**Statistical Analysis Plan**

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|---|---|
| **Protocol Title:** | A Multicenter, Randomized, Double blinded Study Evaluating the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Multiple Switches Between Humira® (adalimumab [US]) and ABP 501 Compared With Continued Use of Adalimumab in Subjects with Moderate to Severe Plaque Psoriasis |
| **Short Protocol Title:** | A Study to Investigate Interchangeability of ABP 501 for the Treatment of Subjects with Moderate to Severe Plaque Psoriasis |
| **Protocol Number:** | 20200497 |
| **NCT Number:**<br>**EudraCT:** | NCT05073315<br>2021-000542-18 |
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| **SAP Date:** | **Document Version** — **Date**<br>**Current (v2.0)** — 10FEB2023 |

| Version Number | Date (DDMMMYYYY) | Summary of Major Changes, including rationale |
|---|---|---|
| Current (v2.0) | 10FEB2023 | • Updated the definition of the PK Concentration Analysis Set in section 6.3 to clarify that PK samples on or after randomization date should be included.<br>• Updated the definition of the PK Parameter Analysis Set in section 6.3 to consist of all randomized subjects who receive at least one IP dose post-randomization from who receive all assigned IP doses post-randomization, and who have an evaluable ABP 501 or Humira serum concentration-time profile between weeks 28 and 30. The Per-protocol PK Parameter Analysis Set was changed accordingly and consists of all subjects in the PK Parameter Analysis Set who do not have an important protocol deviation during the study that could affect the primary PK endpoints.<br>• Clarified Lead in Treated Set would be used for all analyses for the Lead-in Period in section 6.7. The previous version mentioned safety analyses and PK concentration summary only.<br>• Added PK summary statistic reporting precision in section 9.1.<br>• Added clopper-pearson as the CI calculation method for PASI and sPGA response rates in section 9.6.2.<br>• Added COVID related analyses for the Lead-in Period and COVID-19 SMQ search strategy in section 9.7.1. |
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## List of Appendices

## List of Abbreviations and Definition of Terms

| Abbreviation | Explanation |
|---|---|
| ADA | antidrug antibody |
| ALT | alanine aminotransferase |
| AMQ | Amgen MedDRA Query |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{tau}$ | area under the curve from time 0 over the dosing interval |
| BSA | body surface area |
| CI | confidence interval |
| $C_{max}$ | maximum concentration |
| CRF | case report form |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| $C_{trough}$ | trough concentration at steady state |
| EOI | events of interest |
| EOS | end-of-study |
| FAS | full analysis set |
| GMR | geometric mean ratio |
| IP | investigational product |
| IXRS | Interactive Web/Voice Response System |
| LLOQ | lower limit of quantification |
| LOCF | last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NRI | non responder imputation |
| PASI | Psoriasis Area and Severity Index |
| PK | pharmacokinetic(s) |
| PT | preferred term |
| LTS | Lead in Treated Set |
| SAP | statistical analysis plan |
| SMQ | standardized MedDRA query |
| sPGA | Static Physician's Global Assessment |
| SAS | Safety Analyses Set |

| | |
|---|---|
| SOC | system organ class |
| TEAE | treatment-emergent adverse events |
| TFL | Tables, Figures, and Listings |
| $t_{max}$ | time of maximum concentration |
| $t_{last}$ | time of the last concentration reported |

## 1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within protocol (No. 20200497) version 1.0 for ABP 501 study 20200497, dated 03 Jun 2021The scope of this plan includes the final analysis that is planned and will be executed by Parexel International, the designated contract research organization.

## 2. Objectives, Endpoints and Hypotheses

### 2.1 Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| | |
| **Primary:**<br>To demonstrate pharmacokinetic similarity in subjects with multiple switches between Humira® (adalimumab) and ABP 501 compared to subjects receiving continued use of Humira | Primary pharmacokinetic endpoints:<br>• $AUC_{tau}$ between week 28 and week 30<br>• $C_{max}$ between week 28 and week 30<br>Secondary pharmacokinetic endpoints:<br>• $t_{max}$ between week 28 and week 30<br>• $C_{trough}$ between week 14 and week 28 |
| | |
| **Secondary:**<br>To assess the efficacy, safety and immunogenicity in subjects with multiple switches between ABP 501 and Humira compared with subjects receiving continued use of Humira | Secondary Endpoints:<br>Efficacy related Endpoints:<br>• PASI percent improvement from baseline (day 1) to week 30<br>• PASI 75 response at week 30<br>• PASI 90 response at week 30<br>• PASI 100 response at week 30<br><br>Safety related Endpoints:<br>• Treatment-emergent adverse events and serious adverse events, post randomization<br>• Events of interest, post randomization<br><br>Immunogenicity-related Endpoints:<br>• Incidence of antidrug antibodies, post randomization |

Enter Exploratory Objectives Endpoints

### 2.2 Hypotheses and/or Estimations

The analyses of the primary pharmacokinetic(s) (PK) endpoints will test the following hypotheses for each endpoint:

Null Hypothesis ($H_0$): The geometric means ratio (GMR) between ABP 501 and Humira is outside a prespecified margin of (0.8, 1.25),

versus

Alternative Hypothesis ($H_a$): The GMR between ABP 501 and Humira is within a prespecified margin of (0.8, 1.25).

To establish that the risk in terms of safety or diminished efficacy of switching between ABP 501 and Humira is not greater than the risk of using Humira without such switching, both 90% confidence intervals (CIs) of GMR of ABP 501 versus Humira for $AUC_{tau}$ and $C_{max}$ from the primary analysis must fall within the prespecified margin above.

## 3. Study Overview

### 3.1 Study Design

This is a randomized, double-blinded, phase 3 study in adult subjects with moderate to severe plaque psoriasis. This study is planned to be conducted globally at study centers including but not limited to North America and Europe.

The total duration of study participation for each subject will be about 36 weeks, with up to 4 weeks for screening and approximately 32 weeks after the first investigational product administration.

Subjects will receive an initial 6 doses of Humira on week 1 (day 1) ([redacted] mg loading dose), 1 week later on week 2 ([redacted] mg), then 2 weeks later on week 4, week 6, week 8, and week 10 ([redacted] mg), administered subcutaneously (SC). At week 12, subjects will be randomized to either the continued use group or switching group in a 1:1 ratio, stratified by geographic region and prior biologic use at baseline (week 1/day 1, yes vs. no). Subjects in the continued use group will stay on Humira Q2W with last dose at week 28 and subjects in the switching group will switch to ABP 501 Q2W at week 12 (dosed week 12 and week 14), then back to Humira Q2W at week 16 (dosed week 16 and week 18), and again to ABP 501 Q2W at week 20, (dosed week 20, week 22, week 24, week 26, and last dose at week 28).

At Week 12, efficacy assessments will be conducted including evaluation of PASI.

Subjects who do not achieve a PASI 50 response or better improvement at Week 12 are considered as non-responders and will not be randomized at Week 12; these subjects will complete End of Study (EOS) procedures at Week 12. The Lead-in Period will occur from day 1 until prior to randomization at Week 12. Those unable to complete the Week 12 visit will be discontinued from the study. All enrolled subjects not randomized at Week 12 will be considered lead-in failures and the lead-in failure reason will be documented.

### 3.2 Sample Size

Approximately 414 subjects will be enrolled to receive Humira during the Lead-in Period. Subjects with prior biologic use for psoriasis will be capped at 50% of the total enrolled subjects. This sample size will ensure approximately 342 subjects will be randomized at Week 12 after the Lead-in Period, considering 17% lead-in failures (including treatment failure defined as subjects who do not achieve PASI 50 response or better improvement at Week 12), in a 1:1 ratio to the continued use group or the switching group. The randomization will be stratified by prior biologic use for psoriasis at baseline (week 1/day 1, yes vs. no) and geographic region. The number of subjects enrolled may be adjusted during the study with the actual lead-in failure rate seen to ensure approximately 342 subjects will be randomized at Week 12. Subjects already enrolled will be allowed to be randomized at Week 12. The sample size of 342 randomized subjects will provide at least 90% power to demonstrate similarity of the primary PK endpoints based on the Two One Sided Tests at a 0.05 significance level, assuming a between-subject variability (as measured by coefficient of variation) of 53% for ABP 501 and Humira , a true GMR of 1 between ABP 501 and Humira , a similarity margin of (0.8, 1.25), and 15% drop outs after randomization through Week 30 (including subjects who discontinue the study prior to Week 28 and those reaching Week 28 but do not have evaluable primary PK endpoints between weeks 28 and 30).

### 3.3 Adaptive Design

None.

## 4. Covariates and Subgroups

### 4.1 Planned Covariates

Unless stated otherwise, the stratification factors (prior biologic use for psoriasis [“yes” versus “no”] at baseline [week 1], and geographic region) will be included as covariates in the statistical models for the PK and efficacy analyses. In addition, weight and PK trough concentration at the end of the Lead-in Period (week 12) will be included as

covariates in the statistical model for the primary PK endpoints. For continuous efficacy endpoints (e.g. PASI percent improvement from baseline, Body Surface Area (BSA) change from baseline), in addition to the stratification factors, the corresponding baseline scores will also be included as covariates in models.

Covariate values may be discordant if collected via case report form (CRF) and Interactive Web/Voice Response System (IXRS). Analyses that are intended to evaluate the treatment effect and include stratification variables as covariates in the model will be based on the CRF stratification values, regardless of the subject's IXRS stratification values, to provide unbiased estimates of the effects of treatment and stratification variables without loss of efficiency (Ke et al, 2017).

### 4.2 Subgroups

Subgroup analyses will be conducted for the primary PK parameter endpoints for the neutralizing antidrug antibody (ADA) negative subgroup (see definition in Section 5.1).

## 5. Definitions

### 5.1 General

**Actual Treatment Received During Lead-in Period**

If a subject received any dose of ABP 501 during the Lead-in Period, the actual treatment for the subject is defined as ABP 501. Otherwise, the actual treatment for the subject is defined as Humira.

**Actual Treatment Received During Post-randomization Period**

For a subject randomized to switching group or continued use group and receiving all assigned treatments, the actual treatment received is defined as the switching group or the continued use group. Subjects randomized to the switching group that deviate from the switching regimen will be analyzed in a separate group and their actual treatment will be labeled "Deviated from Switching Regimen". Similarly, subjects randomized to the continued use group and deviate from this treatment regimen will be in actual treatment group labeled "Deviated from Continued use Regimen".

**Baseline**

Unless stated otherwise, the baseline of the study is defined as the last non-missing assessment taken prior to the first dose of investigational product (IP) a subject received (see definition of first dose date). In cases where baseline assessments are taken on the

same day as the first dose of IP, and either no times are reported or the IP and assessment times are the same, it will be assumed that these assessments are taken prior to IP being administered.

**Change from Baseline**

Change from baseline is defined as (value at post-baseline visit – value at baseline).

**Concomitant and Prior Medication**

Prior medications are defined as medications with a stop date prior to first dose of IP the subject received (see definition of first dose date). Concomitant medications are defined as any medications ongoing at the start of IP treatment for the subject or with a start date on or after the first dose date.

**Developing ADA incidence**

Developing antibody incidence during the Lead-in Period is defined as the number of subjects in the Lead in Treated Set (LTS) with a negative or no antibody result at baseline and a positive antibody result post-baseline (including unscheduled visits) during the Lead-in Period divided by the number of subjects in the LTS with at least one post-baseline result during the Lead-in Period.

Developing antibody incidence during the Post-randomization Period is defined as the number of subjects in the Safety Analysis Set (SAS) who have a positive result post randomization and have never tested positive (i.e., negative or no results) prior to the first dose of post-randomization IP divided by the number of subjects in the SAS who have at least a result post randomization.

**End of Study (EOS) Date**

The EOS date is the date recorded on the End of Study page of the CRF.

**First Dose Date**

It is defined as the date the subject received the first dose of IP.

**First Post-randomization Dose Date**

It is defined as the date the subject received the first post-randomization dose of IP.

**Last Dose Date**

It is defined as the date the subject received the last dose of IP.

**Last Observation Carried Forward (LOCF)**

A method of imputation where missing post-baseline data will be imputed by carrying forward the last non-missing post-baseline value for that endpoint. Baseline values will not be carried forward.

**Neutralizing ADA Negative Subgroup**

Defined as subjects in the subset of Safety Analysis Set (SAS) who have never tested positive (i.e. tested negative or no results) prior to the first dose of post-randomization IP, have at least one neutralizing ADA result post-randomization, and all available post-randomization neutralizing ADA results are negative.

**Non Responder Imputation (NRI)**

A method of imputation where a subject with missing post-baseline binary response data will be imputed as a non-responder, regardless of the reasons for missing data.

**Study Analysis Visit**

If more than one actual visit (including the unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the later visit with non-missing data will be considered for analysis.

For Efficacy, Vital, Safety Lab & PK

| Study Analysis Visit | Target Day | Study Day | Interval (days) | Endpoint | | |
|---|---|---|---|---|---|---|
| | | | | Efficacy | Vital & Safety Lab[a] | PK |
| Baseline[b] | 1 | ≤1 | NA | X | X | X |
| Week 2 | 8 | 2-21 | 20 | | X | |
| Week 6 | 36 | 22-56 | 35 | X | X | X |
| Week 12[b] | 78 | 57-91 | 35 | X | X | X |
| Week 16 | 106 | 92-119 | 28 | X | X | X |
| Week 20 | 134 | 120-161 | 42 | X | X | X |
| Week 28 | 190 | 162-196 | 35 | | X | X |
| Week 30 | 14 days post week 28 dose | 197-210 | 14 | X | X | |
| Week 32 | 218 | ≥211 | NA | | X | |

[a] Safety lab is not scheduled at week 2 and week 16. Laboratory parameters assessment will not be included at these two visits in the output tables.
[b] If a subject has laboratory measurements on the same day as the first dose date at week 1/Day 1 or week 12 but at a time after the first dose of IP at week 1/Day 1 or week 12, respectively is administered, the laboratory measurements will not be defined as baseline or week 12, but will be included in consideration for week 6 or 20 measurements, respectively.

PK concentrations between Week 28 – Week 30 are summarized by nominal study visit per the following table as listed in the protocol:

Tolerance Windows for Pharmacokinetic Endpoint Sample Collection

| **Study Visit** | **Tolerance Windows[a]** |
|---|---|
| Week 28 predose | Within 3 hours prior to week 28 investigational product administration |
| 1 hour post week 28 dose | ±15 minutes |
| 1 day post week 28 dose | ±5 hours |
| 3 days post week 28 dose | ±6 hours |
| 4 days post week 28 dose | ±6 hours |
| 7 days post week 28 dose | ±6 hours |
| 11 days post week 28 dose | ±24 hours |
| 14 days post week 28 dose | ±48 hours |

[a] The week 28 visit and dose should be performed with a window of ± 3 days. Subsequent visits are done in relation to the actual week 28 investigational product dose date (eg, for the 3 days post week 28 dose timepoint, the PK sample should be collected 3 days after the actual week 28 dose, with a collection window of ± 6 hours).
PK: pharmacokinetic(s)

For ADA

| Study Analysis Visit | Target Day | Study Day |
|---|---|---|
| Baseline | 1 | <=1 |
| Week 6 | 36 | <=56 |
| Week 12 | 78 | <=91 |
| Week 16 | 106 | <=119 |
| Week 20 | 134 | <=161 |
| Week 28 | 190 | <=196 |
| Week 30 | 14 days post week 28 dose | <=210 |
| Week 32 | 218 | <=EOS Visit Date |

**Study Day**

Study day is defined as the number of days from Study Day 1.

Before Study Day 1: Study Day = (Date of assessment – Date of Study Day 1)

On or After Study Day 1: Study Day = (Date of assessment – Date of Study Day 1) +1

Therefore, the day prior to Study Day 1 is -1.

**Study Day 1**

Study day 1 is defined as the first day of IP the subject received (see definition of first dose date).

**Study Period**

The following definitions will be used for PK, safety and efficacy analyses.

Lead-in Period

It is defined as the time period from the first dose of IP the subject received (see definition of first dose date for the subject) until prior to the first post-randomization dose for subjects who are randomized and treated post-randomization, or to the EOS visit for subjects not randomized or for subjects who were randomized but not treated post-randomization.

Post-randomization Period

For subjects who are randomized and treated post-randomization, it is defined as the time period from the first post-randomization dose to the EOS visit.

**Study Randomization**

Study randomization is defined as when subject receives a random treatment allocation via the IXRS system.

**Total IP Exposure Duration**

The total IP exposure duration for the subject (in weeks) for each study period (Lead-in Period, Post-randomization Period) will be derived as: (the period end date – the period start date+1)/7. The Lead-in Period end date for the subjects who are randomized and treated post-randomization is the date of the first IP post randomization -1.

**Transient ADA**

A transient ADA result during the Lead-in Period is defined as a positive antibody result post-baseline (including unscheduled visits) during the Lead-in Period with a negative or no antibody result at baseline and a negative result at the subject's last visit tested within the Lead-in Period.

A transient ADA result during the Post-randomization Period is defined as a positive antibody result post-randomization (including unscheduled visits) during the Post-randomization Period with negative or no antibody results prior to the first dose of post-randomization IP and a negative result at the subject's last visit tested within the Post-randomization Period.

### 5.2 Pharmacokinetic

Pharmacokinetic parameters will be calculated from the serum concentration-time data using noncompartmental methods (Phoenix WinNonlin®, version 8.2 or higher, Pharsight Corp, St. Louis, MO) and actual sampling times. The following PK parameters will be reported:

| Variable | Definition |
|---|---|
| $AUC_{tau}$ | area under the curve from week 28 over the dosing interval up to week 30 using the observed values. |
| $C_{max}$ | Maximum observed serum concentration obtained directly from the concentration time profile. If multiple maxima occur at equal concentrations, the first temporal value will be taken. |
| $t_{max}$ | Time at which the maximum serum concentration was observed obtained directly from the concentration time profile |
| $C_{trough}$ | trough concentration |

The $AUC_{tau}$ is the sum of areas up to the dosing interval and will be calculated using the linear trapezoidal rule. $AUC_{tau}$ will be calculated based on actual time post dose for the observed values between week 28 and 30 without extrapolation or interpolation, and estimated up to the last measurable concentration. Individual $AUC_{tau}$ will be flagged and excluded from summary statistics and statistical testing if less than 2 post $t_{max}$ concentration values are reported or less than 2 post $t_{max}$ concentration values are above LLOQ. $C_{trough}$ at a specific week is defined as the pre-dose level for the respective week.

### 5.3 Efficacy

**Body Surface Area (BSA)**

The percent of BSA affected by Psoriasis (%BSA) is estimated by assuming that the subject's palm, excluding the fingers and thumb, represents roughly 1% of the body's surface (Chandran, 2009).

**PASI**

The PASI is a measure of the average redness (erythema), thickness (induration), and scaliness (scaling); each graded on a 0–4 scale of the lesions, weighted by the area of involvement (Feldman and Krueger, 2005). PASI combines the assessment of the severity of lesions and the area affected (extent of skin Ps) into a single score in the range 0 (no disease) to 72 (maximal disease).

**PASI Percent Improvement from Baseline**

PASI percent improvement from baseline is defined as 100 × (value at baseline – value at post-baseline visit) / value at baseline. A percent improvement will not be calculated if the baseline value is missing. A positive value will be considered PASI improvement. Hence, PASI percent improvement will be in a positive direction while PASI percent worsening will be in a negative direction.

**PASI Response**

PASI Response is defined as a subject meeting or surpassing a pre-specified threshold for percent improvement in PASI score compared to the baseline PASI score. An improvement of at least 75% qualifies a subject as being a PASI 75 responder, an improvement of 90% qualifies a subject as being a PASI 90 responder and an improvement of 100% qualifies a subject as being a PASI 100 responder.

**Static Physician's Global Assessment (sPGA)**

The sPGA is a 6-point scale (0-5) used to measure the severity of disease (induration, scaling, and erythema). The sPGA should be completed by the same assessor performing the PASI assessments. All assessments for a given subject should be made by the same observer whenever possible.

**sPGA Response**

An sPGA response is defined as a subject meeting sPGA assessment values of 0 (Clear) or 1 (Almost Clear).

### 5.4 Safety

**Adverse Events Leading to Discontinuation from IP/Study**

AEs leading to discontinuation from IP/study are those with an action taken with IP indicating “drug withdrawn” or other action taken of “study discontinued”.

**Event of Interest (EOI)**

An EOI is defined as a noteworthy event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals (Council for International Organizations of Medical Sciences [CIOMS] VI, 2005). The EOIs for this study will include:

- Serious infections,
- malignancies,
- hypersensitivity reactions,
- demyelinating disease,
- hematological reactions,
- heart failure,
- lupus-like syndrome,
- liver enzyme elevations,
- and injection site reaction.

The detailed search strategies for the EOIs are included in Appendix A.

**Treatment-emergent Adverse Event**

Treatment emergent adverse events (TEAEs) during the Lead-in Period are defined as adverse events that start on or after the first dose of IP and prior to the first dose post randomization for randomized and treated subjects, or EOS for lead-in failures or for subjects who were randomized but not treated post-randomization.

TEAEs during the Post-randomization Period are defined as adverse events that start on or after the first dose of IP post-randomization and prior to the EOS.

If the adverse event starts on the same day as the first dose of IP, then the flag indicating whether the adverse event started prior to the first dose on the adverse event CRF page will be used to determine whether this is a TEAE during the Lead-in Period. For randomized and treated subjects, an adverse event that starts on the same day as the first post-randomization dose will be considered as a TEAE post-randomization.

## 6. Analysis Sets

### 6.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized subjects. This analysis set will be used for sensitivity analyses of efficacy endpoints and will be analyzed according to randomized treatment group.

### 6.2 Safety Analysis Set

The Safety Analysis Set (SAS) consists of all randomized subjects who received at least 1 dose of IP post-randomization. This analysis set will be used for analyses of the safety endpoints during the Post-randomization Period according to actual treatment received.

### 6.3 PK Analysis Sets

**PK Concentration Analysis Set**

The PK Concentration Analysis Set which will include all randomized subjects who received at least 1 dose of IP post-randomization and have at least 1 reported serum concentration of ABP 501 or Humira on or after the day of randomization. This analysis set will be used for analyses of PK concentrations during the Post- randomization Period according to actual treatment received.

**PK Parameter Analysis Set**

The PK Parameter Analysis Set consists of all randomized subjects who receive at least one dose post-randomization and who have an evaluable ABP 501 or Humira serum concentration-time profile between weeks 28 and 30. This analysis set will be used for the primary analysis of the primary and secondary PK endpoints and will be analyzed according to actual treatment received.

**Per-protocol PK Parameter Analysis Set**

The Per-protocol PK Parameter Analysis Set consists of all subjects in the PK Parameter Set who do not have an important protocol deviation during the study that could affect the primary PK endpoints. This analysis set will be used for a sensitivity analysis of the primary PK endpoints and will be analyzed according to actual treatment received.

### 6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

None.

### 6.5 Per-protocol Efficacy Analyses Set

The Per-protocol Efficacy Analysis Set consists of all subjects who are randomized and receive all assigned doses post-randomization and who have not experienced an important protocol deviation that may affect the evaluation of the efficacy endpoints. This analysis set will be used for primary analysis of the secondary efficacy endpoints and will be analyzed according to actual treatment received.

### 6.6 Interim Analyses Set(s)

None.

### 6.7 Study-specific Analysis Set

**Lead in Treated Set**

The Lead in Treated Set (LTS) consists of all enrolled subjects treated with at least 1 dose of IP during the Lead-in Period. This analysis set will be used for all analyses for the Lead-in Period and will be analyzed according to actual treatment received.

## 7. Planned Analyses

### 7.1 Interim Analysis and Early Stopping Guidelines

None.

### 7.2 Primary Analysis

None.

### 7.3 Final Analysis

The final analysis for the study will be performed after all subjects reach Week 32 or terminate early.

## 8. Data Screening and Acceptance

### 8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

Data screening process will be documented in a data management plan by Parexel and agreed by Amgen. In addition to the data screening built into the Parexel Data Management Plan, the programming of analysis datasets, tables, figures and listings (TFL) provides additional data screening.

When the database has been declared to be complete and accurate, the database will be locked. Database lock will follow the standard operating procedure(s) at Parexel.

### 8.2 Data Handling and Electronic Transfer of Data

Clinical data will be entered in RAVE database and exported as SAS® version 9.4 or higher datasets. Converted datasets will be created using SAS® and following standard Clinical Data Interchange Standards Consortium Standard Data Tabulation Model (CDISC SDTM, version 1.4, Implementation Guide version v3.2) conventions. Analysis datasets will be created using SAS® and following CDISC Analysis Data Model (ADaM, version 2.1, Implementation Guide 1.1) standards.

Medical history and AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of the final analysis to assign a system organ class (SOC) and preferred term (PT) to each event. Adverse events and abnormal laboratory results considered as AEs are assigned a toxicity grade according to National Cancer Institute (NCI-US) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Prior and concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary (WHO-DD) at the time of the final analysis.

### 8.3 Handling of Missing, Below LLOQ and Incomplete Data

Missing PK concentration data and endpoints will not be imputed.

For the purpose of calculating $AUC_{tau}$, concentrations that are below the LLOQ after $t_{max}$ will be excluded; values less than the LLOQ that are encountered prior to $t_{max}$ will be set to zero and included. Individual $AUC_{tau}$ will be flagged if less than 2 post $t_{max}$ concentration values are reported or less than 2 post $t_{max}$ concentration values are above LLOQ.

For summary statistics and linear plots for the PK concentrations, concentration values < LLOQ will be set to zero. For log-linear plots, concentration values below LLOQ will not be displayed.

The handling of missing values for efficacy endpoints are detailed in Section 9.6.

Missing safety and ADA endpoints will not be imputed.

**Imputation for Partial or Missing Dates**

If dates are missing or incomplete for an AE (including deaths) or concomitant medication, the following algorithm will be used for imputation:

| Start Date | Stop Date |
|---|---|

| | | Complete: yyyymmdd | | Partial: yyyymm | | Partial: yyyy | | Missing |
|---|---|---|---|---|---|---|---|---|
| | | <1st dose | ≥1st dose | <1st dose yyyymm | ≥1st dose yyyymm | <1st dose yyyy | ≥1st dose yyyy | |
| Partial: yyyymm | = 1st dose yyyymm | 2 | 1 | n/a | 1 | n/a | 1 | 1 |
| | ≠ 1st dose yyyymm | | 2 | 2 | 2 | 2 | 2 | 2 |
| Partial: yyyy | = 1st dose yyyy | 3 | 1 | 3 | 1 | n/a | 1 | 1 |
| | ≠ 1st dose yyyy | | 3 | | 3 | 3 | 3 | 3 |
| Missing | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

1 = Impute as the date of first dose

2 = Impute as the first of the month

3 = Impute as January 1 of the year

4 = Impute as January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then there is a data error and do not impute the start date.

Imputation rules for partial or missing stop dates:

1. Initial imputation
    a. For partial stop date “mmyyyy”, impute the last of the month.
    b. For partial stop date “yyyy”, impute December 31 of the year.
    c. For completely missing stop date, do not impute.
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date.

Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
    a. If “mmyyyy” for last contact date = “mmyyyy” for death date, set death date to the day after the last contact date.
    b. If “mmyyyy” for last contact date < “mmyyyy” for death date, set death date to the first day of the death month.
    c. If “mmyyyy” for last contact date > “mmyyyy” for death date, data error and do not impute.
2. If both month and day are missing for death date or a death date is totally missing, set death date to the day after the last contact date.

The imputed dates will be used to assess whether AEs should be considered as treatment-emergent and if medications should be included in the safety summaries as prior or concomitant, however the original, partial dates will be included in data listings.

### 8.4 Detection of Bias

None.

### 8.5 Outliers

Individual ABP 501 and Humira serum concentration-time points, if considered anomalous, may be excluded from the analysis. If a subject has a protocol deviation that is thought to potentially affect serum concentration assessment, the pharmacokineticist may decide to exclude the value following a review of the available documentation (bioanalytical report, clinical report, etc). Any such exclusion will be documented and clearly outlined in the clinical study report (CSR).

Entire individual PK profile for a subject may be excluded following review of the available documentation. Any such exclusion will be clearly listed in the CSR along with justification for exclusion.

### 8.6 Distributional Characteristics

None.

### 8.7 Validation of Statistical Analyses

All report outputs will be produced/all statistical analyses will be performed using SAS® version 9.4 or a higher version in a secure and validated environment.

Programs will be developed and maintained and output will be verified in accordance with current standard operating procedures at Parexel. The validation process is repeated any time TFLs are re-delivered with different data. Execution of this validation process is documented throughout the study. The entire set of TFLs will be checked for completeness, accuracy prior to its delivery to Amgen.

## 9. Statistical Methods of Analysis

### 9.1 General Considerations

All statistical analyses will be performed using SAS® (Version 9.4 or higher).

Unless otherwise specified, descriptive data summaries will be tabulated by treatment for all endpoints. Categorical data will be summarized using number of subjects, frequency and percentages of subjects falling into each category, with the denominator

for percentages being the number of subjects in the analysis sets for each treatment group, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place.

All continuous variables will be summarized using mean, standard deviation, median, minimum, maximum, 25th percentile (Q1), 75th percentile (Q3), and number of subjects with observations. The mean, geometric mean, median, Q1, and Q3 will be presented to one decimal place greater than the original data, standard deviation will be two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

For PK endpoints, additional precision rules are as follow:

Pharmacokinetic serum concentrations will be reported in ng/ml with 3 decimal places and will follow the general conventions for summary statistics.

Pharmacokinetic parameters with units of ng/ml or h*ng/ml will be converted to ug/ml or h*ug/ml with 1 decimal place.

| Summary Statistics | Reporting Precision |
|---|---|
| CV%/geometric CV% | 1 d.p. |
| Geometric LS mean | 2 d.p. |
| Geometric LS mean ratios | 4 d.p. |
| CI | Same number of decimal places as the associated statistic |

d.p.= decimal place(s)

Confidence intervals may also be provided (when specified).

For any of the summaries that are to be done by visit, the derived analysis study visit as defined in Section 5.1 will be used for analysis unless otherwise noted.

### 9.2 Subject Accountability

The following information will be summarized for subject disposition and accountability for each of the analysis sets defined in Section 6, unless stated otherwise:

- Number of subjects enrolled in the Lead-in Period will be summarized by region, country, and site using LTS. Similarly, number of subjects randomized will be summarized by region, country, and site using the FAS.
- Subject disposition summary will include

- Number of subjects in the LTS who discontinued treatment with reason of discontinuation, discontinued treatment with reason of discontinuation related to COVID-19, completed the Lead-in Period and who failed the Lead-in Period (i.e., lead-in failures) with reason for lead-in failures for the Lead-in Period and reason for lead-in failures related to COVID-19 for the Lead-in Period;
- Number of subjects who were randomized, who were treated with IP post-randomization, completed treatment, discontinued treatment with reason of discontinuation, discontinued treatment with reason of discontinuation related to COVID-19, completed study, and discontinued study with reason of discontinuation and discontinued study with reason related to COVID-19 for the Post-randomization Period

- Summary of analysis sets with reasons for exclusion from each analysis set (for all screened subjects)
- Randomization list for the FAS
- List of discontinued subjects from IP and/or study using the LTS for the Lead-in Period and using the FAS for the Post-randomization Period

### 9.3 Important Protocol Deviations and COVID-19 Related Protocol Deviations

Important Protocol Deviations (IPDs) data will be identified and recorded. The study team will conduct on-going reviews of the IPD data throughout the study and the resulting set of subjects to be included in the Per-protocol PK Parameter and Per-protocol Efficacy analysis sets. The Per-protocol analysis sets must be finalized prior to database lock of the final analysis.

For the Post-randomization Period, a summary of incidence of IPDs will be based on FAS and tabulated using number and percentage of subjects by deviation type (including COVID-19 related) and randomized treatment group. A listing of subjects with IPDs will be provided (with a flag indicating whether the deviation leads to exclusion from the Per-protocol PK Parameter or Efficacy analysis sets and a flag indicating whether an IPD is COVID-19 related) based on FAS.

For the Lead-in Period, a summary of incidence of IPDs will be based on LTS and tabulated using number and percentage of subjects by deviation type (including COVID-

19 related). A listing of subjects with IPDs (with a flag indicating whether an IPD is COVID-19 related) will be provided based on LTS.

All COVID-19 related Protocol Deviations (PDs) will be summarized by COVID-19 related deviation type for the FAS and LTS. A listing of subjects with COVID-19 related PDs will be provided for the FAS and LTS.

A listing of subjects affected by COVID-19 related study disruptions in the LTS for the Lead-in Period and in the FAS for the Post-randomization Period will also be provided, if applicable. The definition of “COVID-19 related study disruption” will be determined by the Amgen's study team.

### 9.4 Demographic and Baseline Characteristics

The following demographics and baseline characteristics will be summarized descriptively by treatment group for each of the analysis sets defined in Section 6.

- age (in years, at time of signing informed consent) and age category (<65 vs ≥65),
- race,
- sex,
- ethnicity,
- height,
- weight,
- body mass index (BMI),
- geographic region,
- prior biologic use for psoriasis,
- duration of psoriasis (in years) and duration of psoriasis category,
- BSA affected by psoriasis,
- sPGA,
- baseline PASI score,
- Prior use of systemic or photo therapies.

Medical history will be coded according to MedDRA and unresolved findings will be summarized by SOC and PT for the LTS.

## 9.5 PK Analyses

### 9.5.1 Analyses of Primary PK Endpoint(s)

#### 9.5.1.1 Primary Analysis

The primary analysis of the primary PK endpoints, $AUC_{tau}$ and $C_{max}$, between Week 28 and 30 will be performed based on the PK Parameter Analysis Set according to the actual treatment groups (switching group versus continued use group).

The point estimates and 90% CIs for the GMRs between ABP 501 and Humira for $AUC_{tau}$ and $C_{max}$ between Week 28 and 30 will be estimated using an analysis of covariance (ANCOVA) model adjusting for stratification factors, weight and PK trough concentration at the end of the Lead-in Period (week 12). Prior to statistical testing, the PK parameters will be logarithmically transformed (natural log). Point estimates and 90% CIs for the mean difference in logarithmic PK parameters will be estimated using the ANCOVA model, which will then be transformed back to the original scale to obtain the point estimates and 90% CIs for GMR. To establish interchangeability, the 90% CIs of GMR of ABP 501 vs Humira for $AUC_{tau}$ and $C_{max}$ (between Week 28 and 30) from the primary analysis should fall within the prespecified similarity margin (0.8, 1.25).

#### 9.5.1.2 Secondary Analyses

$AUC_{tau}$ and $C_{max}$ of ABP 501 and Humira between weeks 28 and 30 will be listed by subject and summarized descriptively by treatment group using PK Parameter Analysis Set.

To assess the robustness of the primary analysis result, the ANCOVA analysis described above will be repeated using the Per-protocol PK Parameter Analysis Set. Furthermore, the primary ANCOVA analysis will be repeated by adding gender as a covariate in addition to the covariates specified for the primary analysis (stratification factors, weight and PK trough concentration at the end of the Lead-in Period [Week 12]) using PK Parameter Analysis Set.

### 9.5.2 Analyses of Secondary PK Endpoints

The analyses of the secondary PK endpoints of $t_{max}$ between Week 28 and 30 and $C_{trough}$ between Week 14 and 28 will be based on the PK Parameter Analysis Set according to the actual treatment groups. $t_{max}$ will be listed by subject and summarized descriptively (only median, min and max) by the treatment group. $C_{trough}$ between Week 12 and 28 will be summarized descriptively by visit and treatment group. For post-randomization $C_{trough}$ assessment (between Week 14 and 28), the point estimates and 90% CIs for GMR for $C_{trough}$ between the two treatment groups will be estimated using an ANCOVA model

adjusting for stratification factors, weight and PK trough concentration at the end of the Lead-in Period (Week 12).

In addition, $C_{trough}$ between Week 12 and 28 will be summarized descriptively and presented graphically by box plot by analysis visit and actual treatment group using the PK Concentration Analysis Set.

#### 9.5.3 Analyses of Other PK Endpoint(s)

PK concentrations during the Lead-in Period will be summarized descriptively by visit based on the LTS. Boxplots of serum concentration over time during Lead-in Period will be presented graphically using the LTS.

PK concentrations between Week 28 and 30 will be summarized descriptively by nominal visit and actual treatment group based on the PK Concentration Analysis Set. Individual and mean (+/- STD) serum concentration time-profiles between Week 28 and 30 by actual treatment group will be presented graphically on semilogarithmic and linear scales using the PK Concentration Analysis Set.

$t_{last}$ of ABP 501 and Humira between weeks 28 and 30 will be listed by subject and by treatment group using PK Parameter Analysis Set.

#### 9.5.4 Subgroup Analyses

The primary PK endpoints will be summarized and compared within the neutralizing ADA negative subgroup for the PK Parameter Analysis Set and employing the analysis methods described in Section 9.5.1.1.

### 9.6 Efficacy Analyses

#### 9.6.1 Analyses of Primary Efficacy Endpoint(s)

None.

#### 9.6.2 Analyses of Secondary Efficacy Endpoint(s)

##### 9.6.2.1 Primary Analysis

The primary analysis will be performed based on the Per-protocol Efficacy Analysis Set according to the actual treatment groups with missing PASI score at Week 30 visit imputed by LOCF and missing PASI 75, PASI 90 and PASI 100 response at week 30 imputed by NRI. Confidence interval for response rates will be calculated by the Clopper-Pearson method.

The point estimate and 90% CI of the mean difference in PASI percent improvement from baseline at Week 30 will be estimated from an ANCOVA model adjusting for the baseline PASI value and the stratification factors.

The point estimate and 90% CI of the risk difference in PASI 75**,** PASI 90**,** and PASI 100 response rates at Week 30 will be estimated from a generalized linear model with an identity link adjusting for the stratification factors.

#### 9.6.2.2 Secondary Analyses

These endpoints will also be summarized descriptively by actual treatment group based on Per-protocol Efficacy Analysis Set using observed data.

Sensitivity analyses will be conducted by repeating the models in section 9.6.2.1 using observed data in the FAS according to randomized treatment groups and in the Per-protocol Efficacy Analysis Set according to the actual treatment groups.

### 9.6.3 Analyses of Other Efficacy Endpoint(s)

The analyses of the other efficacy endpoints in this section will be based on the Per-protocol Efficacy Analysis Set by actual treatment group.

The PASI percent improvement from day 1 at weeks 6, 12, 16 and 20 and the PASI 75, PASI 90 and PASI 100 response rates at weeks 6, 12,16 and 20 will be summarized descriptively by treatment group based on observed data.

BSA absolute values and changes from baseline will be summarized descriptively by visit (at weeks 6, 12, 16, 20 and 30) and treatment group using observed data. In addition, the point estimate and 90% CI of the mean difference in the change from baseline for BSA at Week 30 between the two groups will be estimated from an ANCOVA model adjusting for the baseline BSA value and the stratification factors with missing values imputed by LOCF.

sPGA scores will be summarized descriptively by visit (at weeks 6, 12, 16, 20 and 30) and treatment group. sPGA response (0/1) will also be summarized descriptively by visit and treatment group using observed data. The sPGA response (0/1) at Week 30 will be analyzed by a generalized linear model adjusting for the stratification factors with missing values imputed by NRI. Confidence interval for response rate will be calculated by the Clopper-Pearson method.

## 9.7 Safety Analyses

Safety analyses of the safety endpoints during the Post Randomization Period and the Lead-in Period will be performed based on the SAS and LTS, respectively, according to actual treatment received.

### 9.7.1 Adverse Events

For summary of AEs, the following summaries, (a) through (n), will be provided for the Post Randomization Period. In addition, summaries (a), (e), (f), (l) without risk difference, (m) and (n) will be provided for the Lead-in Period.

(a) overall summary of TEAEs,

(b) TEAEs by PT,

(c) TEAEs by SOC and PT,

(d) TEAEs by SOC, PT, and maximum severity grade,

(e) treatment-emergent SAEs by PT,

(f) treatment-emergent SAEs by SOC and PT,

(g) grade 3 or higher TEAEs by PT,

(h) TEAEs leading to discontinuation from IP/study by PT,

(i) TEAEs leading to dose delayed of IP by PT,

(j) fatal TEAEs by PT,

(k) treatment-emergent EOIs by PT,

(l) overall summary of treatment-emergent EOIs with risk difference,

(m) treatment-emergent COVID-19 AEs by PT,

(n) treatment-emergent SAEs occurring on or after the presumed start date of COVID-19 infection by PT

Counting of AEs will be by subject, and subjects will be counted only once within each SOC or PT by study period. For tables categorized by severity, subjects with multiple event PTs within a particular SOC will be counted under the category of their most severe event PT within that SOC.

AEs tabulated by preferred term will be presented in descending order of frequency of the switching group for the Post-randomization Period or the Humira group for the Lead-in Period.

The risk difference and 90% CI of each treatment-emergent EOI will be calculated using Wald asymptotic confidence limits or exact confidence limits if the number of subjects for any treatment is less than 25.

A listing of treatment-emergent SAEs will be provided for the Post-randomization Period and the Lead-in Period separately.

All serious TEAEs occurring on or after the presumed start date of COVID-19 infection will be listed.

COVID-19 AEs will be flagged based on COVID-19 standardized query (SMQ) of the current MedDRA version at the time of the final analysis.

### 9.7.2 Laboratory Test Results

Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to Système International units for reporting and processing purposes.

For the Post-randomization Period, absolute values and changes from baseline by visit will be presented descriptively. In addition, shift tables of the worst post-randomization laboratory toxicity based on CTCAE grading relative to randomization at week 12 will be presented. The shift tables will take into account all post-randomization (schedule and unscheduled) laboratory results in the determination of the worst post-randomization laboratory toxicity. Furthermore, subject incidence tables of grade ≥ 3 laboratory toxicities will be provided. Standard ranges will be used for the laboratory analysis.

For the Lead-in Period, absolute values and changes from baseline by visit will be presented descriptively.

Lab assessments will be grouped for summary as follows:

**Hematology:** white blood cell parameters: white blood cell count and differential,

**Hematology:** red blood cell parameters: hemoglobin, hematocrit, red blood cell count, absolute neutrophil count,

**Hematology:** other parameters: platelets,

**Serum chemistry:** hepatobiliary parameters: alanine aminotranferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, gamma glutamyl transferase,

**Serum chemistry:** general chemistry: sodium, potassium, albumin, total protein, glucose (random),

**Serum chemistry:** renal function tests: blood urea nitrogen, creatinine,

**Urinalysis:** pH, specific gravity, glucose, bilirubin, blood, and protein.

### 9.7.3 Vital Signs

Observed and change from baseline for each vital sign parameter will be summarized descriptively by visit for the Post-randomization Period.

### 9.7.4 Physical Measurements

None.

### 9.7.5 Electrocardiogram

None.

### 9.7.6 Antibody Formation

The number and percent of subjects developing binding or neutralizing ADA will be tabulated descriptively by treatment group and visit in the SAS for the Post-randomization Period and in the LTS for the Lead-in Period.

The incidence of transient antibody will also be summarized for each study period.

### 9.7.7 Exposure to Investigational Product

Exposure to ABP 501/Humira will be summarized descriptively by actual treatment group for the LTS for the Lead-in Period and for the SAS for the Post-randomization Period, respectively. Summary statistics will be provided for the total number of doses administered, total dose received, subjects with at least one dose delay/not administered and reasons (including whether or not it is due to COVID-19 related reasons), subjects with at least one dose of IP missed due to COVID-19 related reasons, and total duration of IP exposure.

A subject listing of each administered lot number(s) for IP and a listing of unique manufacturing lot numbers used in the study will be provided.

### 9.7.8 Exposure to Non-investigational Product

None.

### 9.7.9 Exposure to Other Protocol-required Therapy

None.

### 9.7.10 Exposure to Concomitant Medication

Prior and concomitant medications will be coded using the latest available World Health Organization Drug Dictionary as of the time of the final analysis.

For the Lead-in Period, concomitant medication use by PT is summarized descriptively for the LTS and for the SAS by actual treatment group.

For the Post-randomization Period, concomitant medication use by PT is summarized descriptively by actual treatment group based on SAS.

**Enter Other Analyses**

Enter Analyses of Pharmacokinetic or Pharmacodynamic Endpoints

Enter Analyses of Clinical Outcome Assessments

Enter Analyses of Health Economic Endpoints

Enter Analyses of Biomarker Endpoints

## 10. Changes from Protocol-specified Analyses

The definition of PK Parameter Analysis Set could be too restrictive and may result in exclusion of evaluable subjects, and the protocol is not required to be amended. The PK Parameter Analysis Set was changed to consist of all randomized subjects who receive at least one IP dose post-randomization from who receive all assigned IP doses post-randomization, and who have an evaluable ABP 501 or Humira serum concentration-time profile between weeks 28 and 30. The Per-protocol PK Parameter Analysis Set was changed accordingly and consists of all subjects in the PK Parameter Analysis Set who do not have an important protocol deviation during the study that could affect the primary PK endpoints. These changes will also be documented in the Clinical Study Report.

## 11. Literature Citations / References

Ke C, Wang J, Zhang C, Jiang Q, Snapinn S. On errors in stratified randomization. Statistics in Biopharmaceutical Research. 2017 Apr 3;9(2):225-33.

Chandran V, Gottlieb A, Cook RJ, Duffin KC, Garg A, Helliwell P, Kavanaugh A, Krueger GG, Langley RG, Lynde C, McHugh N. International multicenter psoriasis and psoriatic arthritis reliability trial for the assessment of skin, joints, nails, and dactylitis. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2009 Sep 15;61(9):1235-42.

Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Annals of the rheumatic diseases. 2005 Mar 1;64(suppl 2):ii65-8.

## 12. Prioritization of Analyses

None.

## 13. Data Not Covered by This Plan

None.

## 14. Appendices

## Appendix A. List of Events of Interest and the Associated SMQ and EOI Searching Strategies

For the following events of interest, the table below summarizes the search strategy that will be conducted:

| Event of Interest | Category of EOI query (SOC, SMQ / Amgen query) |
|---|---|
| Serious Infections | Use the infections and infestations system organ class. Any adverse event with a system organ class of infections and infestations, CTCAE grade ≥3 and/or serious (Yes) will be included. |
| Malignancies | Use Malignant tumors SMQ (narrow). |
| Hypersensitivity | Use Hypersensitivity SMQ (narrow). |
| Demyelinating Diseases | Use Demyelination SMQ (narrow). |
| Hematological Reactions | Use Hematopoietic cytopenias SMQ (narrow). |
| Heart Failure | Use Cardiac failure SMQ (narrow). |
| Lupus-like Syndromes | Use Systemic lupus erythematosus SMQ (narrow). |
| Liver Enzyme Elevations | Use drug related hepatic disorders – comprehensive search SMQ (narrow). |
| Injection Site Reactions | AMQ Injection site reactions (narrow) |

Enter Appendix Concomitant Medications

Enter Appendix Clinical Outcome Assessment Forms Instruments

Enter Appendix Health Economic Forms Instruments

Enter Appendix Details of PK or PK/PD Methods for Modeling