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STATISTICAL ANALYSIS PLAN

VERSION: 1.0

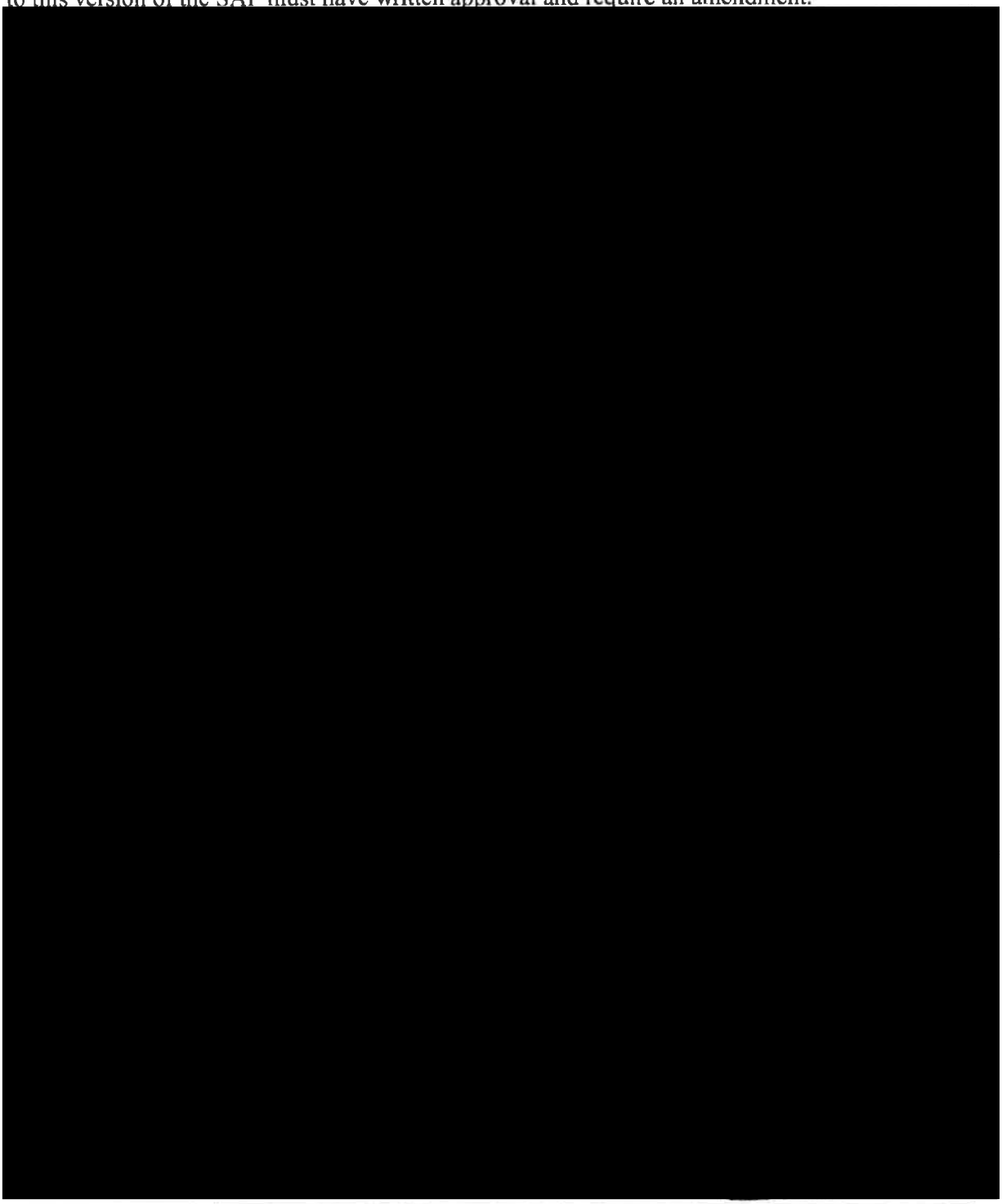
DATE: 8 February 2022

SPONSOR:	Aldeyra Therapeutics, Inc.
PROTOCOL NUMBER:	ADX-629-PS-001
[redacted]**PROJECT NUMBER:**	249-12851-201
PROTOCOL TITLE:	A Multi-Center, Open-Label Phase 2 Clinical Trial to Evaluate the Safety, Tolerability, and Efficacy of ADX-629 Administered Orally to Subjects with Plaque Psoriasis
PROTOCOL DATE:	October 23, 2020

[redacted]

SAP APPROVAL

The following individuals approve version 1.0 of the SAP dated February 08, 2022. All changes to this version of the SAP must have written approval and require an amendment.



ABBREVIATIONS

AE	Adverse Event
BID	Twice daily
BSA	Body Surface Area
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	enzyme-linked immunosorbent assays
EOT	End of Treatment
FSH	Follicle Stimulating Hormone
HepB – sAg	Hepatitis B surface antigen
HepC - Ab	Hepatitis C antibody
HIV	Human Immunodeficiency Virus
PASI	Psoriasis Area Severity Index
PGIC	Patient Global Impression of Change
PO	Orally
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TI	Therapeutics, Inc.

TABLE OF CONTENTS

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol ADX-629-PS-001, A Multi-Center, Open-Label, Phase 2 Clinical Trial to Evaluate the Safety, Tolerability, and Efficacy of ADX-629 Administered Orally to Subjects with Plaque Psoriasis.

This SAP was created using Clinical Protocol ADX-629-PS-001 Version 3.0 dated June 9, 2021, and the eCase Report Forms (eCRF) Version v1.0 dated April 7, 2021.

2. PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol ADX-629-PS-001. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of ADX-629-PS-001 is to evaluate the safety, tolerability, and efficacy of ADX-629 in subjects with plaque psoriasis.

3.2 Clinical Efficacy Endpoints

1. Change from baseline in Psoriasis Area Severity Index (PASI) score at Week 12/end of treatment (EOT).
2. Proportion of subjects with PASI-50 (defined as a reduction of $\geq$ 50% from baseline) at Week 4, 8, and 12/EOT
3. Proportion of subjects with PASI-75 (defined as a reduction of $\geq$ 75% from baseline) at Week 4, 8, and 12/EOT
4. Change from baseline in Investigator's Global Assessment (IGA) score at Week 4, 8, and 12/EOT
5. Patient Global Impression of Change (PGIC) score at Week 4, 8, and 12/EOT

3.3 Safety Endpoints

1. Incidence (severity and causality) of any local and systemic adverse events (AEs)
2. Changes from Baseline in vital signs at Week 4, 8, and 12/EOT
3. Changes from Baseline in clinical laboratory tests (chemistry, hematology, and urinalysis) at Week 4, 8, and 12/EOT
4. Changes from Baseline in overall interpretation of the electrocardiogram (ECG) at Week 4, 8, and 12/EOT

3.4 Biomarker Endpoint(s)

1. Analyses of biomarkers in peripheral blood and skin tape strips

2. Change from baseline in the expression of select biomarkers in the skin and peripheral blood

3.5 Metabolite Profiling Endpoint

Presence/absence of urine and plasma drug metabolite(s) at Week 4.

4. STUDY DESIGN

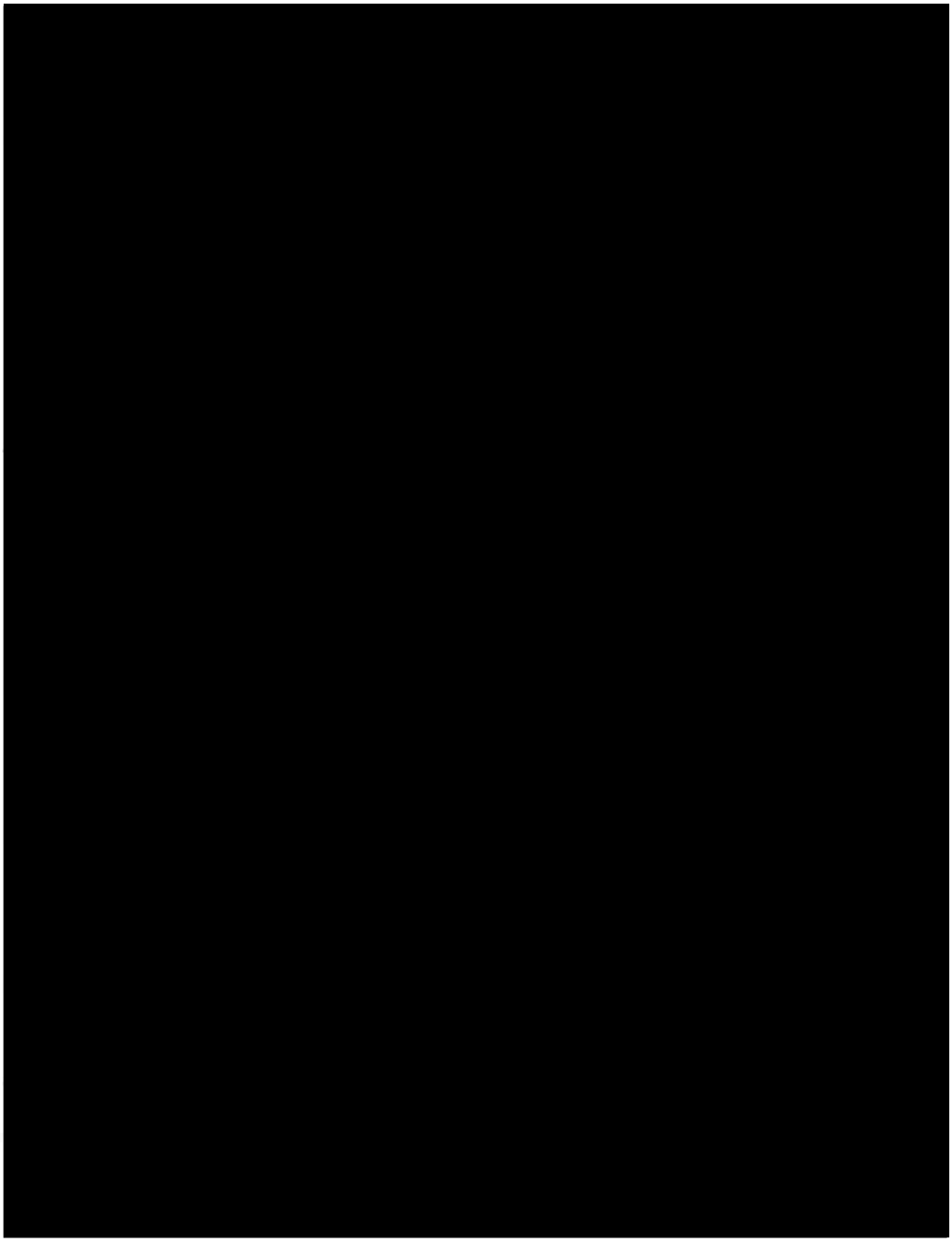
ADX-629-PS-001 is a multi-center, open-label trial of ADX-629 in adult subjects with stable plaque psoriasis. Approximately 10 subjects with stable moderate to severe plaque psoriasis (IGA score $\geq$ 3, PASI score of $\geq$ 12, and body surface area [BSA] $\geq$ 8%) who fulfill the inclusion/exclusion criteria will be enrolled at 3 trial sites in the United States.

All subjects will be assigned to the following treatment group in an open-label manner:
ADX-629, 250 mg BID for 12 weeks.

All subjects will administer the test article orally (PO) BID.

Subjects will have 7 trial visits: 5 in-person visits and 2 phone calls. Activity will be assessed via PASI, Skin Biomarker Analysis, Blood Biomarker Analysis (RASP enzyme-linked immunosorbent assays [ELISAs] and cytokine levels), IGA, and PGIC. Safety will be assessed by vital signs, physical examinations, clinical laboratory tests, ECG, and AEs. Metabolite profiling will be assessed by urine and plasma drug metabolite analysis.

SCHEDULE OF EVENTS



5. DEFINITIONS

- Study Day: The study day is the day of study relative to the date of test article application (Baseline visit / Day 1). Study Day = follow-up visit date – first dose date +1.

- Baseline: The baseline assessment is defined as the last non-missing measurement collected at the Baseline visit (Visit 2) prior to test article application.

6. CLINICAL EVALUATIONS

6.1 Psoriasis Area and Severity Index - PASI

The severity of plaque psoriasis by body region (head, upper limbs, trunk, and lower limbs) and the percentage area affected by body region will be assessed. For each body region, erythema, induration/thickness, and scaling will be graded using a 5-point scale (0=clear, 1=slight (mild), 2=moderate, 3=severe, 4=very severe) and the percent involvement of each body region will be assigned a numeric score (from the BSA assessment described below): 0% (0), 1% – 9% (1), 10% – 29% (2), 30% – 49% (3), 50% – 69% (4), 70% – 89% (5) or 90% – 100% (6). The sign scores for each body region will be summed and multiplied by the Area Score, and then multiplied by the amount of BSA assigned to that body region (0.1 for head, 0.2 for upper limbs, 0.3 for trunk, and 0.4 for lower limbs). The sum of PASI scores by body region will give the total PASI score, which may range from zero (0) to a maximum of 72.

6.2 Investigator's Global Assessment

The IGA score is a static evaluation of the overall severity or "average" degree of severity of a subject's disease, taking into account all of the subject's psoriatic lesions (excluding those on the face, scalp, groin, axillae, and other intertriginous areas) by the investigator or designee as the subject appears on the day of the evaluation. The evaluation takes into consideration the 3 individual characteristics of psoriasis (plaque elevation, scaling, and erythema) with the IGA score at each visit representing the average degree of plaque elevation, scaling, and erythema that is present amongst all of the lesions on a rating scale ranging from 0 (clear) to 4 (severe).

6.3 Patient Global Impression of Change

The PGIC is a single item measure that assesses the subject's impression of overall change from Baseline of plaque psoriasis signs and symptoms at the time the questionnaire is administered, using a 7-point visual rating scale ranging from 1 (much improved) to 7 (much worse).

7. SAFETY EVALUATIONS

7.1 Physical Examination

Brief physical examinations at Visit 1/Screening and Visit 2/Baseline will include examination of head and neck, dermatologic (except the indication being studied), cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait. Clinically significant abnormalities at Visit 1/Screening and Visit 2/Baseline will be recorded as medical history. A targeted physical examination will be conducted at follow-up visits driven by the subject's signs and symptoms. Any new or worsening clinically significant abnormalities at any post-Baseline visits will be recorded as AEs.

7.2 Vital Signs

Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured at every clinic visit. Assessments will be made after the subject has rested in a seated position for at least 5 minutes. Height and weight will also be measured at Visit 1/Screening.

7.3 Electrocardiogram

12-lead ECGs will be performed at every clinic visit after the subject has rested for at least 10 minutes in the supine positions. Heart rate, PR interval, QRS duration, QT interval, P axis will be measured. Any ECG machine findings will be recorded. The cardiologist will review as normal, abnormal not clinically significant, or abnormal clinically significant. And the investigator will assess if the results are clinically significant (yes or no).

7.4 Photography

Photography documentation is not required in ADX-629-PS-001. However, the investigator may elect to photograph the subject to document the effects of treatment, AEs, or other findings during the trial. All photographs taken as part of ADX-629-PS-001 are for informational purposes only and are not to assist in grading or for any other assessment.

Any photographs taken of readily identifiable features (e.g., the face) will be de-identified (i.e., a masking bar over the eyes). In addition, subject identifiers (i.e., codes) will be used to identify photographs to the appropriate subject.

7.5 Laboratory Tests

Blood and urine specimens will be collected at every clinic visit for chemistry, hematology, and urinalysis. At Visit 1/Screening, serology will be performed for HIV, hepatitis B, and hepatitis C (i.e., HepB-sAg and Hep C-Ab) in all subjects and FSH levels will be evaluated in all females. The post-menopausal range for FSH will be based on the central laboratory's range [typically $\geq$ 40 IU/L]).

7.6 Blood Biomarker Analysis

Plasma samples will be collected, stored at -70°C, and sent under frozen conditions to Charles River Laboratories for cytokine assays and RASP ELISAs for malondialdehyde and 4-hydroxynonenal.

7.7 Skin Biomarker Analysis

Skin tape strips will be collected from all participants for NexGen whole genome sequencing. The purpose of these analyses will be to retrospectively evaluate biomarkers predictive of subject response at baseline, prior to test article administration, as well as to potentially identify additional correlative and pharmacodynamic biomarkers.

7.8 Drug Metabolite Analysis

At Visit 4 only, a urine sample and a plasma sample will be taken from subjects between 2 and 4 hours after test article dosing and sent to Charles River Laboratories (Mattawan, MI) for drug metabolite analysis.

7.9 Urine Pregnancy Tests

The UPTs will be performed at the trial site as permitted by applicable local and national health authority laws and regulations. In the United States, the site must be registered and conform to CLIA regulations for such testing (possesses a current valid CLIA Certificate of Waiver or higher), or at an appropriately registered reference laboratory. The investigator will report the UPT results on the eCRFs, in the subject's medical records, and in independent records maintained at the trial site.

8. STATISTICAL METHODS

8.1 General Considerations

All statistical processing will be performed using SAS®. Summary tables (descriptive statistics or frequency tables) will be provided for screening or baseline variables and safety variables. Summaries will be provided for treatment group. In general, continuous variables will be summarized by number of subjects with non-missing data (N), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by frequency and percentage of subjects within each category.

In general, all summary tables will be supported by relevant subject data listings which will be sorted by study site, subject identification, and visit, as applicable. Figures may be created to aid in the interpretation of results.

8.2 Analysis Populations

8.2.1 Safety Population

The Safety population will include all subjects who received and took the test article.

8.3 Final Analyses and Reporting

Final database lock will occur after all subjects have completed the study assessment period (or withdrew from the study prematurely) and all subject data have been monitored and all queries resolved.

Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not described in this SAP will be clearly identified as such in the CSR.

8.4 Sample Size

Sample size calculations were not performed, as this is primarily a safety and tolerability trial. The number of subjects (N=10) to be enrolled is standard for trials of this type.

8.5 Subject Disposition

The number and percent of subjects who completed the study, who withdrew from the study, and their reasons for withdrawal will be summarized. Subject disposition will be summarized using all subjects who signed informed consent forms and were enrolled in the study.

8.6 Screening and Baseline Assessments

8.6.1 Demographics

Demographic information including sex, age, race, and ethnicity will be summarized for the Safety population as well as screen failures.

8.6.2 Medical History

Medical histories will be provided in a subject listing for the Safety population. Findings noted during the Screening and Baseline physical examinations will be recorded in the medical history.

8.6.3 Vital Signs

Descriptive statistics of vital signs (weight, height, temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) at Baseline will be provided.

8.6.4 Baseline Clinical Evaluations

Descriptive statistics will be provided for the Screening and Baseline data of PASI and IGA.

8.6.5 Dosing Compliance

Subjects will be instructed to take the test article twice daily for 12 weeks so that the expected number of doses will be 168 (or 167 for subjects for whom only the evening dose (after 4PM) is taken on Day 1). Dosing compliance (percent of expected doses) = 100 x [(reported number of doses) / (expected number of doses)]. Reported number of doses will be calculated from the difference between the number of pills in the bottle dispensed and collected. Compliance will be reported as unknown for any subjects who do not return any study drug bottles. Descriptive statistics will be provided for dosing compliance.

Subjects who take at least 80% of the expected total number of doses and have no other evidence of material dosing non-compliance will be considered to be compliant with test article dosing. The number and percent of compliant subjects will be presented.

8.7 Clinical Evaluation

8.7.1 Analysis of Clinical Evaluation

The clinical endpoints evaluation will be conducted on the Safety population.

[redacted]

For all by-visit analyses of clinical endpoints, the final visit is either Week 12/Visit 6 if a subject completed the study, or the discontinuation visit.

PASI

The PASI will be analyzed for the following endpoints:

- Change from Baseline at Week 4, 8, and 12/EOT (the primary clinical efficacy endpoint)
- Proportion of subjects with PASI-50 (defined as a reduction of ≥ 50% from baseline) at Week 4, 8, and 12/EOT
- Proportion of subjects with PASI-75 (defined as a reduction of ≥ 75% from baseline) at Week 4, 8, and 12/EOT

IGA

The IGA will be analyzed for the following endpoints:

- Change from baseline at Week 4, 8, and 12/EOT (the key secondary clinical efficacy endpoint)

  The proportion of subjects in three categories: ≥1 grade decrease, ≥2 grade decrease, IGA=0 or 1 and ≥2 grade decrease from baseline at Week 4, 8, and 12/EOT

BSA

The BSA will be analyzed for the following endpoint:

- Change from Baseline in BSA score at each study visit (Week 4, 8, and 12/EOT)

PGIC

The PGIC will be analyzed for the following endpoint:

- PGIC score at each study visit (Week 4, 8, and 12/EOT)

8.7.2 Statistical / Analytical Issues

8.7.2.1 Analysis Visit Windows for Assigning Observed Data

Clinical evaluation data will be assigned to analysis visits based on its nominal scheduled visit. Early termination visit will be assigned to analysis visits as defined in the visit window tables below. If the early termination visit occurs within the same analysis visit window as a nominally scheduled visit, the nominally scheduled visit will be used. After applying visit window, each analysis visit should contain no more than one record and is called observed data.

Table 8.5-1. Visit Windows for Assessments[1] On-Treatment at Weeks 4, 8, 12

Week/Visit	Target Day	Study Days
Week 4/Visit 4	29	2-41
Week 8/Visit 5	57	42-69
Week 12/Visit6	85	≥ 70

[1]PASI, IGA, PGIC

8.7.2.2 Handling of Dropouts or Missing Data

Missing data will not be imputed. All analyses will be based on observed data. For all by-visit analyses of clinical endpoints, the final visit is either Week 12/Visit 6 if a subject completed the study, or the discontinuation visit.

8.7.2.3 Interim Analyses

No interim analysis is planned.

8.7.2.4 Multicenter Studies

All study sites adhered to the same protocol and will have their data pooled for summary purposes.

8.7.2.5 Multiple Comparisons / Multiplicity

None

8.7.2.6 Examination of Subgroups

None

8.8 Safety Evaluation

8.8.1 Extent of Exposure

Descriptive statistics will be used to summarize the extent of exposure in the Safety population. The total number of doses taken will be assessed by tablet counts. The frequency and percentage of exposure extent will be summarized based on the following categories: < 4 weeks, ≥ 4 weeks, ≥ 8 weeks, and ≥ 12 weeks.

8.8.2 ADX-629 Metabolite Analysis

Urine and plasma drug metabolite(s) at Day 29 will be analyzed in a separate report by the vendor to be appended to the Clinical Study Report.

8.8.3 Adverse Events

All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome. Verbatim terms will be coded to preferred terms (PTs) and system organ class (SOC) using version 24.0 of the Medical Dictionary for Regulatory Activities mapping system. The PTs and SOC will then be tabulated. For all AE summaries, if a subject has more than one AE within a PT, the subject is counted once in that PT. If a subject has more than one AE within a SOC, the subject is similarly counted once in that SOC.

The number and percentage of unique subjects reporting each treatment emergent AE (TEAE) will be summarized by SOC and PT. The number and percent of unique subjects reporting each TEAE will also be summarized by SOC, PT, and maximum severity (mild, moderate, severe) and closest relationship to test article (not related, unlikely related, possibly related, probably related, and definitely related).

Serious AEs, if any, will be summarized by SOC, PT and treatment group.

8.8.4 Physical Examinations

Physical examination results will be included in medical history listings (from Screening and Baseline) or AE summaries and listings if new or clinically significant worsening abnormalities were observed at post-Baseline physical examinations.

8.8.5 Vital Signs

Descriptive statistics will be provided for the observed and change from Baseline values for temperature, systolic and diastolic blood pressure, heart rate, and respiration rate at Week 4, 8, and 12/EOT. A subject data listing will also be provided.

8.8.6 Electrocardiograms

Descriptive statistics will be provided for the observed and change from Baseline values for ECG parameters (heart rate, PR interval, QRS duration, QT interval, P axis). Changes in overall

cardiologist interpretation of the ECG (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) from Baseline to Week 4, 8, and 12/EOT will be summarized by shift table. A subject data listing will also be provided of the data above, including listing any findings and the investigator's determination of clinical significance.

8.8.7 Clinical Laboratory Tests

All laboratory data (chemistry, hematology, urinalysis, and serology) will be summarized and listed in the units received by the laboratory at each study visit. Shift tables will be presented to facilitate the evaluation of change from Baseline to Week 4, 8, and 12 /EOT. Results outside of normal limits will be classified as clinically significant or not clinically significant. Clinically significant laboratory results may or may not have been coded as AEs, at the discretion of the Investigator.

8.8.8 Urine Pregnancy Tests

Urine pregnancy test data will be summarized and listed for visit at each study visit (screening, Day 1/baseline, Week 4, 8, and 12/EOT).

8.8.9 Concomitant Medications and Concurrent Therapies/Procedures

Concomitant medications will be coded using the March 1, 2021 version of WHODrug Global Dictionary. Current medications/therapies and any medications/therapies taken in the 30 days prior to the start of the trial (Visit 1/Screening) will be recorded as concomitant medications or concurrent procedures, respectively, with the dose (for medications only) and corresponding indication.

A subject listing of the concomitant medications will be provided. In addition, a separate listing of concurrent procedures and therapies will also be provided, as applicable.

8.8.10 Peripheral Blood Biomarker Analyses

[redacted]

8.8.11 Tissue Biomarker Analyses

Whole genome sequencing will be analyzed and reported by the vendor, [redacted]. The final data and analysis will be maintained by the vendor and summarized for the Clinical

Study Report. Generally, change from baseline will be analyzed as a function of time and adjusted by baseline, if feasible.

9. CHANGES TO PLANNED PROTOCOL ANALYSIS

None.