STATISTICAL ANALYSIS PLAN

ADA-IJZ-3001

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)

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibody
AEs	Adverse Events
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Adalimumab Concentration-time Curve
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum Observed Adalimumab Concentration
C_{min}	Minimum Observed Adalimumab Concentration
COVID-19	Coronavirus disease 2019
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ENR	All Patient Enrolled
EOS	End of study
EOT	End of treatment
ET	Early termination

HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
IGRA	Interferon γ release assay
ISR	Injection Site Reaction
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MR	Mean Ratio
NAb	Neutralizing antibody
NYHA	New York Heart Association
PASI	Psoriasis area and severity index
PD	Protocol Deviation
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred term
SAEs	Serious adverse events
SAF	Safety
SAP	Statistical Analysis Plan
SC	Subcutaneously

SD	Standard deviation
SOC	System organ class
sPGA	Static physicians global assessment
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
T_{max}	Time to maximum observed adalimumab concentration
WHO	World health organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of pharmacokinetics, efficacy, safety, and immunogenicity data for Protocol ADA-IJZ-3001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 2.0, dated 24 Aug 2022.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective is to evaluate interchangeability of Hulio and Humira by examining adalimumab steady-state PK in a switching arm (following 3 switches between Humira and Hulio) as compared to a non-switching arm (receiving only Humira).

2.1.2. Secondary Objectives

The secondary objective is to evaluate other serum adalimumab PK parameters, efficacy, immunogenicity, safety, and tolerability, in the switching arm and the non-switching arm.

2.1.3. Other Objectives

Not applicable.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints include the assessment of the below mentioned pharmacokinetic parameters:

- $AUC_{\tau, 26\text{-}28}$ (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 of Week 26-28).

2.2.2. Secondary Endpoints

The secondary endpoints are:

- Other adalimumab PK parameters, including Tmax, 26-28 and Cmin, 26-28 during the intensive PK sampling interval between Weeks 26 and 28 and Ctrough obtained at the scheduled PK sample time points.
- Proportion of PASI 50, PASI 75, PASI 90 and PASI 100 responders at Week 28
- Proportion of 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 [ISRs], 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

3. STUDY DESIGN

3.1. General Description

This is a multicenter, randomized, blinded, parallel group, interchangeability study in moderate to severe chronic plaque psoriasis evaluating PK, efficacy, safety, and immunogenicity between patients receiving Humira continuously and patients undergoing repeated switches between Humira and Hulio.
A study schema is provided in Table A – Study Diagram.
This study is planned to enroll 370 patients at approximately 36 study centers located in Europe. The total duration of the study for an individual patient 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:
Patients will be enrolled into the study after successfully completing screening activities between Day -21 to Day -1.
Run-in Period:
Patients will receive Humira (initial dose of 80 mg [2 × 40 mg]; Day 1, Week 1) administered subcutaneously (SC), followed by 40 mg SC given every other week starting 1 week after the initial dose (last dose at Week 10/Visit 6).

Randomized Interchangeable Treatment Period:

Patients achieving at least a PASI 50 response at beginning of Week 12 /Visit 7 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: Patients continue to receive Humira (40 mg every other week) until Week 26 /Visit 14.

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

- Hulio (40 mg every other week) for 4 weeks,
- Humira (40 mg every other week) for 4 weeks, and
- Hulio (40 mg every other week) for 8 weeks.

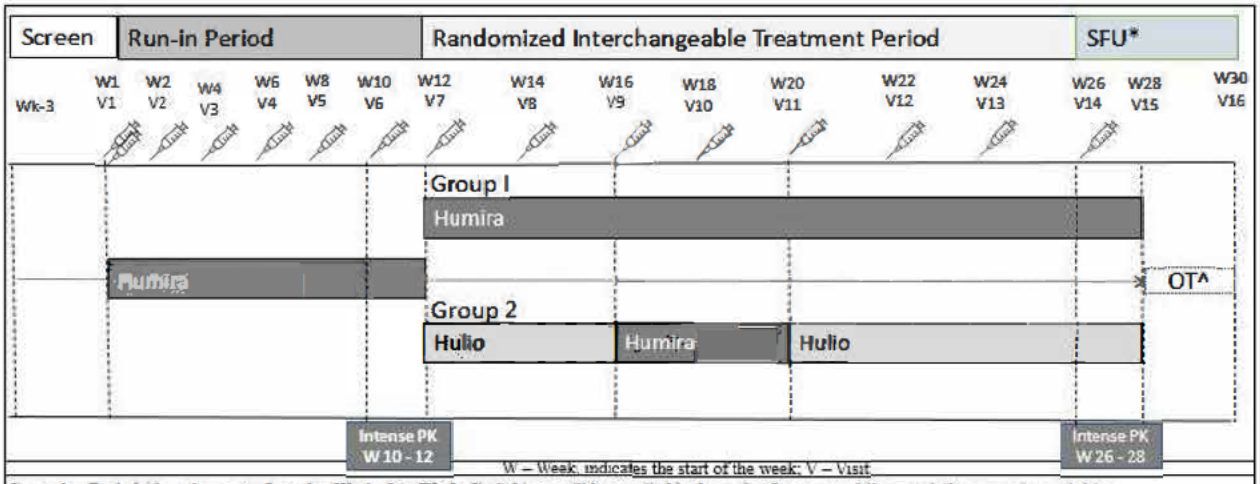
Randomization will be stratified based on Week 12/ Visit 7 PASI response: ≥ PASI 50 to < PASI 75 or ≥ PASI 75.

Last dose in the Randomized Interchangeable Treatment Period will be at Week 26. Follow-up safety assessment will be done 4 weeks post last dose of study drug treatment received during the Randomized Interchangeable Treatment Period. The last efficacy and PK assessments are at start of Week 28/ Visit 15.

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.

Table A: Study Diagram



Screening Period (duration-up to 3 weeks; Week -3 to Week -1): Subjects will be enrolled in the study after successfully completing screening activities.

Run-in Period (duration-11 weeks; Visit 1 to Visit 6): Subjects will receive Humira® (initial dose of 80 mg [2 × 40 mg]; Week 1/ Visit 1) administered subcutaneously (SC), followed by 40 mg SC given every other week starting 1 week after the initial dose (last dose at Week 10/Visit 6).

Randomized interchangeable treatment period (duration-16 weeks; Visit 7 to Visit 14): Subjects at the start of Week 12 /Visit 7 will be randomly assigned in a 1:1 ratio to either of the following groups and receive 40mg of the study drug every other week: **Group 1:** Subjects continue to receive Humira® (Week 12/Visit 7 until Week 26/Visit 14 including both visits); **Group 2:** Subjects undergo repeated switches up to Week 26/Visit 14: Hulio at Week 12/Visit 7 and Week 14/Visit 8, Humira® at Week 16/Visit 9 and Week 18/Visit 10, and Hulio at Week 20/Visit 11, Week 22/Visit 12, Week 24/Visit 13 and Week 26/Visit 14.

***SFU – Safety Follow-up assessment** done for 4 weeks post last dose of treatment received during the randomized treatment period.

^OT - Optional Treatment: To ensure continuity of treatment and for benefit of the subjects during the safety follow up period and per the discretion of the investigator and willingness of the subject, all the subjects 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.

3.2. Schedule of Events

Schedule of events can be found in Table 1: Study Schedule (Schedule of Assessment) of the protocol.

3.3. Changes to Analysis from Protocol

- Not applicable.

4. SAMPLE SIZE DETERMINATION

Assuming a Mean Ratio (MR; switching arm vs non-switching arm) of 93.5% and a coefficient of variation (CV) of 38% for each of the PK parameters, AUCτ and Cmax and, also assuming independence between AUCτ and Cmax, an anticipated non evaluable rate of 15%, a sample size of approximately 330 participants (280 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 randomize 330 subjects, 165 subjects per treatment arm. To account for 10% Run-in failures, approximately 370 subjects will be enrolled into the study.

Here are the R program codes used for the sample size calculation:

```
library(PowerTOST)
sampleN.RatioF(CV = 0.38, theta0 = 0.935, targetpower= 0.9487, design='parallel', alpha=0.05)
```

N=282 from the above R output.

Applicant's assumption of coefficient of variation (CV) of 38% was calculated from the published adalimumab interchangeability study (VOLTAIRE-X trial, https://clinicaltrials.gov/ct2/show/results/NCT03210259).
The residual CVs, which were calculated after covariates adjustment in the model, were approximately estimated from the above published study in three ways:

First, the reported 90.2% Confidence Intervals of AUCt & Cmax were used to calculate the CV using Fieller's theorem. This is the direct back-calculation using the Voltarie-X's SAP and their reported CIs. The CV was estimated at 37% for AUC and 36% for Cmax. The SAS program for AUC, and output for AUC are listed below as reference.
SAS program:

```
data cv;
CIhigh=114.62; CIlow =96.58;      /* CI for AUC */
n1=102; n2=93;                    /* N for AUC */
CIpercent=90.2;                   /* as stated in BI report, 90.2% CI was reported */
alpha=0.5+CIpercent/100/2;
t=tinv(alpha, n1+n2-2);
CVi = 0.367; /* Initial CV value */
G=t**2*CVi**2/N2;
ratio=(CIhigh/100 + CIlow/100)*(1-g)/2;
sqrt=sqrt(1/N1*(1-G)+ratio**2/N2);
cv=(CIhigh/100*(1-G)-ratio)/t/sqrt; /* final CV */
drop CIpercent;
proc print data= CV;
run;
```

SAS output:

Obs	CIhigh	CIlow	n1	n2	alpha	t	CVi	G	ratio	sqrt	**cv**
1	114.62	96.58	102	93	0.951	1.66268	0.367	.004003738	1.05177	0.14717	**0.36714**

Secondly, the reported 90.2% Confidence Intervals of AUCt & Cmax were used to calculate the CV assuming that log transformation was used. This gave an approximate estimation with a clear limitation. The CV was estimated at 37% for AUC and 36% for Cmax. The SAS program for AUC, and output for AUC are listed below as reference.

SAS program:

```
data intercv;
CIhigh=114.62; CIlow =96.58; /* CI for AUC */
n1=102; n2=93;              /* N for AUC */
CIpercent=90.2;             /* as stated in BI report, 90.2% CI was reported */
t=0.5+CIpercent/100/2;
diff=log(CIhigh/100) - log(CIlow/100);
stdeest=diff/2/tinv(t,n1+n2-2);
sigma=stdeest/sqrt(1/n1+1/n2);
interCV=sqrt(exp(sigma**2)-1)*100;
proc print dat=interCV;
run;
```

sas output:

Obs	CIhigh	CIlow	n1	n2	CIpercent	t	diff	stdeest	sigma	**interCV**
1	114.62	96.58	102	93	90.2	0.951	0.17125	0.051498	0.35919	**37.1087**

Thirdly, the CV was back calculated using the sample size calculation formula description in Section 15 of the Boehringer Ingelheim (BI)'s SAP (Page 39 of 121) which resulted in a maximum CV (AUCt and Cmax) of 37%.

Here is the formula used by Boehringer Ingelheim (BI) in their SAP:

sampleN.RatioF(alpha=0.049, CV= , theta0=0.92, targetpower=0.8, design="parallel"),

Based on the VOLTAIRE-X trial information posted on clinicaltrial.gov, 102 & 93 patients from each arm was included in the final analysis. That is 195 subjects in total.

If it was assumed that the calculated N was 196, then the CV was estimated at 37% when BI performed Blinded

Review of Sample size. It further validated the CV estimation.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

5.1. Data Monitoring Committee (DMC)

There will be no DMC for this study.

5.2. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics for non-PK related items and Viatris Biostatistics for PK related items following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, and Sponsor Authorization of Analysis Sets.

6. ANALYSIS POPULATIONS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the unblinding of the study.

6.1. All Patient Screened [SCR] Population

The All Patient Screened (SCR) Population will contain all patients who provide informed consent for this study.

6.2. All Patient Enrolled [ENR] Population

The All Patient Enrolled (ENR) Population will contain all patients from SCR Population patients who meet eligibility criteria and enrolled into the study.

6.3. Run-in Period Population [RPP]

The Run-in Period Population (RPP) will contain all enrolled patients who received at least one dose of Humira in the Run-in Period.

6.4. Safety Population [SAF]

The safety population (SAF) will contain all patients who received at least one dose of randomized study medication (i.e., patients who received at least one dose of Humira in Group I or Hulio in Group II of the Randomized Interchangeable Treatment Period).

6.5. Per Protocol Population [PPP]

The Per Protocol Population (PPP) will contain all randomized patients 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.
Reasons for exclusion can be, but not limited to:
Non-compliance with the inclusion or exclusion criteria.
Insufficient essential efficacy data for the secondary analysis.
Intake of prohibited medication.
Non-compliance with randomization criteria.
Non-compliance with the study treatment.

6.6. Pharmacokinetic Population (PKP)

The Pharmacokinetic Population (PKP) will contain all patients, who provide at least one primary PK parameter from the intense PK sample intervals in both run-in phase and randomization phase without major protocol violation relevant for primary endpoint evaluation.

Relevant major protocol deviation critical for primary endpoint evaluation may include:
Incorrect trial medication taken, i.e., the patient received at least one dose of trial medication the patient was not assigned to during the study until including Visit 14 (Week 26) dosing.
Incorrect or incomplete dose of trial medication taken; the incomplete dose will be treated as missed dose.

Use of restricted medications with suspected impact on PK

Dosing day deviation of trial medication.
An early or delay of dosing by 7 or more days (resulting in a dosing interval length of less than 7 days or more than 21 days) will be considered as a missed dose.

Missed doses during run-in phase (until including Visit 6).
If only one dose until including Visit 4 (Week 6) was missed, the subject can be included in the statistical analysis population. If more than one dose was missed until including Visit 6 (Week 10), the subject will be excluded from statistical analysis population. If dose at Visit 5 or 6 was missed, the subject will be excluded from statistical analysis population.

Missed doses during randomized phase (from Visit 7 until Visit 14).
If only one dose from Visit 7 (Week 12) until Visit 12 (Week 22) was missed, the subject can be included in the statistical analysis population. If more than one dose was missed until including Visit 14 (Week 26), the subject will be excluded from statistical analysis. If dose at Visit 13 or 14 was missed, the subject will be excluded from statistical analysis population.

Missed doses after randomized phase including Visit 15 (Week 28).
If doses are missed from Visit 15 (Week 28) until end of the study, the subject will not be excluded in statistical analysis population.

Blood draw deviations from planned PK sampling times.
PK sampling windows in the protocol were defined for operative reasons. Deviations will not necessarily lead to exclusion from analysis of PK endpoints. In the intensive PK interval in run-in phase, any PK sample deviation is more than half of the interval between the two samples, the PK sample will be treated as missing for the scheduled time point and it will be considered as the sample at the other time point. In the intensive PK interval in the randomization phase, except the Predose of Visit 15 (Week 28) any PK sample deviation of more than 24 hours, the PK sample will be treated as missing for the scheduled time point and it will be considered as the sample at the other time point. For Visit 15 (Week 28), samples will be treated as missing if the deviation is more than 168 hours (7 days).

Missing PK samples.
If missing two or more plasma samples during the intense PK sample interval from Visit 6 (week 10) to Visit 7 (Week 12), the subject will be excluded from the statistical analysis population.

If missing three or more plasma samples during the intense PK sample interval from Visit 14 (Week 26) to Visit 15 (Week 28), the subject will be excluded from the statistical analysis population.

For analyses and displays based on PKS, subjects will be classified according to treatment received.

7. GENERAL CONSIDERATIONS

7.1. Reference Start Date and Study Day

All summaries by period defined in the SAP refers to the analysis period. The analysis period consists of screening, Run-in Period, and Randomized Interchangeable Treatment Period (study diagram). Each period is defined as below:

Screening period is defined as study period from informed consent date prior to administration of Humira at Week 1.

Run-in Period is defined as study period on or after administration of Humira at Week 1 and before randomization at Week 12, or until last study participation date if patients withdrew/discontinued before Week 12.

Randomized Interchangeable Treatment Period is defined as study period from the randomization at Week 12 until Week 28 or until last study participation date if patients withdrew/discontinued. While presenting the data Week 28 (EOT) assessment will also be included.

Overall period is defined as study period consisting of above 3 periods and including follow up (Week 30/EOS).
Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It will appear in every listing where an assessment date or event date appears.

Reference start date is defined as the day of the first dose of study medication, i.e., Humira in the Run-in Period (Week 1/ Visit 1) (Day 1 is the day of the first dose of study medication).

- If the date of the event is on or after the reference date, then:
- Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear

partial or missing in the listings.

7.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). i.e., Baseline is the last non-missing measurement taken prior to the first dose of Humira in the Run-in Period (Week 1/ Visit 1). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline if the assessment is planned per protocol to take place prior to first study medication administration. For Hematology, Clinical chemistry, Urinalysis, Vital signs (HR, RR, BP, temperature) and 12-Lead ECG assessments, baseline value for Randomized Interchangeable Treatment Period will be the last non-missing measurement collected prior to the first medication dose taken in Randomized Interchangeable Treatment Period (i.e., Week 12/Visit 7).

7.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.
In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.
Early termination data will be mapped to the ET/End of Study Follow-Up visit for by-visit summaries.
Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.4. Windowing Conventions

Window convention is not applicable for this study.

For subjects who are randomized, have Week 12/ Visit 7 assessments for efficacy parameters (PASI and sPGA) and terminated from the study early, their PASI and sPGA assessments performed at the early termination visit will be remapped to the nearest protocol defined scheduled Visit for PASI and sPGA assessments (target day ±3 days). If an assessment cannot be remapped to a scheduled visit, the assessment will be considered as unscheduled and hence will not be considered for efficacy analysis. This remapping is done since in the EDC there is no separate early termination visit and for subjects who terminated early, their assessments performed at early terminations visits are captured at Week 28/ Visit 15 even though they are not actual Week 28/ Visit 15 assessments.

7.5. Statistical Tests

Confidence intervals will be 90% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

7.6. Common Calculations

For quantitative measurements, change and percent change from baseline at Visit X will be calculated as:

- Change from baseline at Visit X = Test Value at Visit X – Baseline Value
- Percent change from baseline at Visit X = (Test Value at Visit X - Baseline Value) / Baseline Value × 100

7.7. Software Version

All analyses will be conducted using SAS Enterprise Guide version 8.2.

8. STATISTICAL CONSIDERATIONS

The following descriptive statistics will be presented in summary tables for non-PK data:
For continuous variables: the number of contributing observations (n), mean, standard deviation (SD), median, minimum, and maximum.
For categorical variables: the number and percentage of patients in each category.
If the original data has N decimal places, then the summary statistics will have the following decimal places:
Minimum and maximum: N;
Mean, median, lower and upper bounds of two-sided CI: N + 1;
Percentage of patients in each category, SD: N + 2
p-values will be presented with 4 decimal places
See Section 20 for descriptive statistics of PK data.

8.1. Multicenter Studies

This study will be conducted by multiple investigators at approximately 36 study centers located in Europe. Randomization to treatment groups will be stratified based on Week 12/Visit7 PASI response: ≥ PASI50 to < PASI75 or ≥ PASI75.
Center pooling will not be carried out for use in analyses for this study.

8.2. Missing Data

Safety, missing PK, or immunogenicity data will not be imputed.
Missing PASI and sPGA data will be imputed as per section 17.2.2.

8.3. Intercurrent Events

Not applicable.

8.4. Multiple Comparisons/ Multiplicity

Not applicable.

8.5. Examination of Subgroups

No subgroup analyses will be performed for this study.

9. Output Presentations

Appendix 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

10. Disposition and Withdrawals

All patients who provide informed consent will be accounted for in this study.

10.1. Disposition

A clear accounting of the disposition of all patients who enter the study will be provided for the ENR, from enrolment to study completion. The patient disposition summaries include the following:
A summary of the number of screened patients, the number and percentage of screen failures and reasons for screen failure (Withdrawal by patient, Adverse Event, lost to follow up, Entry criteria not met, Sponsor decision, and Other), using the SCR population.

Patients entering the Run-in Period at Week 1, patients completed Run-in period, patients discontinued during the run-in period, reasons for not completing the Run-in Period, patients Run-in failed, patients completed the Run-in Period but not randomized, reasons for completed Run-in period but not randomized , patients randomized at Week 12, patients completed the full course of study treatment, patients discontinued treatment, reason for treatment discontinuation, patients completed the study, patients discontinued the study, reason for study discontinuation will be summarized by planned treatment group.

Additionally, separate tables for reasons for exclusion from each analysis population, including inclusion and exclusion criteria will be presented for the Enrolled population.

10.2. Protocol Deviations

Protocol deviations are the deviations from the procedure outlined in the protocol. All the Protocol Deviations (PDs) will be summarized using the Run-in period population as obtained from Clinical Trial Management System (CTMS) logs. PDs will be identified and discussed with the Investigator/Sponsor in PD review discussion to categorize them, and to finalize analysis population assignment.
Any PDs will be categorized into critical, major, and minor protocol deviations and will be summarized based on severity categories. An additional table summarizing the number and percentage of patients with Important PDs will be presented. Critical and Major protocol deviations having impact on primary analysis will be considered while finalizing the Per Protocol (PP) population. PDs log will be used for reporting purpose in tables.

10.3. COVID-19 IMPACT

The impact of COVID-19 on study related visits are collected on 'Pandemic Visit Impact' in eCRF. Impact information will be presented in a data listing for Run-in period population.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by the planned treatment group for the Run-in period population.
No statistical testing will be carried out for demographic or other baseline characteristics.
The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent

- Sex
- Childbearing potential
- Race
- Ethnicity
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline PASI score
- Baseline sPGA Total Average score and Severity Score (0-5 scale)
- BMI (kg/m^2)
- A listing of patient demographic data and other baseline characteristics will be presented for the Run-in period population.

11.1. Derivations

- BMI (kg/ m^2) = weight (kg)/ height (m)^2

12. MEDICAL HISTORY AND PROCEDURES/SURGICAL HISTORY

Medical History information is obtained from the 'Medical History' form of the eCRF. Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 25.1 or latest) dictionary and summarized using SOC and PT for Run-in period population. A listing of medical history will be provided.
Status of heart failure and NYHA class will be summarized.
Procedures/Surgical History will be summarized separately by system organ class (SOC) and preferred term (PT) by planned treatment group for the Run-in period Population. A separate listing for Procedure/Surgical History information collected on eCRF form "Procedure/Surgical History" will be presented by planned treatment group for the Run-in period Population. Information collected on eCRF form "Subject History" will also be listed.

13. CONCOMITANT DISEASE

Concomitant Disease will be presented for the Run-in period population. A listing of concomitant disease will be provided. Information collected "Concomitant Disease" section in "Medical history" eCRF form will be presented.

- Concomitant Disease will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 25.1 or latest) dictionary.

- Concomitant Disease are conditions which started prior to or at Screening and are ongoing at the date of Screening or ended after screening. Any conditions which started after the first dose of study medication are also considered as Concomitant Disease.
- Presented by SOC and PT.
- Concomitant Disease information is obtained from the 'Medical History' form of the eCRF with Ongoing status as 'Yes' or have start date after the treatment start date.

14. MEDICATIONS

Prior and Concomitant medications will be presented for the Run-in Period Population and coded using WHO Drug dictionary Version _202303_B3. Medications are recorded in the form 'Prior and Concomitant Medications' of the eCRF.

See Appendix 3 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, or concomitant, the medication will be classified by the worst case, i.e., concomitant.

Prior and concomitant medications will be summarized by primary therapeutic subgroup (3rd level ATC code) and preferred name.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication (i.e., first dose of Humira in the Run-in Period).
- 'Concomitant' medications are medications which:
  - started prior to, on or after the first dose of study medication (i.e., first dose of Humira in the Run-in Period),
  - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.

If Concomitant medication started and ended during Run-in period, it will be part of Run-in period. If concomitant medication started during Run-in period and end date is missing it will be part of Run-in period. If concomitant medication started during Randomized Interchangeable Treatment Period, it will be part of Randomized Interchangeable Treatment Period. If start and stop date of concomitant medication is missing, then it will be part of Run-in period.

15. STUDY MEDICATION EXPOSURE

Exposure to randomized study medication in weeks will be presented for the Run-in Period Population and SAF separately.

Duration of Run-in period is 11 weeks i.e., Week 1 to Week 10 and duration for Randomized Interchangeable Treatment Period is 16 weeks i.e., Week 12 to Week 26.
The date of first study medication administration will be taken from the eCRF "Exposure (log)" form. The date of last study medication will be taken from the eCRF "End of Study Treatment" form (Date of treatment completion/discontinuation).
Interruptions, compliance, and dose changes are not considered for duration of exposure.
The duration of exposure to IP in weeks and number of IP administrations will be summarized descriptively including n, mean, median, standard deviation, minimum, and maximum for Humira for Run-in Period Population and for each treatment group for SAF. Count and percentage of patient exposed to IP will be provided (Week 1, Week 2, Week 4, Week 6, Week 8, Week 10 for Run-in period, and Week 12, Week 14, Week 16, Week 18, Week 20, Week 22, Week 24, Week 26 for Randomized Interchangeable Treatment Period).

Location of drug administration, number of patients who administered full dose, dose adjusted, and reason of dose adjustment will be tabulated on SAF population.

15.1. Derivations

Duration of exposure in Run-in period (weeks)
= (date of last study medication administration in Run-in period – date of first study medication administration in Run-in period + 1)/7.
If the last IP administration date was unknown,
Exposure duration = (last available visit date in Run-in period – first IP administration date in Run-in period + 1)/7

Duration of exposure in Randomized Interchangeable Treatment Period (weeks)
= (date of last study medication administration in Randomized Interchangeable Treatment Period – date of first study medication administration in Randomized Interchangeable Treatment Period + 1)/7.
If the last IP administration date was unknown,
Exposure duration = (last available visit date in Randomized Interchangeable Treatment Period – first IP administration date in Randomized Interchangeable Treatment Period + 1)/7

16. STUDY MEDICATION COMPLIANCE

Compliance to randomized study medication will be presented for the SAF only for the patient who entered Run-in

period and Randomized Interchangeable Treatment Period. Compliance will be checked. Treatment compliance for patients will be summarized for 26 weeks along with the number and percent of patients with compliance in each of the following groups:

- Compliant: percentage of compliance =>80% - <=110%
- Non-Compliant: percentage of compliance <80% - >110%

Total number of planned injections from week 12 to week 26 is 8.

16.1. Derivations

Compliance with randomized study medication is based on the eCRF "Exposure (log)" form. An administered injection is considered when the question "Was full dose administered?" is answered "Yes".

Compliance is defined as actual number of injections divided by number of assigned injections.

Overall compliance (%) for Run-in period = (Total Number of injections administered in Run-period) *100/ (Total Planned number of injections in Run-in period)

Overall compliance (%) for Randomized Interchangeable Treatment Period = (Total Number of injections administered in Randomized Interchangeable Treatment Period) *100/ (Total Planned number of injections in Randomized Interchangeable Treatment Period)

17. EFFICACY OUTCOMES

17.1. Primary Efficacy

Not applicable.

17.2. Secondary Efficacy

The secondary efficacy analyses will be performed for the PP population.

17.2.1. Secondary Efficacy Variables & Derivations

17.2.1.1. PROPORTION OF PASI 50, PASI 75, PASI 90 AND PASI 100 RESPONDERS AT WEEK 28

A PASI 50, PASI 75, PASI 90, and PASI 100 response is defined as a ≥ 50%, ≥ 75%, ≥ 90% and ≥ 100% improvement of PASI score from baseline (Week1/ Visit1).

- PASI50 at Week X:
  Yes if percent change of PASI score at Week X ≤ -50
  No if percent change of PASI score at Week X > -50
- PASI75 at Week X:
  Yes if percent change of PASI score at Week X ≤ -75
  No if percent change of PASI score at Week X > -75
- PASI90 at Week X:
  Yes if percent change of PASI score at Week X ≤ -90
  No if percent change of PASI score at Week X > -90
- PASI100 at Week X:
  Yes if percent change of PASI score at Week X ≤ -100
  No if percent change of PASI score at Week X > -100

where, percent change of PASI score (%) at Week X = [(PASI score at Week X – PASI score at Baseline)/ PASI score at baseline] x100)).

Example, if percent change of PASI score (%) ≤ - 90 then it would be considered as PASI 90 responder.

17.2.1.2. PROPORTION OF sPGA SUCCESS (CLEAR OR ALMOST CLEAR) AT WEEK 28

The sPGA is used to determine the patient's psoriasis lesions overall at a given time point. It will be used to assess the improvement in the overall severity of the disease in individual patients and thus arrive at the number and percentage of patients achieving sPGA responses of clear (0) or almost clear (1).

- sPGA Success at Week X
- Yes, if sPGA response at Week X ≤ 1
- No, if sPGA response at Week X > 1

17.2.2. Data Imputation for Secondary Efficacy Variable(s)

Missing data will be handled using a combination of non-responder imputation and multiple imputation methods. After applying multiple imputation, non-responder imputation will be performed.

Multiple imputation (MI) is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that

adequately incorporate missing data uncertainty. Below steps will be applied on the PASI score and the sPGA separately.

- Step 1: Creation of multiple imputed data sets

The first step of the multiple imputation is to transform a non-monotone missing data structure to a monotone one. Intermediate missing variables will be multiple imputed using the Markov Chain Monte Carlo (MCMC) method and assuming Missing at Random (MAR) and multivariate Normality. The SAS procedure PROC MI with the MCMC option will be used. Missing values for the 'change from baseline PASI score' or 'sPGA score' will be imputed. The change from baseline in PASI score appears to follow closer to a normal distribution than the actual PASI score. Assuming normality for the 'sPGA score' as well. This step will be performed on longitudinal continuous change from baseline PASI score or sPGA score between Baseline and week 28 (Week 12, 16 and 20 inclusive).
For each variable, the imputations will be done separately for each randomized treatment group including baseline weight as additional covariate.
The number of imputations will be set to 500. The SAS code used to generate the multiple imputed data sets will be like that shown below:
The input data set <Efficacy> should have one record per patient with baseline PASI score or sPGA score as well as all changes from baseline PASI or post baseline sPGA score.
(A) - Creation of monotone missing data structure

```
PROC MI DATA=<Efficacy> OUT=<impdata> SEED=3001 NIMPUTE=500;
VAR <baseline weight> <baseline PASI/baseline sPGA> <change from baseline PASI week X/sPGA week X> -
<change from baseline PASI week secondary endpoint/sPGA week secondary endpoint>;
BY <treatment group>;
mcmc chain=single nbiter=1000 impute=monotone;
Run;
```

(B) - The dataset with monotone missing data will be imputed using regression model by considering the stratification factors and respective timepoints

```
PROC MI DATA =< impdata > OUT=<Output data> NIMPUTE =1 SEED=3001 ;
BY _IMPUTATION_;
CLASS <treatment group>;
VAR <baseline weight> <baseline PASI/baseline sPGA> <change from baseline PASI week X/sPGA week X> -
<change from baseline PASI week secondary endpoint/sPGA week secondary endpoint>;
MONOTONE REGRESSION ;
Run;
```

The imputed data are saved in data set <Outputdata>. The outcomes of interest, i.e., the PASI 90 response or sPGA response will be calculated, e.g. as follows:

DATA <impdata2>;
SET <impdata>;
*** PASI 90 response
IF <change from baseline PASI week secondary endpoint>/<baseline PASI <= -0.90 THEN <PASI 90 response> =1;
ELSE <PASI 90 response>=2;
*** sPGA response
IF <baseline sPGA> >=3 THEN DO;
IF <sPGA week secondary endpoint> < 1.5 THEN <sPGA 0/1 response> =1;
ELSE IF <sPGA week secondary endpoint> >=1.5 THEN <sPGA 0/1 response> =2;
END;
RUN;

- **Step 2: Non-responder imputation**

Patients will be considered as non-responder if

- discontinued the study treatment before Week 28
- lost to follow up before Week 28 (As per End of study CRF page)
- any severe violation related to any therapy that may significantly impact efficacy assessment before Week 28 (which will be decided during [redacted]

- **Step 3: Calculation of proportion in each treatment arm for each imputed data set**

PROC FREQ DATA=<Inpdata>;
TABLES <PASI X Category> /binomial(LEVEL=1 CL=WALD) alpha=0.10;
BY _Imputation_ <treatment group>;
ODS OUTPUT BINOMIAL=prop;
RUN;

- **Step 4: Combining proportion estimates in each treatment arm and the difference between proportions**

For the proportions, the proportion estimates and their asymptotic standard errors provided by PROC FREQ for each imputed data set can be passed directly to PROC MIANALYZE.

PROC MIANALYZE DATA=<PROP> ALPHA=.10;
MODELEFFECTS <Proportion>;
STDERR <Standard error>;

BY <treatment group>;
ODS OUTPUT PARAMETERESTIMATES=<OUTPUTDATA>;
RUN;

For the difference between proportions in two arms, the standard error of the estimated difference is computed as the square root of the sum of squared standard errors for each proportion. This standard error is then passed to PROC MIANALYZED along with the estimated difference in proportions.

- **Step 5: Compute estimates of the difference in proportions of responders between treatment arms and their standard errors**

DATA prop_diff;
MERGE <Treatment group 1 data> <Treatment group 2 data>
BY _Imputation_;
prop_diff = (p1-p2);
se_diff = sqrt(se1*se1 + se2*se2);
RUN;

- **Step 6: Combine estimates of the proportion differences**

PROC MIANALYZE DATA=<prop_diff> ALPHA=.10;
MODELEFFECTS <prop_diff>;
STDERR <se_diff>;
ODS OUTPUT PARAMETERESTIMATES=mian_prop_diff;
RUN;

17.2.3. Analysis of Secondary Efficacy Variables

17.2.3.1. Proportion of PASI 50, PASI 75, PASI 90 and PASI 100 responders at Week 28

Number and proportion of patients with a PASI 50, PASI 75 and PASI 90 response at Week 28 will be presented by treatment groups. 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. Additionally, a descriptive statistics table of PASI total score will be provided by treatment group for observed value, change from baseline and percent improvement from baseline for each post-baseline visit. Also, the number and proportion of patients with a PASI 50, PASI 75 and PASI 90 response based on observed value at each post-baseline visits will be presented by treatment groups.

17.2.3.2. PROPORTION OF SPGA SUCCESS (CLEAR OR ALMOST CLEAR) AT WEEK 28

Number and proportion of sPGA success will be analyzed same as PASI response.

The number and proportion of patients with a sPGA scores (Clear, almost clear, Mild, Moderate, Moderate to severe, Severe) and sPGA success response based on observed value at each post-baseline visits will be presented by treatment groups.

17.3. Exploratory Efficacy

Not applicable.

18. QUALITY OF LIFE ANALYSIS

Not applicable.

19. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Run-in period and SAF populations.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

19.1. Adverse Events

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 25.1 or latest. AEs are recorded in the 'Adverse Events' form of the eCRF.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the date/time of first dose of study medication.

TEAEs that occurred or worsened on or after the date/time of the first administration of Humira in the Run-in period but before the date/time of the first administration of Humira/ Hulio in the Randomized Interchangeable Treatment Period will be summarized under Run-in period population.

TEAEs that occurred or worsened on or after the date/time of the first administration of Humira/ Hulio in the Randomized Interchangeable Treatment Period will be summarized under SAF population.

If TEAE end date is missing and started in Run-in period then it will be part of Run-in period.

See Appendix 3 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e., treatment emergent.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates.
Listings will include TEAEs and Non-TEAEs.
Adverse event of special interest (AESI) defined in the protocol will be summarized and listed. AEs which are classified as "Event qualify AESI" as per Adverse event CRF form will be used.

19.1.1. All TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication.

19.1.1.1. SEVERITY

Severity is classed as mild (grade 1)/ moderate (grade 2)/ severe (grade 3)/ life-threatening (grade 4)/ fatal (grade 5) based on CTCAE criteria, version 5.0. TEAEs starting after the first dose of study medication with a missing severity will not be classified. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

19.1.1.2. RELATIONSHIP TO STUDY MEDICATION

Relationship, as indicated by the Investigator, is classed as unrelated/ not related, Unlikely, possible, probable, and definite (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship to study medication as possible, probable, or definite to study medication. TEAEs with a missing relationship to study medication will be regarded as possible related to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

19.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication are those events for which 'Action Taken with study treatment' is recorded as 'Drug withdrawal' on the 'Adverse Events' form of the eCRF.
For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

19.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the 'Adverse Events' form of the eCRF. A

summary of serious TEAEs by SOC and PT will be prepared.

19.1.4. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as 'Fatal' for the outcome field on the 'Adverse Events' form of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

19.2. Deaths

If any patients die during the study as recorded on the 'Death Details' form of the eCRF, the information will be presented in a summary table and a data listing using Run-in period and SAF populations.

19.3. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology and Serum Chemistry. Results from the local/central laboratory will be reported for Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol, Section 7.3.2 (Table 5: Laboratory Safety Tests).
Presentations will be based on SI Units.
Quantitative laboratory measurements reported as "< X", i.e., below the lower limit of quantification (BLQ), or "> X", i.e., above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the listings.
Descriptive summaries of observed values and change from baseline will be presented for clinical laboratory evaluations (Serum chemistry and hematology) by actual treatment group. Assessments of laboratory variables according to clinical relevance will be tabulated by visit and actual treatment group for each clinical laboratory parameter in frequency tables. Additionally, for each laboratory parameter, shifts in value from baseline to all post-baseline visits will be presented by actual treatment group in shift tables.
The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by actual treatment group in frequency tables. Additionally, for each of the urine parameters, shifts in assessments from Baseline to all Post-baseline visits will be presented for each treatment group in shift tables.
For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each post-baseline visit relative to whether the baseline value was normal, low, or high.

The following summaries will be provided for laboratory data by the actual treatment group:

- Actual and change from baseline by visit (for quantitative measurements – Hematology and Serum Chemistry)

- Summary of the number and percentage of patients by visit (for qualitative measurements – Urinalysis)
- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)
- A by-patient listing of all laboratory data

19.3.1. Laboratory Reference Ranges and Markedly Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

19.4. ECG Evaluations

The following summaries will be provided for ECG data:

- A by-patient listing of all ECG data collected in the 'ECG' form of the eCRF.

19.5. Immunogenicity Analysis

The assay includes three tiers of analysis designated as screening, confirmation, and titration, respectively. Samples identified as positive in the screening assay will be tested in a confirmatory assay that employs a 0.1% false positive rate. Confirmed positive samples will be further evaluated for ADA titer. Neutralizing capacity (Nab) of the antibodies will be evaluated for samples in which anti-drug antibodies have been confirmed to be present.
Immunogenicity data, including subject ID, visit, anti-drug antibody (ADA) results, ADA titers, and neutralizing antibody results (Nab) will be presented.

Immunogenicity to adalimumab will be descriptively summarized by treatment group at Week 28 time point and include:

- Incidence of positive ADA and NAb response
- Titer of subjects with positive ADA response
- Change from Week 12 in ADA and NAb incidence, and ADA titer

19.6. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature (^{0} C)

The summary of actual and change from baseline by visit will be provided for vital sign data. In case of multiple measurement timepoints at one visit, the pre-injection data will be used for summary tables.
Vital signs data will be listed.

19.7. Physical Examination

The following summaries will be provided for physical examination data:

- A by-patient listing of physical examination data as recorded in the 'Physical Examination' form of the eCRF.

19.8. Other Safety Assessments

The following summaries will be provided:

- A by-patient listing of Chest X-Ray data as recorded in the 'Chest X-Ray' form of the eCRF.
- A by-patient listing of pregnancy test data at screening visit as collected in the 'Pregnancy' form of the eCRF.
- A by-patient listing of serology test data at screening visit as collected in the 'Laboratory Assessment: Serology (HBsAg, HBcAb, HCVAb, HIV)' form of the eCRF.
- A by-patient listing of IGRA or Purified Protein Derivative Test data at screening visit as collected in the 'Laboratory Assessment: IGRA or Purified Protein Derivative Test' form of the eCRF.
- A by-patient listing of Urine Drug Screen data at screening visit as collected in the 'Laboratory Assessment: Urine Drug Screen' form of the eCRF.
- A frequency table for the injection site reactions: pain, tenderness, erythema/redness, induration/swelling, and pruritus (itching) will be presented along with a by-patient listing as collected in the 'Injection Site Reaction - Investigator Assessment' form of the eCRF.
- A by-patient listing of the monitor for signs and symptoms of TB and other serious infections, for progression to

NYHA Class III/IV Heart failure2, and examination for non-melanoma skin cancer will be presented as recorded in the 'Signs and Symptoms' form of the eCRF.

20. PHARMACOKINETIC ANALYSIS

All PK analyses will be performed on the Pharmacokinetic Population (PKP).
Descriptive statistics of plasma concentrations and PK parameters will be also done on PKP. For PK parameter analysis on Run-in Period Population (RPP) the same rules regarding exclusion as for PKP will be applied.

20.1. General Pharmacokinetic considerations

The PK parameters will be calculated according to the Viatris SOP GCRD-GPK-0030 'Standard Pharmacokinetic Parameter Definitions and Calculations'.

The actual sampling times will be used for the calculation of PK parameters, except the first (Predose) and the last time point (Predose before next dose) for each intensive PK intervals (Week 10-12 and Week 26-28). If the first time point is within 12 hours before dosing of Week 10 or Week 26 then the time will be set to 0 for PK parameter calculation purpose. Should the PK blood sample collected during the final timepoints, either Week 12 or Week 28, after 506 hours following the preceding dose, the PK concentration values for that sample at Week 12 or 28 will be marked as missing. Consequently, such samples will be excluded from the calculation of PK parameters. When the Week 12 or 28 PK blood sample is missing (including those treated as missing due to large time deviations as define above), the PK concentration will be extrapolated using two previous PK concentration values using log linear method. When the Week 12 or 28 PK blood sample is not missing but the time deviations is more than 12 hours, the PK concentration at 336 hours will be determined for AUC calculation purpose. This will be achieved through interpolation or extrapolation using the log-linear method, with interpolation being the preferred method if feasible. If the PK blood sample at Week 12 or 28 is not missing and the time deviation is within 12 hours, the time will be standardized to 336 hours for the purpose of AUC calculation.

Concentrations used in the PK analysis will be in mcg/mL, instead of ng/mL as reported in bioanalytical report.

If a measured level for a given PK sample is BLQ then 1/2 LLOQ of the assay will be used for the PK parameter calculation purpose. For samples taken at baseline (visit 1) BLQ values will not be replaced by 1/2 LLOQ but reported as 0 instead.

20.2. Pharmacokinetic Endpoints

20.2.1. Primary Pharmacokinetic Variables

Pharmacokinetics will be assessed as the primary objective in this trial.
The primary pharmacokinetic endpoints are:

- AUCτ, 26-28 (Area under the adalimumab plasma concentration-time curve over the dosing interval of Week 26-28)
- Cmax, 26-28 (Maximum observed adalimumab plasma concentration during the dosing interval of Week 26-28)

20.2.2. Secondary Pharmacokinetic Variables

The secondary pharmacokinetic endpoints are:

- Cmin, 26-28 (Minimum observed adalimumab plasma concentration during the dosing interval of Week 26-28)
- Tmax, 26-28 (Time to maximum observed adalimumab plasma concentration during the dosing interval of Week 26-28)

20.2.3. Handling of Missing Data

If actual PK sampling date is missing, the dosing date of the same visit will be used instead.
If actual dosing date is missing, the PK sampling date of the same visit will be used instead.
If actual dosing time is missing and the dosing and PK sampling dates are identical then the PK sampling time of the same visit will be used instead.
If actual PK sampling time for pre-dose PK samples is missing and the dosing and PK sampling dates are identical then the dosing time of the same visit will be used instead.
If actual PK sampling time for sub-visits 6a-c or 14a-f is missing, the clock-time of preceding dosing will be used instead.
If it is not possible to impute missing date or times, the respective date or time will stay missing.

20.2.4. Duplicated PK samples

There are duplicated PK sample collected by clinic and analyzed by bioanalytical lab, the PK concentration values from the same samples will be averaged as the single PK sample collection and the correct time will be used.

20.2.5. Unscheduled PK samples

There are unscheduled PK sample collected by clinic and analysed by bioanalytical lab, those sample will be used by the actual time sample was collected for PK parameter calculation purpose.

20.2.6. Analysis of Pharmacokinetic Endpoints

Descriptive statistics of plasma concentrations and PK endpoints, as well as the tables and graphs for the pharmacokinetic noncompartmental analyses, will follow specific definitions in this SAP.

20.2.7. Analysis of Primary Pharmacokinetic Endpoints

Pharmacokinetic parameters of a patient will be included in the statistical analyses of PK endpoints (ANCOVA) if they are not flagged for exclusion due to a major protocol violation relevant to the evaluation of PK.
The primary objective of this trial is to test the hypothesis of PK similarity between the switching arm and continuous Humira® arm on the two PK parameters: AUCτ, 26-28 and Cmax, 26-28.

The test for PK similarity will be performed with respect to the switching vs. continuous Humira® arm. For the primary endpoint analysis, the BE margins 80% – 125% on the ratio will be applied.

The hypotheses for the primary endpoint analysis can be written as follows:

- H0: Ratio of the means of AUCτ, 26-28 (switching arm versus continuous Humira® arm) is less than 80% or more than 125%
- H1: Ratio of the means of AUCτ, 26-28 (switching arm versus continuous Humira® arm) is within [80%, 125%]
- and
- H0: Ratio of the means of Cmax, 26-28 (switching arm versus continuous Humira® arm) is less than 80% or more than 125%
- H1: Ratio of the means of Cmax, 26-28 (switching arm versus continuous Humira® arm) is within [80%, 125%]
-

Two one-sided tests of significance level of 5% was chosen to ensure overall type I error control at 5% per the current regulation standard.
The two endpoints are considered coprimary (i.e., the trial is considered positive if the results for both endpoints are simultaneously positive), therefore no multiplicity-adjustment with respect to the alpha level will be performed.

It is well known that adalimumab can trigger ADA response which in turn leads to reduced exposure and extreme low Pk parameter values. Log-transforming the PK parameter values with extreme low values will skew the normal distribution. Similarly, Voltarire-X trial has used the same approach of non-log-transformed PK for primary analysis due to the same reason stated above. Hence the use of the original scale is considered reasonable and proposed in this study. Fieller's theorem will be used to calculate CIs of the ratio without log-transforming of PK parameter values.

The statistical model used for the analysis of AUCτ, 26-28 and Cmax, 26-28 will be an analysis of covariance (ANCOVA) model. This model will include effects accounting for:

- Treatment (switching arm versus continuously Humira® arm)
- Natural Logarithm of rPASI, where rPASI is the ratio of PASI at Week 12 and PASI at Week 1 (continuous
- value as covariate variable). If PASI at Week 12 is zero, then the score for Week 12 will be set to 0.05 (otherwise the logarithm is not defined). Note that this imputation is only done for the purpose of creating the covariate used in this PK analysis
- Weight at screening period (continuous value as covariate variable)
- AUCτ, 10-12 or Cmax, 10-12 (continuous value as covariate variable)

as a source of variation. As the measurements at Week 12 will be prior to randomization and all subjects will have received the same treatment with the reference treatment only, the covariates listed above are all considered adequate baseline values.
All effects will be considered as fixed. The model is described by the following equation:

response (AUCτ, 26-28 or Cmax, 26-28) = overall mean + Ln(rPASI) + weight at screening period
+ (AUCτ, 10-12 or Cmax, 10-12) + treatment effect + random error

where the random errors are assumed to be independent and normally distributed with zero mean and variance σ^2.
The analysis will be adjusted for the covariates as stated in above model which will be implemented with the SAS® procedure PROC MIXED in conjunction with the LSMEANS statement. The LSMEANS statement is used to estimate the treatment LSMeans of the switching and non-switching arms which will be used to construct the point estimate for the ratio of means. The CI will be derived based on Fieller's theorem.

Equivalently to rejecting both null hypotheses for the primary endpoints, PK similarity between Switching arm and Continuous Humira® arm will be concluded if the two-sided 90% Fieller CI for the ratio of the means is fully contained within the standard equivalence limits of 80.00% to 125.00%.

20.2.8. Analysis of Secondary PK endpoint

The secondary PK endpoint Cmin, 26-28 will be analysed in the same way as the primary endpoints. However, only the mean ratio and CIs will be calculated and presented. The 90% Fieller CI will not be required to be within the 80.00% to 125.00% limits.

The secondary PK endpoint tmax, 26-28 will be analyzed in a descriptive manner only.

20.2.9. Sensitivity Analysis of PK endpoints

A similar model as the primary PK endpoint analysis will be performed on the natural log-transformed (Ln) PK endpoints as sensitivity analysis.

The model is described by the following equation:

Ln (AUCτ, 26-28, Cmax, 26-28 or Cmin, 26-28) = overall mean + Ln(rPASI) + weight at screening period + Ln (AUCτ, 10-12, Cmax, 10-12 or Cmin, 26-28) + treatment effect + random error.

The 90% CIs will be generated from the above model to further support BE equivalency.

21. REFERENCES

1. 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), Protocol version 2.0, 24 Aug 2022
2. Subject Case Report Forms ADA_IJZ_3001_Version_0.91_18OCT2022.
3. Combining Analysis Results from Multiply Imputed Categorical Data, PharmaSUG 2013 - Paper SP03, Bohdana Ratitch et.al

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following:

Use the following document as a guide and copy ONLY the relevant sections into this appendix. Make sure that once the customer agrees with the contents of this appendix, the templates/shells follow exactly what is written here. Global Bios > Processes > GBIOS Processes - Implementation Guidelines and Templates > General Guidelines and Templates > Output Conventions.

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English UK.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in the given order:

Period	Group	Treatment Group	For Tables, Listings and Figures
Run-in Period		Humira	Humira
Randomized Interchangeable Treatment Period	Group 1	Humira	Group 1
Randomized Interchangeable Treatment Period	Group 2	Hulio/Humira/Hulio	Group 2

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Period	Switch (Switch is applicable to Group 2 only)	Long Name (default)	Short Name
Screening Period		Screening	Scr
Run-in Period		Baseline (Week1/ Visit 1)	BL (W1/V1)
		Week 2 (Visit 2)	W2 (V2)
		Week 4 (Visit 3)	W4 (V3)
		Week 6 (Visit 4)	W6 (V4)
		Week 8 (Visit 5)	W8 (V5)
		Week 10 (Visit 6)	W10 (V6)
Randomized Interchangeable Treatment Period	Switch 1	Week 12 (Visit 7)	W12 (V7)
		Week 14 (Visit 8)	W14 (V8)
	Switch 2	Week 16 (Visit 9)	W16 (V9)
		Week 18 (Visit 10)	W18 (V10)
	Switch 3	Week 20 (Visit 11)	W20 (V11)
		Week 22 (Visit 12)	W22 (V12)
		Week 24 (Visit 13)	W24 (V13)
		Week 26 (Visit 14)	W26 (V14)
		Week 28 (Visit 15)	W28 (V15)
		Week 30 (Visit 16)	W30 (V16)

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Period
- Randomized treatment group (or treatment received if it's a safety output),

- Center-patient ID,
  - Date (where applicable),
- For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'

APPENDIX 2. SAMPLE CODES FOR EFFICACY ANALYSIS

The programming codes for analyzing secondary efficacy endpoints are described in section 17.2.

APPENDIX 3. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

DocuSign

Certificate Of Completion

Envelope Id: A0D4AEFB6BA9486CBDEE1CBE2C489AE2
Status: Completed
Subject: Complete with DocuSign: ADA_IJZ_3001_Statistical Analysis Plan_V2.0_VTRS_IQVIA_29NOV2023 (002).docx
Project Code (Enter 0 for non-billable projects): HAB34991
IQVIA ID (Login ID): q1062727
Business Unit:
Project Leadership
Source Envelope:
Document Pages: 48
Signatures: 4
Envelope Originator:
Certificate Pages: 6
Initials: 0
[redacted]
AutoNav: Enabled
One IMS Way
EnvelopeId Stamping: Disabled
Plymouth Meeting, 19462
Time Zone: (UTC-08:00) Pacific Time (US & Canada)
[redacted]
IP Address: 185.76.230.249

Record Tracking

Status: Original
[redacted]
Location: DocuSign
11/29/2023 7:28:28 AM
[redacted]

Signer Events	Signature	Timestamp
[redacted] [redacted] IQVIA - Default Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 36F1DEE8-090D-4A24-9AE6-596D7F005EE1 Using IP Address: 162.44.150.11 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 11/29/2023 7:32:27 AM Viewed: 11/29/2023 8:47:22 PM Signed: 11/29/2023 8:50:51 PM
Electronic Record and Signature Disclosure: Accepted: 8/17/2020 11:11:27 PM ID: 8c739095-a80e-4d8c-bcdf-52c7d76592ee		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 2182E5C9-BB4D-46BE-AC47-7198660D7356 Using IP Address: 136.144.103.52 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 11/29/2023 7:32:28 AM Viewed: 11/29/2023 11:44:44 PM Signed: 11/30/2023 12:02:53 AM
Electronic Record and Signature Disclosure: Accepted: 11/29/2023 11:44:44 PM ID: ff7542c7-abf7-43c2-9e7e-53550ca79bb1		

Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: B69CF603-A7EA-4C8F-9A2D-CA2017506CC6 Using IP Address: 73.91.86.10 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 11/29/2023 7:32:28 AM Viewed: 11/29/2023 7:34:51 AM Signed: 11/30/2023 3:45:07 AM
Electronic Record and Signature Disclosure: Accepted: 11/29/2023 7:34:51 AM ID: fa8b3627-3bb9-40d7-bfb0-1db9d57470b7		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 8B042F0F-96EC-473F-9538-01F253C4D0DD Using IP Address: 162.44.150.11 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 11/29/2023 7:32:28 AM Viewed: 11/29/2023 7:58:51 AM Signed: 11/29/2023 8:03:50 AM
Electronic Record and Signature Disclosure: Accepted: 11/29/2023 7:58:51 AM ID: 57e5539b-823a-43c4-a197-2844369a39c4		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	11/29/2023 7:32:29 AM
Envelope Updated	Security Checked	11/29/2023 7:52:30 AM
Envelope Updated	Security Checked	11/29/2023 7:52:31 AM
Envelope Updated	Security Checked	11/29/2023 7:52:31 AM
Envelope Updated	Security Checked	11/29/2023 7:52:31 AM
Envelope Updated	Security Checked	11/29/2023 7:52:31 AM
Certified Delivered	Security Checked	11/29/2023 7:58:51 AM
Signing Complete	Security Checked	11/29/2023 8:03:50 AM
Completed	Security Checked	11/30/2023 3:45:07 AM

Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

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Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

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