PROTOCOL SYNOPSIS

24/Aug/2022

Protocol Title	A Multicenter, Randomized, Blinded, Parallel Group, Interchangeability Study in Moderate to Severe Chronic Plaque Psoriasis evaluating Pharmacokinetics, Efficacy, Safety, and Immunogenicity Between Subjects Receiving Humira® Pre-filled Syringe (40 mg/0.4 mL) Continuously and Subjects Undergoing Repeated Switches Between Humira® Pre-filled Syringe (40 mg/0.4 mL) and Hulio® Pre-filled Syringe (40 mg/0.8 mL)
Short Title	Hulio® interchangeability to Humira®, comparing pharmacokinetics, efficacy, safety and immunogenicity
Protocol Number	ADA-IJZ-3001
Study Sites	This study is planned to enroll 370 subjects at approximately 36 study centers located in Europe.

Duration of Individual Treatment	The total duration of the study for an individual subject who completes the study according to the protocol will be up to 32 weeks (inclusive of Screening and follow-up safety assessment periods):
	• Screening period: up to [redacted] weeks
	• Run-in treatment period: 11 weeks of treatment with [redacted]
	• Randomized interchangeable treatment period: 16 weeks of treatment period consisting total of 3 switches
	  ○ Switch-1: [redacted] weeks
	  ○ Switch-2: [redacted] weeks
	  ○ Switch-3: [redacted] weeks
	• In addition, follow-up safety assessment period: 4 weeks (±1 week) post last dose of treatment received during the randomized treatment period
	Note: The last dose of study treatment administration will be at the beginning of Week 26.

End of Study	End of study will be considered when all the subjects complete the safety follow-up assessment period.
Background and Rationale	Hulio is a monoclonal antibody currently approved as a biosimilar to European Union approved and United States (US)-Licensed Humira. This is a multicenter, randomized blinded, parallel group, interchangeability study in subjects with moderate to severe chronic plaque psoriasis, undergoing repeated switches between Humira and Hulio. The study is designed to confirm the pharmacokinetic equivalence of alternating between the use of Humira and Hulio and, Humira without such alternation or switch, in accordance with the US Food and Drug Administration Guidance for

	Industry, Considerations in Demonstrating Interchangeability with a Reference Product. The study will also assess safety, efficacy and immunogenicity between these two groups.
Primary Objectives	To evaluate interchangeability of Hulio and Humira by examining adalimumab steady-state pharmacokinetics in a switching arm (following 3 switches between Humira and Hulio) as compared to a non-switching arm (receiving only Humira).
Primary Endpoint	**Primary Endpoints**: Pharmacokinetics (PK) $AUC_{\tau,\ 26\text{-}28}$ (Area under the adalimumab concentration-time curve [AUC] over the dosing interval of Week 26-28) $C_{max,\ 26\text{-}28}$ (Maximum observed adalimumab concentration during the dosing interval Week 26-28).
Secondary Objectives	To evaluate other serum adalimumab PK parameters, efficacy, immunogenicity, safety, and tolerability, in the switching arm and the non-switching arm.
Secondary Endpoints	Other adalimumab PK parameters, including $T_{max,\ 26\text{-}28}$ (Time to maximum observed adalimumab concentration during the dosing interval Week 26-28) and $C_{min,\ 26\text{-}28}$ (Minimum observed adalimumab concentration during the dosing interval Week 26-28) and C_{trough} obtained at scheduled PK sampling time points. Proportion of Psoriasis Area and Severity Index (PASI) 50, PASI 75, PASI 90 and PASI 100 responders at Week 28 Proportion of static Physician's Global Assessment (sPGA) success (clear or almost clear) at Week 28 Safety measures characterized by type, incidence, severity, timing, seriousness and relatedness of treatment-emergent adverse events (TEAEs) including injection site reactions, hypersensitivity reactions, heart failure, malignancies, serious infections including tuberculosis (TB) and laboratory test abnormalities Incidence of positive anti-drug antibody (ADA) and neutralizing antibody (NAb) response and ADA titers at Week 28
Methodology	This is a multicenter, randomized, blinded, parallel group, interchangeability study in moderate to severe chronic plaque psoriasis evaluating PK, efficacy, safety, and immunogenicity between subjects receiving Humira continuously and subjects undergoing repeated switches between Humira and Hulio. **Screening Period:** Subjects will be enrolled into the study after successfully completing screening activities between [redacted] (Screening visit).

Run-in Period:

Subjects will receive [redacted] ([redacted]/[redacted]) administered subcutaneously (SC), [redacted]

Randomized Interchangeable Treatment Period: Subjects achieving at least a PASI50 response at the start of [redacted] will be randomly assigned in a 1:1 ratio to either of the following groups for participation in the randomized interchangeable treatment period:

Group 1: Subjects continue to receive Humira (40 mg every other week) until Week 26/Visit 14

Group 2: Subjects undergo repeated switches until Week 26/Visit 14:

- [redacted] ([redacted] mg every other week) at [redacted]
- [redacted] ([redacted] mg every other week) at [redacted] and
- [redacted] ([redacted] mg every other week) at [redacted]

Randomization will be stratified based on [redacted] response: [redacted]

Administration of the study treatment may be performed with a window of [redacted] up to Week 10/Visit 6 (run-in period) and [redacted] from Week 12 /Visit 7 onwards.

The last efficacy and PK assessments will be at Week 28/Visit 15.

Follow-up safety assessment will be done 4 weeks post last dose of treatment received during the randomized treatment period (Follow-up safety assessments will be done at Week 30, before administration of treatment with 2nd optional dose of Hulio. If the subjects do not choose optional treatment with Hulio, follow-up safety assessments will be done after completion of 4 weeks from last dose of study treatment).

Additional Two Doses of Optional Hulio Treatment:

To ensure continuity of treatment and for benefit of the subjects during the safety follow up period, all the subjects with ≥PASI 50 at Week 28 (compared to baseline), from both treatment groups, will have an option of receiving Hulio for an additional two doses at Week 28 / Visit 15 and Week 30 / Visit 16. Administration of additional optional doses will be as per the discretion of the investigator and willingness of the subjects.

[redacted]

Pharmacokinetic Sampling:

A pharmacokinetic sample will be collected just prior to dosing (trough sample) at every dosing visit and at Week 28/Visit15.

	An intensive PK sampling will be conducted in a period of [redacted] between [redacted] (during the run-in period) and between Week 26/Visit 14 and Week 28/Visit 15 (during Switch 3). • The sampling time points will be [redacted], [redacted], and [redacted] after [redacted] dosing. A window period of [redacted] will be allowed. • The sampling time-points will be [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted] after the Week 26/Visit 14 dosing. A window period of [redacted] will be allowed. **Immunogenicity Sampling**: Blood samples will be collected for immunogenicity testing (anti-adalimumab antibodies) prior to dosing at [redacted], [redacted], [redacted], [redacted] and at [redacted]. Additionally, immunogenicity samples will be collected whenever a subject reports an AE consistent with the diagnosis of anaphylaxis as per World Allergy Organization (WAO) Amended criteria for the diagnosis of anaphylaxis.
Study Treatment	**Test Product:** Hulio®, (adalimumab-fkjp) 40mg/0.8mL pre-filled syringe (HULIO® Pre-filled syringe). **Reference Product:** Humira® (adalimumab) 40mg/0.4mL pre-filled syringe (HUMIRA® Pre-filled syringe). US-Licensed Humira is planned to be used as reference product.
Inclusion/ Exclusion Criteria	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study: 1. Able to understand and voluntarily provide written informed consent to participate in the study 2. Aged 18 to 75 years, inclusive, at the time of Screening 3. Has moderate to severe chronic plaque psoriasis for at least 6 months prior to screening and that has involved body surface area ≥10%, PASI ≥12, and static Physicians Global Assessment (sPGA) ≥3 (moderate) at Screening and at Baseline 4. Has stable disease for at least 2 months (i.e., without significant changes as defined by the principal investigator [PI] or designee) 5. Is a candidate for systemic therapy or phototherapy 6. Has a previous failure, inadequate response, intolerance, or contraindication to at least 1 conventional antipsoriatic systemic therapy, including methotrexate, cyclosporine, psoralen plus ultraviolet light A (PUVA), and ultraviolet light B (UVB) 7. Willing to follow the contraception requirement, based on the childbearing potential, [redacted].

Exclusion Criteria:

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Has been diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (e.g., eczema), or other systemic autoimmune disorder/ inflammatory disease at the time of the Screening visit that would interfere with evaluations of the effect of the study treatment of psoriasis
2. Prior and concomitant medications: Has prior use of any of the following medications within specified time periods or will require use during the study:
   a. Topical medications within 2 weeks of baseline (Week 1)
   b. Psoralen plus ultraviolet light A (PUVA) phototherapy and/or ultraviolet light B (UVB) phototherapy within 4 weeks prior to Baseline visit
   c. Nonbiologic psoriasis systemic therapies (eg, cyclosporine, methotrexate, and acitretin) within 4 weeks prior to Baseline visit
   d. Any prior or concomitant adalimumab therapy, either approved or investigational
   e. Any systemic steroid in the 4 weeks prior to Baseline Visit
   f. Specified washout periods are as follows:
      i) Investigational agent(s) within 90 days or 5 half-lives (whichever is longer) before Baseline (Week 1)
      ii) Refer to the following table for approved/marketed products

Approved/Marketed Products

Medication or Therapy	Washout [redacted]
Biologic Therapies: [redacted]	Not allowed [redacted] weeks [redacted] weeks [redacted] weeks [redacted] weeks [redacted] weeks [redacted] weeks [redacted] weeks [redacted] weeks
[redacted]	[redacted] weeks
[redacted]	[redacted] weeks
[redacted]	[redacted] weeks
[redacted]	[redacted] weeks
[redacted]	[redacted] weeks
[redacted]	[redacted] weeks

[redacted]

	Note: Low-potency topical corticosteroids applied to the palms, soles, face, and intertriginous areas are permitted during study participation. 3. Has received live or attenuated vaccines during the 4 weeks prior to Screening or has the intention of receiving a live or attenuated vaccine at any time during the study 4. Other medical conditions: Known chronic or relevant acute TB; interferon-γ release assay (IGRA) TB test or purified protein derivative (PPD) skin test will be performed according to the labelling for Humira. If the result is positive, patients may participate in the trial if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB. If latent TB is confirmed, then treatment must have been initiated before treatment in the study and continued according to local country guidelines. 5. Has an underlying condition (including, but not limited to, metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious, or gastrointestinal) which, in the opinion of the PI or designee, significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy 6. Has a planned surgical intervention during the duration of the study and which, in the opinion of the PI or designee, will put the subject at further risk or hinder the subject's ability to maintain compliance with study treatment and the visit schedule 7. Has any active and serious infection or history of infections as follows: a) Any active infection • For which non-systemic anti-infectives were used within 4 weeks prior to enrollment. Note: Subjects receiving topical antibiotics for facial acne do not need to be excluded. • Which required hospitalization or systemic anti-infectives within 8 weeks prior to enrollment b) Recurrent or chronic infections or other active infection that, in the opinion of the PI or designee, might cause this study to be detrimental to the subject c) Invasive fungal infection or mycobacterial infection d) Opportunistic infections, such as listeriosis, legionellosis, or pneumocystis 8. Is positive for human immunodeficiency virus (HIV), hepatitis C virus antibody, or hepatitis B surface antigen (HbsAg) or is positive for hepatitis B core antibody at Screening 9. Has laboratory abnormalities, including but not limited to clinically significant hematological abnormalities, that, in the opinion of the PI or designee, could

	cause this study to be detrimental to the subject. The subjects should be excluded if they have the following laboratory abnormalities a. Hemoglobin <9 g/dL b. Platelet count <100 000/mm^3 c. White blood cell count <3000 cells/mm^3 d. Aspartate aminotransferase and/or alanine aminotransferase that is persistently ≥2.5 × the upper limit of normal. (Persistently indicates elevated transaminases, at least on two separate occasions) e. Creatinine clearance <50 mL/min (Cockcroft-Gault formula) 10. Has severe progressive or uncontrolled, clinically significant disease that in the judgment of the PI or designee renders the subject unsuitable for the study 11. Has a history of malignancy within 5 years except for adequately treated cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma 12. Has an active neurological disease, such as multiple sclerosis, Guillain-Barré syndrome, optic neuritis, and transverse myelitis, or a history of neurologic symptoms suggestive of central nervous system demyelinating disease 13. Has moderate to severe heart failure (New York Heart Association [NYHA] Class III/IV) 14. Has a history of hypersensitivity to the active substance or to any of the excipients of Humira or Hulio 15. Is pregnant or nursing (lactating) woman 16. Has evidence (as assessed by the PI or designee using good clinical judgment) of alcohol or drug abuse or dependency up to 5 years prior to Screening 17. Is unable to follow study instructions and comply with the protocol in the opinion of the PI or designee.
Planned Number of Subjects	[redacted] evaluable participants) would provide 90% power to demonstrate that the 90% confidence intervals (CIs) for the MR are within 80.00% to 125.00% for both primary PK parameters. This study is planned to [redacted] subjects, [redacted] To account for 10% run-in failures, approximately 370 subjects will be enrolled into the study.
Statistical Methods	**Analysis Set**: All Subject Enrolled population: All subjects who provide informed consent for this study.

	Run-in Period population: All enrolled subjects who received at least one dose of Humira in the run-in period. Safety population: All subjects who received at least one dose of randomized study medication. Per Protocol (PP) population: All randomized subjects in the Safety population who have assessments prior to randomization and at least once post-randomization for at least one secondary efficacy endpoint and who do not have any important protocol violations impacting efficacy. PK population: All subjects, who provide at least one primary PK parameter without protocol violation relevant for primary endpoint evaluation **Pharmacokinetic Analysis**: Serum concentrations of Hulio and Humira will be summarized at each scheduled sampling time. Mean serum concentration time profiles of Hulio and Humira will be plotted on linear and semilogarithmic scales based on scheduled sampling times. Individual concentrations and actual sampling times will be presented in a listing by treatment. The statistical model used for the analysis of $AUC\tau_{,\ 26\text{-}28}$ and $C_{max,\ 26\text{-}28}$ will be an analysis of covariance (ANCOVA) model on the original scale. This model will include treatment and covariates: 1. Treatment = fixed treatment effect variable 2. LNrPASI= natural Logarithm of rPASI, where rPASI is the ratio of PASI at Week 12 and PASI at Week 1 (covariate variable) 3. Weight12 = weight at Week 12 (covariate variable) 4. $AUC_{\tau,\ 10\text{-}12}$ or $C_{max,\ 10\text{-}12}$ = AUC or C_{max} at week 10 – Week 12 (covariate variables) All covariates will be measured prior to randomization and all subjects will have received the same treatment with the reference treatment only, the covariates listed above are all considered baseline values for treatment effect comparison. The model is described by the following equation: $AUC_{\tau,\ 26\text{-}28}$ or $C_{max,\ 26\text{-}28}$ = treatment + LNrPASI + weight12 + $AUC_{\tau,\ 10\text{-}12}$ or $C_{max,\ 10\text{-}12}$ The model will be implemented with the SAS® procedure PROC MIXED in conjunction with the LSMEANS statement. The LSMEANS statement is used to estimate the treatment effect. LSMeans of the switching and non-switching arm which will be used to construct the point estimate for the ratio of means. The 90% CI will be derived based on Fieller's theorem. Bioequivalence can be claimed when the 90% CIs are within 80%-125% for both $AUC_{\tau,\ 26\text{-}28}$ and $C_{max,\ 26\text{-}28}$. **Sensitivity Analyses**: The $AUC\tau_{,\ 26\text{-}28}$ and $C_{max,\ 26\text{-}28}$ will be analysed using analysis of covariance (ANCOVA) model on the log transformed scale. This model will include treatment and covariates. Log transformed $AUC_{\tau,\ 10\text{-}12}$ or $C_{max,\ 10\text{-}12}$ will be used as covariates.

	The secondary PK endpoint $C_{min\ 26\text{-}28}$ will be analyzed in the same way as the primary endpoints. However, even the mean ratio and CIs will be calculated and presented. No formal conclusion is required to be within BE limits. The secondary PK endpoint $T_{max\ 26\text{-}28}$ will be analyzed in a descriptive manner only. All PK analysis will be performed on the PK population. **Efficacy Analysis**: All secondary efficacy endpoint analyses will be based on the PP population. The difference in proportions will be calculated as the difference between the observed proportions in each treatment group. An asymptotic 2-sided 90% confidence interval for the difference of proportions will be obtained using the Wald method. **Safety Analyses**: Treatment-emergent AEs, serious AEs and Adverse event of special interest (AESI) will be descriptively summarized by system organ class, preferred term, and treatment group. Overall, descriptive summaries will be produced as well as according to severity and relationship to the study treatment. Local tolerance and antibodies to adalimumab will be descriptively summarized by treatment group. The safety analyses will be performed on the Safety and Run-in Period populations.