and % of subjects with events starting on or after the day of first dose of study drug of Treatment Period 1 through study termination;
TEAE = treatment-emergent adverse event.
Source: CHS-1420-02 CSR Post-text Table 14.3.1.2.30.

CHS-1420-04

This is a 3-dose study to assess the dosing robustness of administration of CHS-1420 AI by RA patients or caregivers. No new safety signals observed: overall, 23 (16.3%) subjects reported TEAEs.

The only TEAE that occurred in ≥ 2% of subjects was urinary tract infection (3 subjects [2.1%]).

Pooled Single-Dose PK Studes (CHS-1420-03, -05 and -07)

Table 60. Treatment-emergent Adverse Events with Incidence ≥ 2% in any Treatment Group by System Organ Class and Preferred Term (Pooled Studies, Safety Population)

System Organ Class / Preferred Term	CHS-1420 (N = 437) n (%)	U.S.-Humira (N = 103) n (%)	Humira Total (N = 211)[a] n (%)	Overall Total (N = 648) n (%)
Subjects with at Least One Event				
Subjects with any TEAEs	165 (37.8)	39 (37.9)	104 (49.3)	269 (41.5)
Gastrointestinal disorders	26 (5.9)	5 (4.9)	19 (9.0)	45 (6.9)
• Abdominal tenderness	0	0	3 (1.4)	3 (0.5)
General disorders and administration site conditions	53 (12.1)	9 (8.7)	29 (13.7)	82 (12.7)
• Injection site erythema	20 (4.6)	1 (1.0)	15 (7.1)	35 (5.4)
• Injection site rash	3 (0.7)	6 (5.8)	7 (3.3)	10 (1.5)
• Injection site pruritus	5 (1.1)	0	3 (1.4)	8 (1.2)
Infections and infestations	47 (10.8)	11 (10.7)	21 (10.0)	68 (10.5)

• Upper respiratory tract infection	20 (4.6)	5 (4.9)	9 (4.3)	29 (4.5)
Investigations	10 (2.3)	0	17 (8.1)	27 (4.2)
• Weight increased	8 (1.8)	0	15 (7.1)	23 (3.5)
Musculoskeletal and connective tissue disorders	30 (6.9)	7 (6.8)	17 (8.1)	47 (7.3)
• Back pain	11 (2.5)	4 (3.9)	6 (2.8)	17 (2.6)
• Myalgia	9 (2.1)	0	4 (1.9)	13 (2.0)
Nervous system disorders	39 (8.9)	10 (9.7)	30 (14.2)	69 (10.6)
• Headache	28 (6.4)	9 (8.7)	26 (12.3)	54 (8.3)
• Dizziness	6 (1.4)	1 (1.0)	4 (1.9)	10 (1.5)
Reproductive system and breast disorders	1 (0.2)	1 (1.0)	6 (2.8)	7 (1.1)
• Dysmenorrhoea	0	0	3 (1.4)	3 (0.5)
Respiratory, thoracic and mediastinal disorders	21 (4.8)	3 (2.9)	11 (5.2)	32 (4.9)
• Oropharyngeal pain	5 (1.1)	0	4 (1.9)	9 (1.4)

Studies included: CHS-1420-03, CHS-1420-05, CHS-1420-07
EU = European Union; TEAE = treatment-emergent adverse event; US = United States.
[a] The comparison of focus is between CHS-1420 and U.S.-Humira; data for EU-Humira have been removed, and Humira Total is provided for informational purposes only. U.S.-Humira was used in CHS-1420-03 and EU-Humira was used in CHS-1420-07. Neither U.S.-Humira nor EU-Humira were used in CHS-1420-05.
Source: Integrated Table 14.3.2.6.

"Drug-related" TEAEs

The "drug-related" TEAEs are those considered by Investigator to be at least possibly related to the study treatment. The following discussion includes events with occurrence in at least 2 subjects in any treatment arm.

CHS-1420-02

Treatment Period 1

Table 61. Drug-related Treatment-emergent Adverse Events Occurring in ≥ 2 Subjects by System Organ Class and Preferred Term (CHS-1420-02, Treatment Period 1, Safety Population)

System Organ Class / Preferred Term	CHS-1420 (N = 274) n (%)	U.S.-Humira (N = 271) n (%)

Subjects with at Least One Event		
Subjects with Any Drug-related TEAE	30 (10.9)	34 (12.5)
General disorders and administration site conditions	12 (4.4)	11 (4.1)
• Asthenia	0	2 (0.7)
• Injection site reaction	9 (3.3)	9 (3.3)
Infections and infestations	8 (2.9)	9 (3.3)
• Nasopharyngitis	1 (0.4)	4 (1.5)
• Oral Herpes	1 (0.4)	2 (0.7)
• Upper respiratory tract infection	2 (0.7)	2 (0.7)
Musculoskeletal and connective tissues disorders	3 (1.1)	1 (0.4)
• Arthralgia	2 (0.7)	1 (0.4)
Nervous system disorders	5 (1.8)	4 (1.5)
• Somnolence	2 (0.7)	1 (0.4)
Skin and subcutaneous tissue disorders	4 (1.5)	10 (3.7)
• Pruritus	0	2 (0.7)
• Psoriasis	1 (0.4)	5 (1.8)

N = number of subjects treated in the treatment period; n = number of subjects with events starting on or after the day of first dose of study drug of Treatment Period 1 and before first dose of study drug of Treatment Period 3; TEAE = treatment-emergent adverse event.

Note: Events with unknown relationship to study drug were counted as study drug-related.
Source: CHS-1420-02 CSR Post-text Table 14.3.1.4.1.

Treatment Period 2

During Treatment Period 2, overall, 8 (3.1%) subjects in the CHS-1420/CHS-1420 group, 1 (0.8%) subject in the Humira/CHS-1420 group, and 5 (3.8%) subjects in the Humira/Humira group experienced at least 1 TEAE considered drug-related by the Investigator.

All of the study drug-related TEAEs were experienced by <2% subjects in the Safety Population in this Treatment Period, and there were no notable differences among the 3 treatment groups.

Treatment Period 3

Table 62. Drug-related Treatment-emergent Adverse Events Occurring in ≥ 2 Subjects by System Organ Class and Preferred Term (CHS-1420-02, Treatment Period 3, Open Label Extension Population)

System Organ Class / Preferred Term	CHS-1420/ CHS-1420/ CHS-1420 (N = 235) n (%)	U.S.-Humira/ CHS-1420/ CHS-1420 (N = 113) n (%)	U.S.-Humira/ U.S.-Humira/ CHS-1420 (N = 126) n (%)
Subjects with at Least One Event			
Subjects with Any TEAE	11 (4.7)	10 (8.8)	7 (5.6)
Investigations	4 (1.7)	5 (4.4)	2 (1.6)
• Alanine aminotransferase increased	1 (0.4)	2 (1.8)	2 (1.6)
• Aspartate aminotransferase increased	0	1 (0.9)	2 (1.6)
• Interferon -γ release assay positive	3 (1.3)	2 (1.8)	0
Skin and subcutaneous tissue disorders	1 (0.4)	3 (2.7)	3 (2.4)
• Psoriasis	0	2 (1.8)	1 (0.8)

CHS-1420-04

Five subjects (3.5%) experienced a drug-related TEAE and only 1 PT was reported in ≥ 2 subjects (injection site erythema in 2 subjects [1.4%]).

Pooled Single-Dose PK Studes (CHS-1420-03, -05 and -07)

Table 63. Drug-Related Treatment-emergent Adverse Events Occurring in ≥ 2 Subjects in Either Treatment Group (Pooled Studies, Safety Population)

System Organ Class / Preferred Term	CHS-1420 (N = 437) n (%)	U.S.-Humira (N = 103) n (%)
Subjects with at Least One Event		
Subjects with any Drug-Related TEAE	74 (16.9)	10 (9.7)
Eye disorders	4 (0.9)	0
• Dry eye	2 (0.5)	0
Gastrointestinal disorders	13 (3.0)	0
• Nausea	5 (1.1)	0
• Abdominal pain lower	3 (0.7)	0
General disorders and administration site conditions	38 (8.7)	7 (6.8)
• Injection site erythema	19 (4.3)	1 (1.0)
• Injection site rash	3 (0.7)	5 (4.9)

• Injection site pruritus	5 (1.1)	0
• Injection site haemorrhage	5 (1.1)	0
• Feeling hot	2 (0.5)	0
• Injection site pain	2 (0.5)	0
• Fatigue	2 (0.5)	0
Infections and infestations	11 (2.5)	3 (2.9)
• Viral infection	3 (0.7)	0
• Herpes zoster	3 (0.7)	0
Metabolism and Nutrition Disorders	2 (0.5)	0
• Decreased appetite	2 (0.5)	0
Musculoskeletal and connective tissue disorders	12 (2.7)	0
• Myalgia	4 (0.9)	0
• Back pain	3 (0.7)	0
• Pain in extremity	2 (0.5)	0
Nervous system disorders	15 (3.4)	0
• Headache	11 (2.5)	0
• Dizziness	3 (0.7)	0
• Somnolence	2 (0.5)	0
• Psychiatric disorders	5 (1.1)	0
• Anxiety	3 (0.7)	0
Renal and urinary disorders	2 (0.5)	0 (0.0)
• Micturition urgency	2 (0.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	9 (2.1)	0
• Oropharyngeal pain	3 (0.7)	0
• Rhinitis allergic	2 (0.5)	0

Studies included: CHS-1420-03, CHS-1420-05, CHS-1420-07
TEAE = treatment-emergent adverse event; US = United States. Source: Integrated Table 14.3.3.6.

The safety data as shown by the TEAE Tables here and those in Section 6 are consistent, with demonstration that there are no clinically meaningful differences in safety between CHS-1420 and U.S.-Humira.

13.5.3. Information Request on Subject (b) (6) in CHS-1420-02

Subject (b) (6) in CHS-1420-02 appears to have had no administration of study product after initial loading dose until Treatment Period 3. FDA sent question in and Coherus answered to Information Request which was received on September 8, 2021. The Q and A are as follows:

Question 1

Subject (b) (6) in CHS-1420-02 was not administered study drug during the double-blind phase (Periods 1 and 2) except for the loading dose on Day 1, and yet did have efficacy, safety, and PK data. His serum drug level was sustained throughout the double-blind phase and this appears unlikely if adalimumab was not administered over Periods 1 and 2 after first dose.
Explain this discrepancy and rectify any errors in his eDiary, with possible adjustments on drug exposure in the datasets and listings.

Response to Question 1

Coherus acknowledges the missing data in the eDiary for subject (b) (6).

- *The subject had difficulties complying with the eDiary entries in Period 1 and Period 2 ("Viaphone" data entry). However, the subject confirmed verbally to the investigator site staff that the drug was administered but did not consistently specify date and time of dosing.*
- *The sustained serum drug levels corroborate that the subject administered the study drug in Period 1 and Period 2.*
- *The subject was compliant with clinical study visits and assessments and efficacy/safety data are currently included in the datasets and listings.*
- *Finally, the eDiary was designed such that data could not be entered retrospectively.*

Based on information above, amending the eDiary and adjusting drug exposure in the datasets and listings are not possible or justified.

The Agency notes that this subject most likely did receive the assigned treatment despite lacking product administration information in the datasets for Treatment Periods 1 and 2. The subject was considered to have completed study, and has already been included in the intent-to-treat analysis.

13.5.4. Schedule of Procedures for CHS1420-02

Table 1: Schedule of Procedures Screening through Week 16

		Treatment Period 1					
	Screening [a]	Baseline/ Randomi-zation/ Dosing [b]					
Day	**-28 to 0**	**0**	**Day 14**	**28, 56**	**42, 70**	**84**	**112**
Week	**-4 to 0**	**0**	**2**	**4, 8**	**6, 10**	**12**	**16**
Window			**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Informed consent	X						
Medical/surgical history and review CXR [c]	X						
Physical examination [d]	X	X	X	X	X	X	X
Injection site assessment [e]		X	X	X	X	X	X
Height [f] and weight	X						
BSA affected by chronic PsO	X						
Vital signs [g]	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X
12-lead ECG	X	X[h]					X
hs-CRP for subjects with PsA (only)		X				X	X
Hematology	X	X[h]		X		X	X
Chemistry	X	X[h]		X		X	X
Urinalysis[i]	X	X[h]		X		X	X
Viral screening (HBsAg, HBcAb, HCV, HIV)[k]	X						
QuantiFERON®-TB Gold[l]	X						
Serum sample for ADA testing		X	X	X		X	X
Serum sample (retention sample)[m]		X	X	X		X	X
Urine pregnancy test[n]	X	X	X	X		X	X
PASI assessment[o]	X	X	X	X	X	X	X
PSGA[p]	X	X	X	X	X	X	X
SGA of Psoriasis[p]	X	X	X	X	X	X	X
DLQI		X				X	
EQ-5D		X				X	
HAQ-DI for subjects with PsA (only)		X				X	X
Assess AEs		X	X	X	X	X	X
eDiary review and compliance evaluation			X	X	X	X	X

Table 1 (Continued): Schedule of Procedures Screening Through Week 16

		Treatment Period 1					
	Screening [a]	Baseline/ Randomi-zation/ Dosing [b]					
Day	**-28 to 0**	**0**	**Day 14**	**28, 56**	**42, 70**	**84**	**112**
Week	**-4 to 0**	**0**	**2**	**4, 8**	**6, 10**	**12**	**16**
Window			**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Contact IxRS	X	X		X (4 only)		X	X
Dispense study drug and/or collect unused study drug and/or Perform drug accountability [q]		X		X (4 only)		X	X
Perform injection training		X					
Perform eDiary registration and training		X					
Administer study drug [r]		X					

Table 2: Schedule of Procedures Week 17 through Week 24

	Treatment Period 2	
Day	**140**	**168**
Week	**20**	**24**
Window	**±3 days**	**±3 days**
Physical examination[d]	X	X
Injection site assessment[e]	X	X
Weight		X
Vital signs[g]	X	X
Prior/concomitant medications	X	X
12-lead ECG		X
hs-CRP for subjects with PsA (only)		X
Hematology	X	X
Chemistry	X	X
Urinalysis[j]	X	X
QuantiFERON®-TB Gold[l]		X
Serum sample for ADA testing	X	X
Serum sample (retention sample)[m]	X	X
Urine pregnancy test[n]	X	X
PASI assessment[o]	X	X
PSGA[p]	X	X
SGA of Psoriasis[p]	X	X
DLQI		X
EQ-5D		X
HAQ-DI for subjects with PsA (only)		X
Assess AEs	X	X
eDiary review and/or compliance evaluation	X	X
Contact IxRS		X
Dispense study drug and/or collect unused study drug and/or Perform drug accountability [q]		X

Table 3: Schedule of Procedures Week 25 through Week 48 and Follow-up or Early Termination Visits

	Treatment Period 3			Follow-up (or ET Visit)
Day	**224**	**280**	**336**	**392 (or 56 Days Post Last dose)**
Week	**32**	**40**	**48**	**55 (8 Weeks post last dose)**
Window	**±1 week**	**±1week**	**+/- 1 week**	**±1 week**
Physical examination[d]	X	X	X	X
Injection site assessment[e]	X	X	X	X
Weight	X	X	X	X[i]
Vital signs[g]	X	X	X	X
Prior/concomitant medications	X	X	X	X
12-lead ECG		X	X	X[i]
hs-CRP for subjects with PsA (only)		X	X	X[s]
Hematology	X	X	X	X[i]
Chemistry	X	X	X	X[i]
Urinalysis[j]	X	X	X	X[i]
QuantiFERON®-TB Gold[l]				X
Serum sample for ADA testing	X	X	X	X
Serum sample (retention sample)[m]	X	X	X	X
Urine pregnancy test[n]	X	X	X	X
PASI assessment[o]	X	X	X	X[s]
PSGA[p]	X	X	X	X[s]
SGA of Psoriasis[p]	X	X	X	X[s]
DLQI				X[s]
EQ-5D				X[s]
HAQ-DI for subjects with PsA (only)		X	X	X[s]
Assess AEs	X	X	X	X
eDiary review and/or compliance evaluation	X	X	X	X
Contact IxRS	X	X		X
Dispense study drug and/or collect unused study drug and/or Perform drug accountability [q]	X	X	X	X

FOOTNOTES TO TABLES 1-3

a All Screening assessments should be completed prior to randomization.
b The first dosing of study drug should occur at the Baseline/Randomization Visit (Week 0/Day 0).
c Obtain a medical/surgical history to include PsA, allergies (including drug, latex, food, and insect venom allergies), recent illnesses, prior illnesses of clinical significance, dates of procedures and of onsets and resolution of illnesses/conditions, and current statuses of illnesses/conditions and nicotine and alcohol use. Review findings from a CXR obtained in the previous 6 months and any viral tests performed within the previous 3 months.
d A complete physical examination will be conducted at Screening that will consist of general, head, eyes, ears, nose, throat, respiratory, gastrointestinal, extremity, musculoskeletal, cardiovascular, nervous system, lymph node, and dermatologic evaluations and height, weight, BSA, and any other physical conditions of note. At subsequent visits, abbreviated physical examinations will be performed by the Investigator or clinically trained designee that will include vital signs and evaluations of skin and joints and cardiovascular, respiratory, neurologic, and any other systems associated with the subject's complaints or AEs. The Week 0/Day 0 examination will be performed pre- randomization. Percentage of BSA affected by chronic PsO, PASI score, and PSGA may also be assessed during physical examinations at post-Screening visits.
e Injection site assessments will occur at the study site for 2 hours after the first dose of study drug. At each subsequent study visit, all injection sites (current and previous) should be assessed and findings recorded in the medical record and in the AE eCRF. For each injection site, the presence of pain/tenderness, erythema/redness, induration/swelling, pruritus/itching and hematoma/ecchymosis/bruising should be recorded.
f Measurement of height does not have to be repeated after Screening.
g Vital signs include blood pressure (use of arm or wrist cuff is acceptable), heart rate, respiratory rate, and temperature (use of oral, aural, or axillary thermometer is acceptable) and are to be performed after the subject has been seated for at least 5 minutes.
h The 12-lead ECG and chemistry, hematology, and urinalysis test collections are to be performed Week 0/Day 0 (pre- randomization) unless Screening tests were obtained within 2 weeks of starting study drug, in which case they do not have to be repeated, and Screening values may be used as Baseline values. ECGs and chemistry, hematology, and urinalysis tests are discussed in Sections 7.2.5, 7.2.7, 7.2.8, and 7.2.9, respectively.
i The following do not need to be repeated at the ET visit 56 days (8 weeks) after the last dose if obtained within 4 weeks of visit: weight, 12-lead ECG (and results were not abnormal and of clinical concern) and chemistry, hematology, and urinalysis tests (and results were within the normal reference ranges or within the specified allowed range for the protocol [e.g., liver function test results within 2 × ULN]).
j A urine microscopic examination will be performed when any of the following 3 dipstick results are abnormal: leukocyte esterase, blood, or nitrite.
k A subject's HIV and hepatitis screen test values that have been obtained by the investigational site within 3 months prior to Screening may be used as Screening values. In accordance with local regulations, an additional consent will be obtained for HIV testing.
l QuantiFERON-TB Gold test will be performed during Screening, at Week 24 and *if the subject discontinues study participation* at an ET visit 56 days (8 weeks) after the last dose of study drug (unless it has been reported in the previous 3 months). Additional monitoring may be performed as indicated in regions with high incidences of TB or to evaluate signs and symptoms that might be due to TB. If the test is positive for TB, perform a CXR to confirm diagnosis.
m Blood samples will be collected and serum retained at Week 0/Day 0 (pre- randomization); at Weeks 2,4,8,12,16,20, 24, 32, 40, 48 and at Follow Up Visit; and, if the subject discontinues study participation, at ET visit 56 days (8 weeks) after the last dose of study drug. Retained serum may be used for evaluation of AEs and adalimumab serum concentrations in conjunction with assessment of AEs, loss of response, or compliance; to correlate with ADA assay results; or to meet any other regulatory requirement. The exact date and time of each sample collection will be recorded.
n Urine pregnancy tests will be performed on women of childbearing potential at Screening; Week 0/Day 0 (pre-randomization); at Weeks 2, 4 ,8, 12,16, 20, 24, 32, 40, 48 and Follow Up Visit; and, *if the subject discontinues study participation*, at an ET visit 56 days (8 weeks) after the last dose.
o PASI assessments will be performed at Screening; Week 0/Day 0 (pre- randomization); at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 48 and, *if the subject discontinues study participation before Week 48*, at an ET visit 56 days (8 weeks) after the last dose of study drug.
p PSGA should be performed before the SGA and both should be performed at Randomization (Week 0/Day 0) and Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 48; and, *if the subject discontinues study participation* at an ET visit 56 days (8 weeks) after the last dose of study drug.
q Study drug will be dispensed at Week 0/Day 0 and at Weeks 4, 12, 16, 24, 32 and 40 all unused study drug will be collected at the end of Treatment Period 1, 2 and 3.Study Drug accountability will be performed at weeks 4, 12, 16, 24.32.40 and 48
r The first dose of study drug (2 injections) should be self-administered by the subject or administered by a caregiver at the investigative site and following training. Drug will be dispensed at Weeks 0, 4, 12, 16, 24, 32 and 40 only. Subsequent doses (single injections) will be self-administered or be administered by a caregiver at home every other week from Week 1 through Week 47 .Used syringes will be placed in the provided sharps container and brought to the clinic for replacement once the sharps container is full.
s Unless obtained at the Week 12 or 16 visit (for subjects discontinuing study participation during Treatment Period 1) or at the Week 24 visit (for subjects discontinuing study participation during Treatment Period: Obtain, blood sample for hs-CRP for subjects with PsA; Perform PASI, PGA and SPGA assessment; Administer HAQ-DI for subjects with PsA; Administer DLQI; Administer EQ-5D;

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

PHARMACOLOGY/TOXICOLOGY BLA ASSESSMENT AND EVALUATION

Application Number*:	761216
Supporting Document Number/s:	1, 7, 21
CDER Receipt Date:	12/18/2020, 3/18/2021, 9/28/2021
Applicant:	Coherus Biosciences, Inc.
Product:	Yusimry (CHS-1420, Adalimumab-aqvh)
Pharmacologic Class:	Tumor Necrosis Factor (TNF) blocker
Indication:	treatment of Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps)
Therapeutic area:	Rheumatology
Clinical Review Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Xiaochun Chen, PhD
Team Leader:	Carol Galvis, PhD
Project Manager:	Elaine Sit, PharmD
Purpose of Review:	Other
If "Other":	Safety Assessment of Extractables and Leachables Studies
Alternative Assays:	None
Reviewer Completion Date:	October 6, 2021

Template Version: Sep 11, 2020

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Coherus Biosciences, Inc. submitted a 351(k) Biologics License Application (BLA) on December 20, 2020, for Yusimry (CHS-1420), a proposed biosimilar to [Humira®] (40 mg injection). Like Humira®, Yusimry is indicated for the treatment of Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps). The extractables and leachables study reports were submitted on December 20, 2020 and March 18, 2021.

The CHS-1420 drug substance (DS) (b) (4) The drug product (DP) is packaged in Prefilled Syringe (PFS, 40 mg/0.8 mL). The primary CCS for PFS includes a (b) (4) staked-in needle 1-mL-long glass PFS stoppered with a (b) (4) plunger stopper. The CCSs contain a formulation of 40 mg CHS-1420 (active pharmaceutical ingredient, API) in 0.8 mL of solution (0.638 mg/mL L-histidine, 5.43 mg/mL L-histidine HCl monohydrate, 12.0 mg/mL glycine, 2.58 mg/mL sodium chloride, 1 mg/mL polysorbate 80 and water for injection) designed for subcutaneous injection. The sponsor provided forced extraction and leachable studies reports of the CCS components.

This review is a nonclinical safety evaluation of potential extractables and leachables for the primary CCSs and in-process materials used in the DS and DP manufacture processes. Leachables from DP during stability study and safety assessment are also reviewed.

1.2 Brief Discussion of Nonclinical Findings

(b) (4)

For the safety evaluation of PFS, components that have direct/potential contact with DS include (b) (4) stopper/plunger stopper, (b) (4) 260 rigid needle shield (RNS), glass barrel, syringe needle, and needle adhesive. The sponsor provided extractable study reports/results by the vendor (b) (4) for these components extracted by (b) (4)

(b) (4)

The sponsor also completed a definitive leachable study with CHS-1420 DP batch# 3-FIN-2587 (b) (4) mg/mL, 0.8 mL/PFS) stored at accelerated conditions (25°C/60%RH) for 6-months and long-term storage conditions (5°C/ambient RH) for up to 36 months.

The above extractable and leachable studies were performed/analyzed under presumably the worst-case scenario. In general, any organic (nonmetal) compound with expected patient exposure below the Qualification Threshold (QT) of (b) (4) µg/day for compounds lacking genotoxic potential and irritant potential or the Safety Concern Threshold (SCT) of (b) (4) µg/day for compounds with genotoxic potential as recommended by Product Quality Research Institute (PQRI) was considered qualified for safety. The maximum maintenance dose of CHS-1420 is 40 mg once a week (QW) or 80 mg once every 2 weeks (Q2W) via subcutaneous (SC) route. The level of exposure to potential extractables/leachables is the same for the 2 regimens. To simplify the description, the 80 mg Q2W regimen will be referred throughout the rest of this report for assessment. The Threshold of Toxicological Concern (TTC) was established as (b) (4) µg/day for organic compounds with genotoxic potential as described in ICH M7 (2018) for chronic, non-daily (> 1 − 10 dose*years) exposure. Accordingly, the highest limit of detection (LOD) will be around (b) (4) µg/mL for all the validated analytical methods for the organic compounds with genotoxic potential for the maximal dose volume of (b) (4) mL/day ((b) (4) mg loading dose, the worst-case scenario). For metals, the Guideline for Elemental Impurities (ICH Q3D, 2014) was followed for safety assessment.

All organic extractables from the primary CHS-1420 DS CCS were well below or close to the TTC of (b) (4) µg/day, as a conservative approach, the following extractables were selected for monitoring in leachables study: (b) (4)

These 3 compounds were monitored under “unknown leachables” category in the leachable study (Report # FR-SP-0084-R05).

Extractables from the primary CHS-1420 DP CCSs selected for monitoring in leachables study included (b) (4)

category in the leachable study (Report # FR-SP-0083-R06).

In the leachable stability study, no leachables were above the TTC or Permitted Daily Exposure (PDE). Overall, it appears that the maximum exposures of all the leachables from the CCSs and in-process materials during the manufacture processes are considered safe.

2 Drug Information

2.1 Drug

Code Name(s): CHS-1420

CAS Registry Number(s): 331731-18-1

Generic Name: Adalimumab (Humira®) biosimilar

Chemical Name: N/A

Molecular Formula/Molecular Weight: ~ 148 kDa

Structure or Biochemical Description:

CHS-1420 is a human monoclonal IgG1 kappa antibody composed of two light (L) chains and two heavy (H) chains, covalently linked with four inter-chain disulfide bonds. The drug substance of CHS-1420 originates from a cell culture bioprocess using a recombinant Chinese Hamster Ovary (CHO) cell line. The complete, experimentally confirmed amino acid sequence of CHS-1420 is shown in Figure 1 (excerpted from the sponsor's submission). Each light chain consists of 214 amino acid residues and each heavy chain consists of 450 amino acid residues.

Figure 1: CHS-1420 Primary Structure (Amino Acid Sequence)

DIQMTQSPSS LSASVGDRVT ITCRASQGIR NYLAWYQQKP GKAPKLLIYA
ASTLQSGVPS RFSGSGSGTD FTLTISSLQP EDVATYYCQR YNRAPYTFGQ
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC

EVQLVESGGG LVQPGRSLRL SCAASGFTFD DYAMHWVRQA PGKGLEWVSA
ITWNSGHIDY ADSVEGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAKVS
YLSTASSLDY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ
TYICNVNHKP SNTKVDKKVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP
QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP
VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG
K

Legend: Blue = the sequence for each heavy chain; Red = the sequence for each light chain; Yellow boxes = Cysteines; Green box = N-linked glycan sites (Asn301) in the Fc region of each heavy chain.

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 119540 for CHS-1420
- BLA 761039 (Udenyca®, pegfilgrastim-cbqv, CHS-1701 for Coherus): FDA's previous finding to support the safety of extractabes and leachables from the primary DS and DP CCSs
- DMF (b) (4)
- DMF
- DMF
- DMF
- DMF
- DMF
- DMF

Statements of the right to reference the DMFs were provided by letter of authorization (LOA) in the BLA.

2.3 Drug Formulation

The DP is provided as a sterile liquid formulation (40 mg CHS-1420, nominal, in 0.8 mL) intended for SC administration. The composition of the DP is described in Table 1 (excerpted from the sponsor's submission).

Table 1. Composition of CHS-1420 (Process D) Drug Product, for Injection

Ingredients	Reference to Standards	Function	Unit Formula	
			40 mg PFS (mg)	(mg/mL)
CHS-1420	Coherus	Drug Substance	40	50
L-Histidine	USP/ Ph. Eur. /JP	(b) (4)	0.51	0.638
L-Histidine HCl monohydrate	Ph. Eur. / JP		4.34	5.43
Glycine	USP/ Ph. Eur./ JP		9.61	12.0
Sodium chloride	USP/ Ph. Eur.		2.06	2.58
Polysorbate 80	NF/ Ph. Eur.		0.8	1
Water for injection	USP/ Ph. Eur.		qs to 0.8 mL	N/A
Sodium hydroxide*	NF / Ph. Eur. / JP	pH Adjustment	qs to pH 5.3	N/A

USP = United States Pharmacopoeia; Ph. Eur. = European Pharmacopoeia; JP = Japanese Pharmacopoeia; NF = National Formulary; qs = quantum sufficient, HCl = Hydrochloric Acid; N/A = Not Applicable; PFS = Prefilled Syringe

*: Added as necessary for pH adjustment (b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients present in the drug product formulation. Excipients are within the ranges that are found in the inactive ingredient database for FDA-approved SC products.

2.5 Comments on Extractables and Leachables Studies

CCS for DS: (b) (4) have direct contact with the DS during storage and are considered critical components for controlled extraction studies

and leachable studies. (b) (4) The compliance information for the CCS is provided in Table 2 (excerpted from the sponsor's submission).

Table 2. Container Closure Applicable Testing Standards for DS

Component	Compliance Information
(b) (4)	

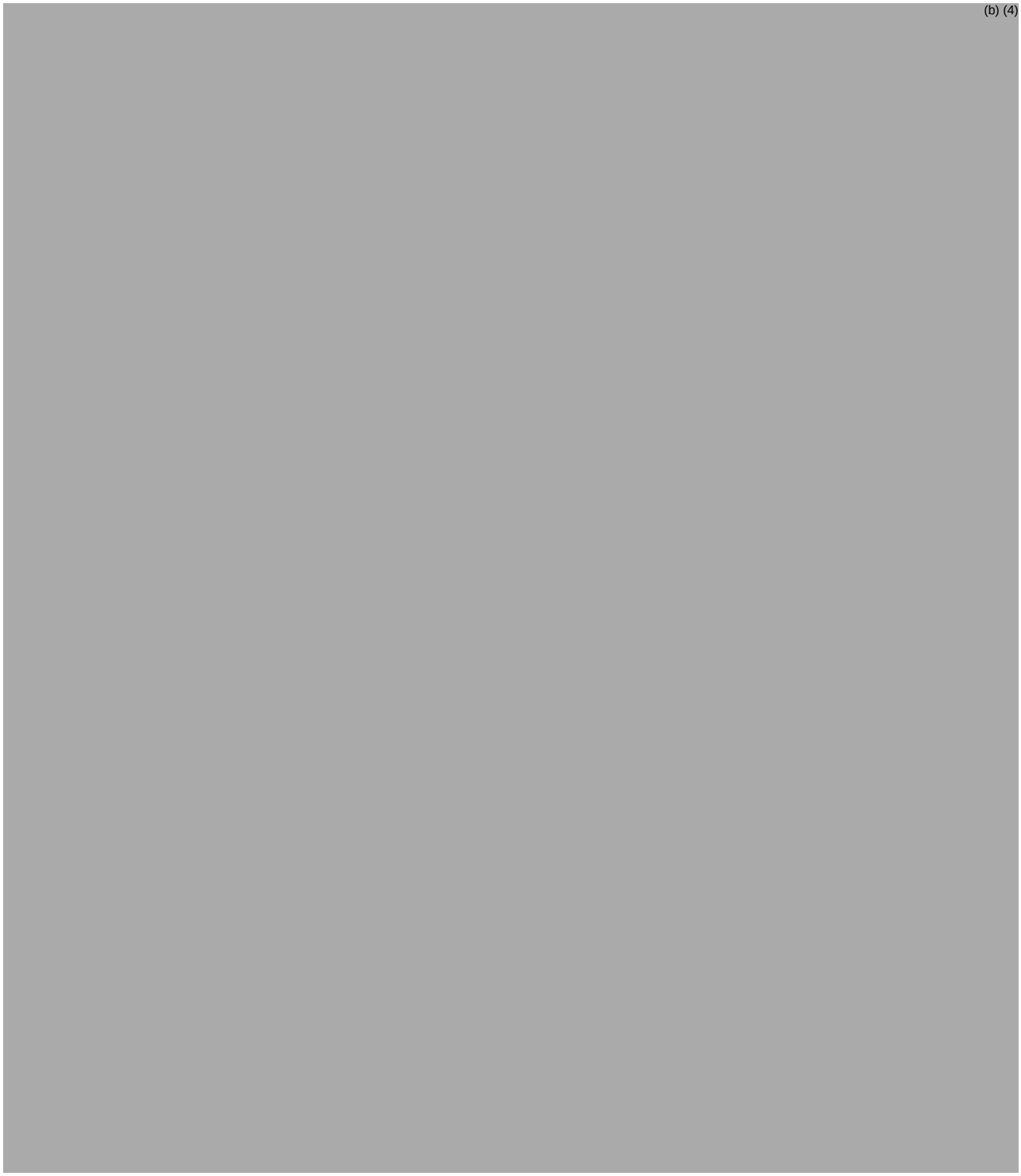
CCS for DP: The primary CCS for CHS-1420 40 mg PFS DP includes a 1-mL long (b) (4) glass syringes with a 29G ½" staked needle, (b) (4) RNS (non-latex) and (b) (4) rubber plunger stopper (Table 3, excerpted from the sponsor's submission). The syringe (Figure 2) and plunger stopper (Figure 3) are provided sterile, clean, and ready-to-use from the component manufacturers (excerpted from the sponsor's submission).

Table 3. Primary Container Closure System Components for DP

Component	Material of Construction	Manufacturer
(b) (4) 1-mL-long syringe barrel with a 29 gauge, ½-inch needle with (b) (4) rigid needle shield (RNS)	Glass Barrel: (b) (4) USP <660> Type (b) (4) Glass Needle: Stainless Steel (b) (4) RNS: (b) (4) Latex Free (b) (4) (b) (4) Lubricant: (b) (4) (b) (4)	(b) (4)
(b) (4) plunger stopper	(b) (4)	(b) (4)

Figure 2. Representative Drawing of the Syringe Barrel with Staked Needle and Rigid Needle Shield

Figure 3. Representative Drawing of the Plunger Stopper



The CHS-1420 finished product (FPP) contains the labeled CHS-1420 DP assembled with plunger rod and finger flange (PFS-FF), packaged in a sealed blister tray and contained in a carton box with Prescribing Information, Instructions for Use, and Medication Guide. Since the glass barrel, plunger stopper, staked needle, needle adhesive and RNS have direct/potential contact with formulation during storage or

dosing, they are considered critical components for controlled extraction studies and leachable studies.

This review is a nonclinical safety evaluation of potential extractables and leachables found in the above critical components. The sponsor also conducted additional leachables assessments for in-process materials used in the manufacture process for CHS-1420 DS and DP. Described in this section are the extractable and leachable studies and the results.

Extractable Studies

Methods:

The sponsor provided extractables studies reports for the critical components for CHS-1701 DS (Study Report # TR-0422 and Summary Report # FMEA-0020.00) and CHS-1701 DP (Study Report # TR-0421, TR-0423 and FR-VP-0221, and Summary Report # FMEA-0019.00). The CCSs for CHS-1701 DS and CHS-1701 DP are the same for CHS-1420 DS and CHS-1420 DP, respectively. CHS-1701 DS (b) (4)

(b) (4)

The methods used in these studies consisted of a set of forced extraction experiments followed by subsequent analyses of the extracts (b) (4)

(b) (4)

Glass barrel, staked needle, needle adhesive, plunger stopper, and RNS: The DMF (b) (4) for (b) (4) and DMF (b) (4) for (b) (4) plunger stopper have been referenced by many FDA -approved products. The current sponsor provided

the summary extraction study report (Report # FMEA-0019.00) for CHS-1701 DP which consists of the same critical components as CHS-1420, i.e. 1-mL long (b) (4) (b) (4) glass PFS with 29G ½" staked needle (glass barrel, stainless steel needle and needle adhesive), (b) (4) RNS, and (b) (4) rubber plunger. These components were (b) (4)

(b) (4)

(b) (4)

For (b) (4) glass syringe, needle, and needle adhesive: The sponsor referenced 3 (b) (4) study reports (2015) of potential extractables for each component in Report # FMEA-0019.00 for CHS-1701 DP. Another 3 extractable study reports for each component by (b) (4) were referenced in the CHS-1420 DP Extractable/Leachable Stability Summary Report (Coherus Report # FR-SP-0083-R06). Qualitative extractable data were provided.

For all DP CCSs extracted by the (b) (4) (Report # FR-VP-0221-R05): Plunger stopper (25), (b) (4) needle shield (25), and glass barrel + needle + needle adhesive (7) were extracted by (b) (4) . For plunger stopper and (b) (4) needle shield, 1g of each in pieces was placed in a GC glass vial and heated at 80 ºC for 30 minutes and analyzed by (HS)-GC/MS for SVOCs and VOCs.

Results:

(b) (4)

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I concur.