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A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AS012 IN SUBJECTS WITH NON-SEGMENTAL VITILIGO

[redacted]

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[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC	Anatomic-Therapeutic-Chemical
BMI	Body Mass Index
[redacted]	[redacted]
CI	Confidence Interval
CSR	Clinical Study Report
[redacted]	[redacted]
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoS	End of Study
FCS	Fully Conditional Specifications
[redacted]	[redacted]
GGT	Gamma Glutamyltransferase
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDL	High-density Lipoproteins
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human immunodeficiency virus
IA	Interim Analysis
[redacted]	[redacted]
INR	International Normalized Ratio
IP	Investigational Product
ITT	Intent-to-Treat
LDL	Low-density Lipoproteins
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PGA	Physician Global Assessment
[redacted]	[redacted]
PI	Principal Investigator
[redacted]	[redacted]
PT	Prothrombin time

[redacted]	[redacted]
QD	Once a day (quaque die)
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
T4	Serum Free Thyroxine
TEAE	Treatment-Emergent Adverse Event
TID	Three times a day (ter in die)
TSH	Thyroid Stimulating Hormone
UPT	Urine Pregnancy Test
VASI	Vitiligo Area and Scoring Index
VES	Vitiligo Extent Score
[redacted]	[redacted]
VIPs	Vitiligo Impact Patient Scale

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol "A Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Efficacy and Safety of AS012 in Subjects with Non-Segmental Vitiligo", [redacted]

Vitiligo is an acquired pigmentary disorder of skin and mucous membranes, manifesting as expanding depigmented lesions, related to selective loss of melanocytes. To date, there are no approved treatments specifically for vitiligo. [redacted] The current study is a Phase II dose ranging study to assess the efficacy and safety of AS012 in treatment of non-segmental vitiligo.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of different doses of AS012 compared to placebo in subjects with non-segmental vitiligo at Week 24 by evaluating the response using Vitiligo Area Score Index (VASI) scale.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the safety of different doses of AS012 in subjects with non-segmental vitiligo treated over 52 weeks.
- To assess the efficacy of different doses of AS012 by using the Physician Global Assessment (PGA), Vitiligo Extent Score (VES), [redacted], VASI [redacted] in subjects with non-segmental vitiligo treated
- [redacted]
- To assess the effect of AS012 on quality of life, as measured by Dermatology Life Quality Index (DLQI) and Vitiligo Impact Patient scale (VIPs) [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

3. STUDY OVERVIEW

3.1 Study Design

Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be assigned to treatment with the investigational products or placebo control according to a randomization scheme.

- **Part I:** 24 weeks: Subjects will be randomized to Placebo, [redacted] or [redacted] AS012 in 3:3:1:3:1 ratio (approximately first 45% of enrolled subjects) or in 1:1:3:1:3 (approximately remaining 55% enrolled subjects).
- **Part II:** week 24 to week 52: Subjects initially randomized to placebo will be re-randomized to [redacted] AS012 in 1:1 ratio. Subjects originally randomized to AS012 doses will remain on their assigned dosing regimen until the end of Part II (week 52).
- **Part III:** week 52 to week 64: After week 52 (or early termination of study treatment prior to week 52), the study treatment will be stopped, and all subjects will enter the follow-up period to monitor safety and tolerability for 12 weeks following last dose of study treatment.

[redacted]

Clinical Evaluations will be performed at:

- Visit 1: Screening Visit (Week ≥ -4 / Day -28 to -1);
- Visit 2: Baseline Visit (Week 1 / Day 1);
- Visit 3: Interim Visit (Week 4 / Day 29 ± 3 Days);
- Visit 4: Interim Visit (Week 12 / Day 85 ± 3 Days);
- Visit 5: Interim Visit (Week 16 / Day 113 ± 3 Days);
- Visit 6: Interim Visit (Week 20 / Day 141 ± 3 Days);
- Visit 7: Interim Visit (Week 24 / Day 169 ± 3 Days);
- Visit 8: Interim Visit (Week 28 / Day 197 ± 3 Days);
- Visit 9: Interim Visit (Week 36 / Day 253 ± 3 Days);
- Visit 10: Interim Visit (Week 44 / Day 309 ± 3 Days);
- Visit 11: Interim Visit (Week 48 / Day 337 ± 3 Days);
- Visit 12: End of Treatment Visit (Week 52 / Day 365 ± 3 Days);
- Visit 13: Follow-up Visit (Week 64 / Day 449 ± 3 Days);

Subjects will be admitted into the study after informed consent has been obtained. An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit. Subjects discontinued from Investigational Product (IP) prior to the end of study will be required to complete the End of Study (EoS) assessment within 2 weeks after the last dose.

[redacted].

Randomization and re-randomization will be stratified by stability of disease (stable vs. non-stable) [redacted]

The assigned IP will be administered orally three tablets three times a day, in the morning, in the afternoon, and in the evening according to a randomization scheme. Subjects will be required to use diaries to document the date of study treatments, any missed treatments, and the occurrence of all adverse events (AEs).

The duration of each Subject's participation in the study will be approximately 64 weeks (449 days).

If the Principal Investigator determines that the Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study (e.g., an increase in VASI score from baseline by ≥25%), the Subject may be discontinued from the study as a treatment failure and treated using the standard care.

A detailed Schedule of Procedures is provided in Appendix 11.1.

3.2 Sample Size

The study will randomize approximately 320 subjects into 5 treatment arms (n=approximately 64 subjects per arm) in a 1:1:1:1:1 ratio. The sample size assumes a drop-out rate of about 20%, with 52 evaluable subjects per treatment arm at the time of analysis. The study is powered at 85%, and assumes a two-sample Z-test with equal variances, two-sided alpha (α) of 0.05, a Baseline VASI mean of 15.7 and standard deviation of 8.9 and an improvement at Week 24 of 35% (Δ 5.50) for AS012 versus an improvement for placebo of 10% (Δ 1.56), for a mean treatment difference of 3.94. Since the correlation between Baseline and Week 24 VASI scores is expected to be >0.5, the standard deviation of the difference is conservatively estimated at 70% of the Baseline SD, or 6.4. The sample size takes into account an interim assessment of futility and efficacy, using an O'Brien-Fleming error spending function to determine the boundaries, once the placebo, [redacted] dose reach 75% completion of the Week 24 VASI assessment. Randomization will be stratified by stability of disease (stable vs. non-stable) [redacted] With a total of six possible stratification levels, 52 evaluable subjects per treatment arm ensures at least 8 subjects per stratification level.

3.3 Randomization and Unblinding Procedures

To maintain the study blind, the randomization schedule will be generated by a third party. Randomization will be performed according to a computer-generated randomization scheme. The placebo and tablets for all strengths of AS012 look alike which ensures blinding. The Investigational Product will be provided in identically labeled and packaged such that neither the Subject nor any Investigator can identify the treatment. The Drug Labeling, Packaging and Shipping facility will hold the randomization code throughout the conduct of the study in order to minimize bias. A sealed copy of the randomization scheme (as a scratch off portion of the product label attached to the drug accountability page) will be retained at the study site. In the event of an emergency, the Subject-specific treatment may be identified; however, every effort should be made to maintain the blind. Where possible, the Medical Monitor should be contacted before breaking the blind for any subject. The Sponsor must be notified in the event the blind is broken.

The treatment assignments will remain blinded until the final database is closed.

If Suspected Unexpected Serious Adverse Reactions (SUSAR) requires unblinding by a Regulatory Agency, a designated member of the Sponsor's safety team will be un-blinded on case-by-case basis by receiving the randomization directly from the study unblinded statistical consultant.

The bioanalytical team will analyze the samples collected from all subjects, including samples from subjects assigned to placebo to ease the selection of samples and avoid releasing the randomization code.

4. STUDY ENDPOINTS/OUTCOMES

4.1.1 Primary endpoint

The primary endpoint is change from baseline in VASI score at Week 24.

4.2 Key secondary endpoints

Key secondary endpoints of this study are:

- Change from baseline in VES at Week 24.
- [redacted]
- Change from baseline in VIPs at Week 24

4.3 Other secondary endpoints

[redacted]

- Change from baseline and percent change from baseline in VES at [redacted] Week 24,
  - [redacted]
- [redacted]

- [redacted]
- Proportion of subjects achieving a PGA score of "no involvement" (score 0) or "limited extent" (score 1) with at least 2-point reduction from baseline, at [redacted] Week 52.
- Change from baseline in DLQI at [redacted] Week 52.
- Incidence and severity of AE

[redacted]

5. ANALYSIS POPULATIONS

5.1 Safety Population

The Safety Population will consist of all subjects who were randomized into the study and dispensed study drug. This population will be the primary population for the safety analysis. Subjects will be analyzed according to the actual treatment received.

5.2 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will consist of all randomized subjects regardless of whether they received the investigational product. This population will be the main population for the efficacy analyses. Subjects will be analyzed according to the treatment they were randomized to receive.

[redacted]

6. STATISTICAL METHODS OF ANALYSIS

6.1 General Principles

The statistical analyses will be performed by Quartesian LLC, with approval of the Sponsor, using SAS Version 9.4 (or higher). All tables, figures and listings will be produced in landscape format.

In general, all data will be listed by subject and visit/time point where appropriate. The summary tables will be stratified by, or have columns corresponding to, treatment groups.

The total number of subjects in the treatment group (N) under the specified population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. Number of subjects with missing values will also be displayed, but only if non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data. The standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be displayed. The count [n] indicates the actual number of subjects in a particular category, which should always be less

than or equal to the total number of subjects in the respective study group with known (non-missing) category [M]. Percentage will be obtained by: % = n/M*100. Unless otherwise specified, all percentages will be expressed to one decimal place.

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated.

Baseline will be defined as the last assessment, scheduled or not, prior to the first dose of the study drug, unless otherwise specified.

In by-visit summaries, only data collected on scheduled visits/timepoints will be summarized. Data from unscheduled assessments will be included in listings and may be used in determination of baseline if applicable.

Relative days will be calculated relative to date of first dose of the study drug. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days).

For assessment on or after the day of first dose of the study drug:

Relative Day = Date of Assessment – Date of First Dose of Study Drug+1.

For assessment before the day of first dose of the study drug:

Relative Day = Date of Assessment – Date of First Dose of Study Drug.

All dates will be displayed in DDMMMYYYY format.

6.1.1 Treatment Groups

Findings collected up to Week 24 visit will be analyzed by treatment groups based on the treatments that subjects take in Part I of the study:

- Placebo
- AS012 [redacted]
- AS012 [redacted]
- AS012 [redacted]
- AS012 [redacted]

Findings collected after Week 24 visit (including those in the follow-up part of the study) will be analyzed by treatment groups based on the treatments that subjects take in Part II of the study:

- Placebo/AS012 [redacted]
- Placebo/AS012 [redacted]
- AS012 [redacted]
- AS012 [redacted]
- AS012 [redacted]
- AS012 [redacted]

Note that subjects initially randomized to Placebo and re-randomized to AS012 doses [redacted] after Week 24 will not be pooled with subjects taking the same doses from the study start due to different exposure times.

Adverse events will be analyzed by actual treatment at the time of event onset, i.e., using the same treatment groups as findings collected up to Week 24.

6.1.2 Adjustment for multiplicity

No adjustment for multiplicity will be needed for the analysis of the primary endpoint due to the step-down testing approach described in Section 6.9.1.2. P-values for other endpoints will be presented nominally, without multiplicity adjustment. No inferences will be drawn from these p-values.

6.2 Subject Disposition

The number of subjects who were screened, were screen failures, were randomized to treatment, included in the Safety, ITT, [redacted] prematurely discontinued from the study (along with the reasons for discontinuation) will be presented.

All disposition information will be listed. Date of completion/discontinuation shown in this listing will be derived as the maximum between then the Date of Completion/Discontinuation collected at the End of Study eCRF and the date of last visit collected at Visit Details eCRF. Also, a listing of enrollment details will provide the date of informed consent and inclusion/exclusion criteria not met, if any.

6.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will include:

- age
- sex
- [redacted]
- ethnicity
- [redacted]

Descriptive statistics will be presented for continuous variables. Frequency counts and percentage will be presented for categorical variables. Height will be presented in centimeters, weight in kilograms, and BMI in kg/m^2.

Age will be derived from Informed Consent Date and Date of Birth as the number of whole years between those two dates.

These analyses will be performed for the Safety, ITT, [redacted] populations.

All demographic parameters and baseline characteristics will be presented in the by-subject listings.

6.4 Medical history

Medical history will be summarized by Medical Dictionary of Regulatory Activities (MedDRA) (Version 23.1) System Organ Class and Preferred Term. One subject will be counted once for each applicable Preferred Term and System Organ Class. This summary will be performed for the Safety population. All medical history information will be listed.

6.5 Protocol Deviations

Protocol deviations will be derived algorithmically as well as reported by sites. [redacted] Specific deviations and their exclusion status are defined in the separate Protocol Deviations Specification document.

[redacted] All classification of protocol deviations will be performed prior to database lock.

6.6 Chest X-Ray

Before Baseline visit a chest X-ray should be evaluated for concurrent medical condition or uncontrolled, clinically significant systemic disease. A chest X-ray is acceptable if performed within the past 6 months and available at a site along with an associated report. All results from the chest x-ray collected on eCRF will be listed.

[redacted]

6.8 Study Drug Exposure and Compliance

Duration of exposure will be defined as follows:

[Date of Last Dose] – [Date of First Dose] + 1

For subjects initially randomized to AS012, Date of Last Dose is collected at the End of Study eCRF and Date of First Dose is collected at the Study Drug Administration eCRF at Visit 2. In case Date of Last Dose is not collected at the End of Study eCRF (e.g. the subject is lost to follow-up), the date of last dose will be assumed to be equal to the date of the last visit in the study.

Duration of exposure will also be defined separately for Part I of the study and Part II of the study.

For Part I, Date of Last Dose is the date preceding the date of study drug administration at Visit 7/Week 24, provided the subject is administered drug at Visit 7; otherwise, it is the Date

of Last Dose as collected at the End of Study eCRF. The Date of First dose is collected at the Study Drug Administration eCRF at Visit 2.

For Part II the Date of Last Dose is collected at the End of Study eCRF and Date of First Dose is collected at the Study Drug Administration eCRF at Visit 7/Week 24.

Compliance will be calculated in terms of total number of tablets taken separately for Part I, Part II and both parts overall. Compliance will be defined in two ways:

1. Based on the diary data as (9*[Number of planned treatment days] – [Total number of missed tablets]) / (9*[Number of planned treatment days]) *100%
2. Based on the drug accountability data as ([Total number of drug bottles dispensed]*105 – [Total number of tablets returned])/ (9*[Number of planned treatment days]) *100%. This is based on the assumption that each dispensed bottle contained 105 tablets.

Number of planned treatment days will be defined as follows:

- For Part I
  - For subjects that completed Part I, i.e. attended Week 24 visit: [Date of Week 24 Visit] – [Date of the first dose of the study drug]
  - For subjects that discontinued in Part I: [Date of discontinuation] - [Date of the first dose of the study drug] + 1
- For Part II
  - For subjects that completed Part II, i.e. attended Week 52 visit: [Date of Week 52 Visit] – [Date of Week 24 Visit] + 1
  - For subjects that discontinued in Part II: [Date of discontinuation] – [Date of Week 24 Visit] + 1
- For overall compliance (for subject initially randomized to AS012)
  - For subjects that completed Part II, i.e. attended Week 52 visit: [Date of Week 52 Visit] – [Date of the first dose of the study drug] + 1
  - For subjects that discontinued in Part I or Part II: [Date of discontinuation] – [Date of the first dose of the study drug] + 1

Total number of missed tablets will be calculated form the diary data by summing up the values “Total Number of Missed Tablets Per Diary (At Morning)”, “Total Number of Missed Tablets Per Diary (At Afternoon)” and “Total Number of Missed Tablets Per Diary (At Evening)” transcribed at the “Study Drug Accountability” eCRF across applicable visits, i.e:

- For Part I: visits up to and including Week 24 Visit, including any unscheduled visits occurring before Week 24 Visit date
- For Part II: visits after Week 24 Visit, including any unscheduled visits occurring after Week 24 Visit date
- For overall compliance (for subject initially randomized to AS012): all visits

If the subject did not return the diary at least once and therefore the number of missed tablets is not known, the compliance will not be calculated.

Total number of dispensed bottles and total number of returned tablets will be calculated from the "Study Drug Accountability" eCRF by summing up the appropriate fields across the applicable visits.

For subjects initially randomized to placebo overall compliance will be calculated separately for Placebo treatment in Part I and for AS012 treatment in Part II.

Subject will be defined as non-compliant if the subject missed more than 14 continuous days of treatments. Information on missing more than 14 continuous days of treatments will be derived from the subject diaries by the sites and entered into eCRF.

Duration of exposure and compliance (both definitions) will be summarized descriptively by treatment group for the Safety population, separately for Part I and for the entire study. Number and percentage of non-compliant subjects will also be provided. In the summary for the entire study subjects initially randomized to Placebo in Part I and re-randomized to AS012 in Part II of the study will be summarized under both treatments they received.

6.9 Efficacy Analyses

6.9.1 Analysis of the primary endpoint

6.9.1.1 Imputation of the primary endpoint

VASI total score will be calculated as explained in Appendix IV to the protocol. Missing Week 24 assessments of VASI will be imputed using multiple imputations methods. For each subject in the ITT population with missing endpoint 50 imputations will be performed using Fully Conditional Specifications (FCS) predictive mean matching imputation model with the factors of the primary analysis model (i.e., treatment, stability of disease [stable vs. non-stable at screening], [redacted] and baseline VASI score as a covariate,) and VASI score at Week 12. Each imputed dataset will be analyzed as described in the next section. The results will be combined using Rubin's rule. See Section 11.2.1 for detailed description of the imputation procedure and SAS sample code.

6.9.1.2 Primary analysis of the primary endpoint

The primary endpoint will be summarized descriptively by treatment group.

Note that approximately 5 sites will be designated to perform VASI, [redacted], and VES by two independent assessors to test reliability and validity of the instruments (see Section 6.9.2.7). Only the assessment by the first assessor will be used for the primary endpoint.

The primary endpoint will be analyzed with an Analysis of Covariance (ANCOVA) model to compare change from baseline in VASI score results between treatment arms at Week 24. The ANCOVA model will include fixed effects for treatment, stability of disease (stable vs. non-stable at screening), [redacted] and baseline VASI score as a covariate. Point estimates and 95% confidence intervals as well as p-values for the hypothesis of no difference will be obtained for the difference between each active dose versus placebo.

Type I error will be preserved in the primary efficacy analysis by use of a closed test step-down approach. Beginning with the highest total daily dose, pairwise comparisons to placebo will be made in the following sequence: [redacted]

[redacted] until a nonsignificant result at the 0.05 level is reached, at which time testing will stop.

[redacted]

6.9.2 Analysis of other endpoints

All endpoints will be summarized using the ITT population. [redacted]

[redacted]

6.9.2.2 Binary endpoints

Binary endpoints include VASI 10, VASI 25, VASI 75, VASI 90, or VASI 100, [redacted] score of "no involvement" or "limited extent" with at least 2-point reduction from baseline. [redacted]

For any number X, "VASI X" is defined as achieving at least X% reduction from baseline in VASI. [redacted]

Number and percentage of subjects achieving these endpoints will be presented by treatment group along with 95% confidence interval for percentages based on binomial proportion.

Maintenance of these endpoint will be assessed by presenting the number and percentage of subjects maintaining these endpoints at Week 64 among those who achieved them at Week 52.

6.9.2.3 Categorical endpoints

Categorical endpoints include [redacted]. Number and percentage of subjects with each category of response will be presented by treatment group and visit.

[redacted]

6.9.2.4 Time to re-pigmentation

Times to re-pigmentation of 10%, 25%, 75%, 90% and 100% are defined as the time from the first dose of the study drug to the first assessment where VASI 10, VASI 25, VASI 75, VASI 90 and VASI 100 correspondingly are achieved. The time will be measured in weeks. For subjects who never achieved the corresponding VASI reduction, the time will be censored at the last VASI assessment.

For subjects who are initially randomized to placebo time to re-pigmentation will be defined separately for the Placebo treatment during Part I of the study and AS012 treatment during Part II of the study. For Placebo treatment the time to re-pigmentation will start with the first placebo dose and will be censored at the last VASI assessment while on placebo. For AS012 treatment the time will start with the first AS012 dose and will be censored at the last assessment after the switch to AS012.

Quartiles of time to re-pigmentation over the 52 weeks of treatment with their 95% confidence intervals will be calculated by treatment group.

[redacted]

[redacted]

6.9.2.7 Endpoints assessed by two independent assessors

Approximately 5 sites will be designated to perform VASI, [redacted] VES by two independent assessors to test reliability and validity of the instruments. Only the assessment by the first assessor will be used for the primary and key secondary endpoints endpoint.

Assessments of the second assessor will be summarized descriptively. Additionally, the coefficient of correlation to the assessments of the first assessor will be presented by visit and treatment group.

6.9.2.8 Subgroup Analysis

The following subgroups of subjects will be identified:

1. By disease stability (stable/unstable) at screening.
[redacted]

The following analyses will be repeated for these subgroups:

1. Analysis of Change from Baseline to Week 24 in VASI [redacted]
2. Analysis of Change from Baseline to Week 24 in VES [redacted]

[redacted]

[redacted]

6.11 Safety Analyses

All safety analyses will be performed on the Safety population.

6.11.1 Adverse Events

Adverse Events will be coded using the MedDRA (Version 23.1) AE coding system for purposes of summarization.

An AE will be considered as treatment-emergent (TEAE) if the date of onset is on or after the date of the first study drug administration. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the study drug start date. If the start date is partially missing, the AE will be considered treatment-emergent, unless the month and year (when available) rule out the possibility that the event occurred post start of study drug dosing.

A TEAE is defined as treatment-related if its relationship to study medication is recorded as "Possible", "Probable" or "Definite" on the eCRF. In case the relatedness was not assessed, the most conservative result (related) will be chosen for the analysis.

For subjects initially randomized to Placebo and later re-randomized to AS012 AEs will be assigned to either Placebo or AS012 treatment based on the date of onset, i.e., AEs that start prior to the first dose of AS012 will be assigned to the Placebo treatment and AEs that start on or after the date of the first AS012 dose will be assigned to the AS012 treatment.

TEAEs will be defined as occurring in Part I of the study if the date of onset is prior to the date of the subject's Week 24 visit. For subjects who discontinue prior to Week 24 visits, all their TEAEs will be defined as occurring in Part I. AEs starting on or after the date of the subject's Week 24 visit will be defined as occurring after Part I.

All summaries of TEAEs will be presented in three ways:

1. Summary of TEAEs in Part I using the treatment groups Placebo, AS012 [redacted], AS012 [redacted], AS012 [redacted], AS012 [redacted].
2. Summary of TEAEs after Part I using the treatment groups Placebo/AS012 [redacted], Placebo/AS012 [redacted], AS012 [redacted], AS012 [redacted], AS012 [redacted], AS012 [redacted].
3. Summary of TEAEs in the entire study for subjects initially randomized to AS012 treatment using the treatment groups AS012 [redacted], AS012 [redacted], AS012 [redacted], AS012 [redacted].

In summaries of TEAEs a subject experiencing the same AE multiple times on the same treatment will only be counted once for that preferred term and treatment. Similarly, if a subject experiences multiple AEs within the same system organ class on the same treatment that subject will be counted only once in that system organ class and treatment. When summarizing AEs by severity, only the most severe occurrence within the preferred term or system organ class and treatment will be used. Similarly, when summarizing AEs by

relationship to study drug, only the most related occurrence within the preferred term or system organ class and treatment will be selected for displays in summary tables.

An overall summary for the Safety population will include, by treatment and overall, the number and percentage of subjects reporting at least 1 TEAE in the following categories:

- Any TEAE
- Treatment-related TEAE
- Serious TEAE
- Treatment-related serious TEAE
- TEAE leading to discontinuation of the study medication
- Treatment-related TEAE leading to discontinuation of the study medication
- TEAE requiring temporary interruption of study medication
- Treatment-related TEAE requiring temporary interruption of study medication
- TEAE leading to death.

The following TEAE frequency tables will be prepared summarizing the overall number of TEAEs, the number and percentage of subjects reporting at least one TEAE by MedDRA System Organ Class (SOC) and preferred term (PT), by treatment group for the Safety population:

- All TEAEs
- Serious TEAEs
- Treatment-related TEAEs
- AEs leading to discontinuation of the study medication
- TEAEs by Severity
- TEAEs by Relationship to Study Drug.

Overall summary of TEAEs and the summary of TEAEs by SOC and PT will be presented separately for TEAEs occurring in Part I, occurring after Part I and for all TEAEs for subjects initially randomized to AS012 treatment.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim, preferred term, system organ class, start date, stop date, intensity, outcome, action taken and causal relationship to the study drug. The AE onset will also be shown relative (in number of days) to the date of first administration of the study drug. In addition the AE duration (if AE Stop Date is available) will be evaluated as below and presented (in number of days).

$$\text{AE Duration} = \text{AE Stop Date} - \text{AE Start Date} + 1$$

6.11.2 Laboratory tests

A central laboratory will be used for all assessments unless noted otherwise. The laboratory assessments include:

Thyroid function: at study Visits 1, 7, and 12 (screening and Weeks 24 and 52) a blood sample will be collected for free T4 and TSH testing.

Hematology: at all study visits a blood sample will be collected for total and differential WBC count, Absolute Neutrophil count (ANC), Absolute Lymphocyte count (ALC), Platelet count, Hemoglobin, Hematocrit.

Lipid profile: at the study Visits 1, 2, 7, and 12 (Screening and study Weeks 1, 24, and 52) a blood sample will be collected for LDL, HDL and total cholesterol and triglycerides testing. The test does not need to be repeated at study Visit 2 if the screening assessment (visit 1) was performed within 2 weeks of Visit 2.

Clinical chemistry: at all study visits a blood sample will be collected for sodium, potassium, chloride, calcium, magnesium, bicarbonate, phosphate, blood urea nitrogen, random glucose, albumin, total protein, alkaline phosphatase, creatinine, Alanine aminotransferase (ALT), AST, gamma glutamyl transferase (GGT), total bilirubin, conjugated bilirubin testing.

Coagulation profile: at the study Visits 1, 2, 7, and 12 (Screening and study Weeks 24, and 52) a blood sample will be collected for PT and INR testing. The test does not need to be repeated at study Visit 2 if the screening assessment (Visit 1) was performed within 2 weeks of Visit 2.

Serology: at Screening visit a blood sample will be collected for: HIV antibodies, HBsAg, and HCV antibodies testing.

Serum pregnancy test: at Screening visit a blood sample will be collected for serum beta-hCG testing.

The following tests will be performed at a clinic site:

Urinalysis dipstick: at the study Visits 1 to 12 (Screening and study Weeks 1 to 52) a urine sample will be collected for pH, specific gravity, protein, glucose, ketones, and blood testing. The test does not need to be repeated at study Visit 2 if the screening assessment (Visit 1) was performed within 2 weeks of Visit 2.

Microscopic exam may be performed at the local or central laboratory at the discretion of the investigator if the dipstick is positive (i.e., trace or above). Only dipstick results will be available in the study database.

Urine Pregnancy Test: at all study visits a urine sample will be collected in women of childbearing potential and the results of all pregnancy tests (positive or negative) will be documented.

A positive result should be confirmed by a different brand of UPT. A confirmed positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment and the subject must be discontinued from the study.

For hematology, chemistry, thyroid function, and coagulation profile the labs that were abnormal and clinically significant at end of treatment (Week 52) are needed at safety follow-up visit (Week 64).

Hematology, chemistry (including lipid profile and thyroid function, and coagulation parameters and their changes from baseline will be summarized descriptively by visit and treatment group. Urinalysis dipstick results will be summarized categorically (positive or negative).

Shifts from baseline among the categories Normal (within the reference range), Low (below the reference range), and High (above the reference range) will be presented by visit.

All results will be listed.

6.11.3 Vital signs

Vital signs, including blood pressure, pulse rate, respiratory rate, and oral body temperature, will be documented at every visit. Vital signs will be measured after the subject has rested in a seated or supine position for at least 5 minutes.

Vital signs and their changes from baseline will be summarized descriptively by visit and treatment group.

All vital signs will be listed.

6.11.4 12-Lead ECG

Digital ECG devices will be used to record 12-lead ECGs at the Screening visit to confirm the subject's eligibility criteria as well as at study Weeks 12, 24, 36, 52, and 64. To avoid impacting results and quality of data, ECG should be done before other invasive or stressful procedures.

The following ECG parameters will be obtained directly from the computerized 12-lead ECG recordings: rhythm, ventricular rate, P-R interval, R-R interval, QRS duration and QT. QTcF will be calculated according to the Fridericia formula. Overall interpretation will be recorded as Normal, Abnormal not clinically significant or Abnormal clinically significant.

Heart rate and intervals as well as their changes from baseline will be summarized descriptively by visit and treatment group. Overall interpretation will be summarized by presenting number and percentage of subjects with each interpretation by visit and treatment group.

All ECG findings will be listed.

6.11.5 Physical Examination

The investigator, sub-investigator or appropriately delegated designee will perform a physical examination, prior to the Subject starting study drug and at the end of treatment. The physical examination will include, at a minimum, examination of the Subject's general appearance, comprehensive skin examination, HEENT (head, eyes, ears, nose and throat), heart, lungs, musculoskeletal system, neurological system, lymph nodes, abdomen and extremities. Each body system will be classified as normal, abnormal not clinically significant or abnormal clinically significant.

Number and percentage of subjects with normal, abnormal not clinically significant or abnormal clinically significant findings will be presented by body system, visit and treatment group.

All results will be listed.

6.11.6 Prior and Concomitant Medication

Prior and concomitant medication will be coded according to the World Health Organization – Drug Dictionary, Version SEP 01, 2020 and the Anatomical Therapeutic Chemical classification system. Prior medications are defined as those taken before the first dose of the study drug (i.e., start and end date before the first dose of the study drug). Concomitant medications are defined as those taken at the time of or after the first dose of the study drug. Any medications that were started before the first dose of the study drug but continued after dosing will be considered a concomitant medication.

All previous and concomitant medication will be listed by subject. Concomitant medications will be summarized by treatment group, Anatomic-Therapeutic-Chemical (ATC) class (highest level available) and preferred name. This analysis will be done for the Safety population.

For subjects re-randomized from Placebo in Part I of the study to an AS012 dose in Part II, any medication that was taken concomitantly with both study drugs will be counted under both.

A medication will be assigned to Part I if it was taken at least once between the date of the first study drug dose and the date of the Week 24 visit; for subjects who discontinue prior to Week 24 visit, all their concomitant medications will be assigned to Part I. Medication will be considered as taken after Part I if it was taken at least once after the date of the Week 24 visit.

The summary of concomitant medications will be presented in three ways:

1. Summary of concomitant medications in Part I using the treatment groups Placebo, AS012 [redacted], AS012 [redacted], AS012 [redacted], AS012 [redacted].
2. Summary of concomitant medications after Part I using the treatment groups Placebo/AS012 [redacted] TOD, Placebo/AS012 [redacted], AS012 [redacted], AS012 [redacted], AS012 [redacted], AS012 [redacted].
3. Summary of concomitant medications in the entire study for subjects initially randomized to AS012 treatment using the treatment groups AS012 [redacted], AS012 [redacted], AS012 [redacted], AS012 [redacted].

All prior and concomitant medications will be listed.

7. INTERIM ANALYSIS

An IA to assess the primary efficacy endpoint will be conducted following the last patient Week 24 visit, once all subject VASI data have been cleaned and soft-locked. The IA for the primary efficacy assessment is planned for Week 24 in order to minimize the exposure of study subjects to placebo, and at the same time assess for efficacy at the earliest time point a

clinical response to treatment could be expected. Analysis outputs will be generated when the last subject has completed 24 weeks of study participation, and may include results for all planned endpoints up to Week 24. At the time of interim analysis at Week 24, the randomization will be unblinded to the sponsor and its designee. The final study database will be locked following last patient last visit at Week 64, once all subject data have been cleaned, and all coding of terms (AE, Concomitant Medications, Medical History) has been finalized.

Investigational sites, subjects, and study team members directly involved in study activities will remain blinded to study treatment assignments until the last subject completes their double-blind follow-up period (Week 64). A designated list of blinded and unblinded study personnel shall be maintained. Sharing of subject-level unblinded information for the IA will be confined to a designated unblinded study team. For the 24-week primary end-point, patient level data will not be provided to the site staff and the blinded study team. The Final CSR will be provided to the PI at the end of the study.

7.1 Content of the interim analysis

A subset of tables, listings and figures to be produced for the interim analysis will be identified in an appendix to this SAP.

7.2 Data cut-off for the interim analysis

The interim analysis will occur after the last subject's Week 24 visit. At this time subjects enrolled in the study earlier will progress well past Week 24 visit and their data from later visits will be present in the study database. While the primary focus of the interim analysis will be on the efficacy at Week 24, all available efficacy data entered into the database up to the pre-defined cut-off date will be used for analysis.

For analyses of safety, only the data up to Week 24 will be used. Any safety finding collected up to 24 visit as well as any adverse events or concomitant medications up to the date of the subject's Week 24 visit will be considered for the purposes of the interim analysis. Adverse events or concomitant medications that started prior to Week 24 visit and ended after it will be considered ongoing.

7.3 Unblinding for the interim analysis

A separate unblinding programming team will be allocated to perform the final run of the interim analysis. A separate "unblinded" folder will be created that will be accessible by the unblinded team only. Analysis programs will be prepared by the main study team, who will remain blinded at the time of the interim analysis and until the final database lock. Once all programs are ready and tested on blinded data, the programs will be transferred to the "unblinded" folder. After the data for the interim analysis are locked, randomization information will be released to the unblinded team only and saved in the "unblinded" folder. The unblinded team will run the analysis programs using the randomization information to produce unblinded tables, listing and figures.

[redacted]

9. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

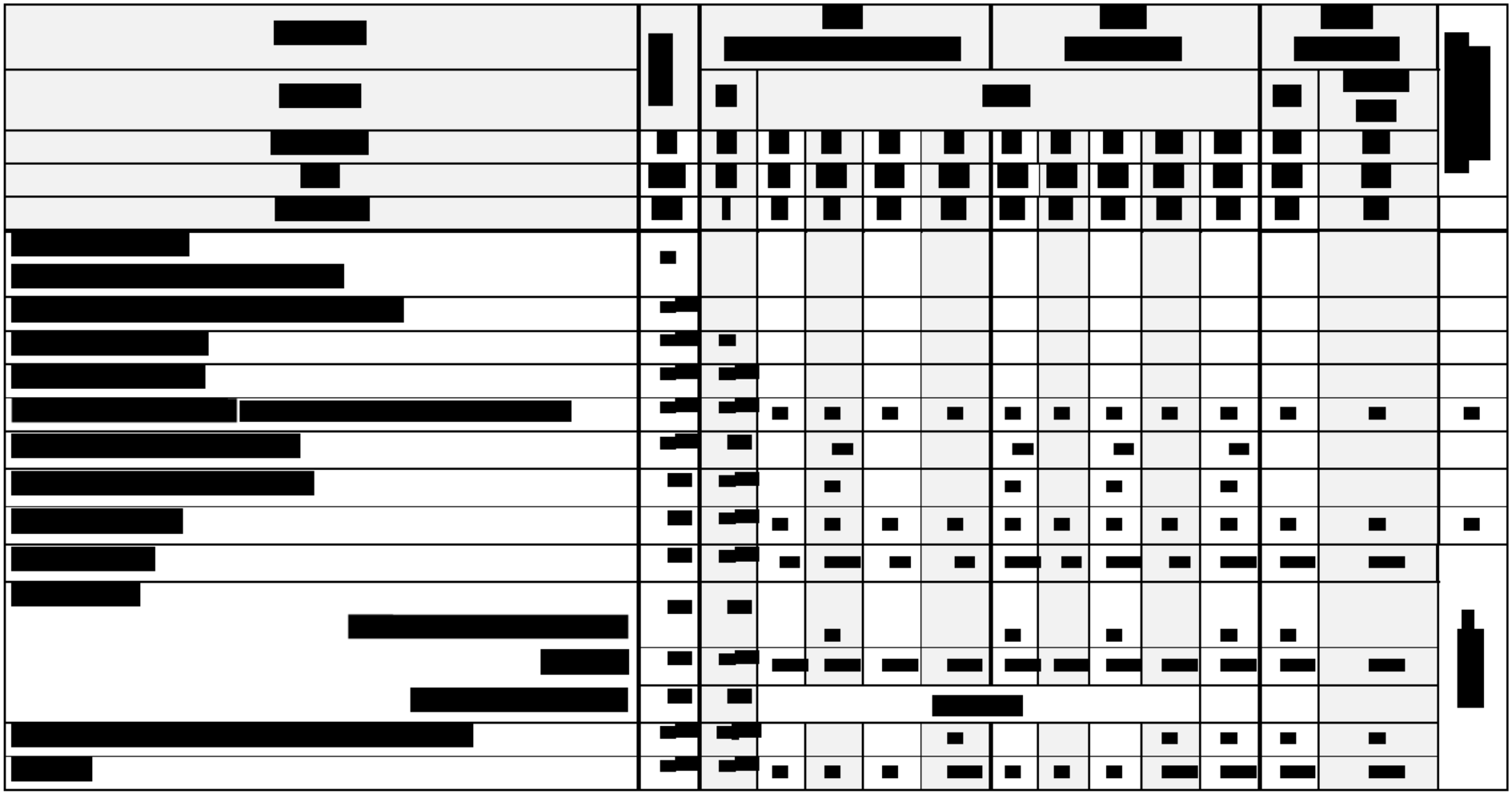
See separate document with the table, figure and listing shells.

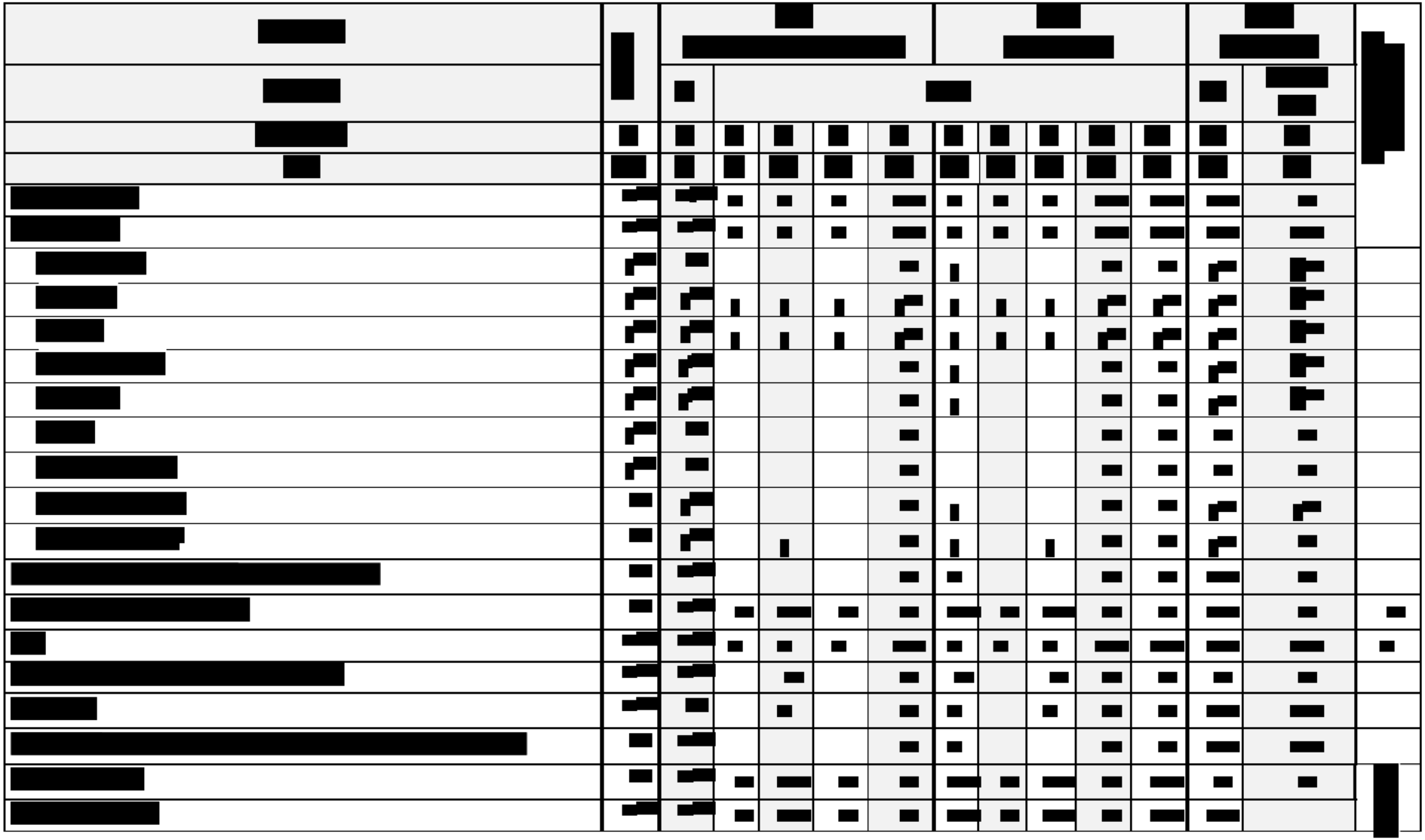
10. LITERATURE CITATIONS / REFERENCES

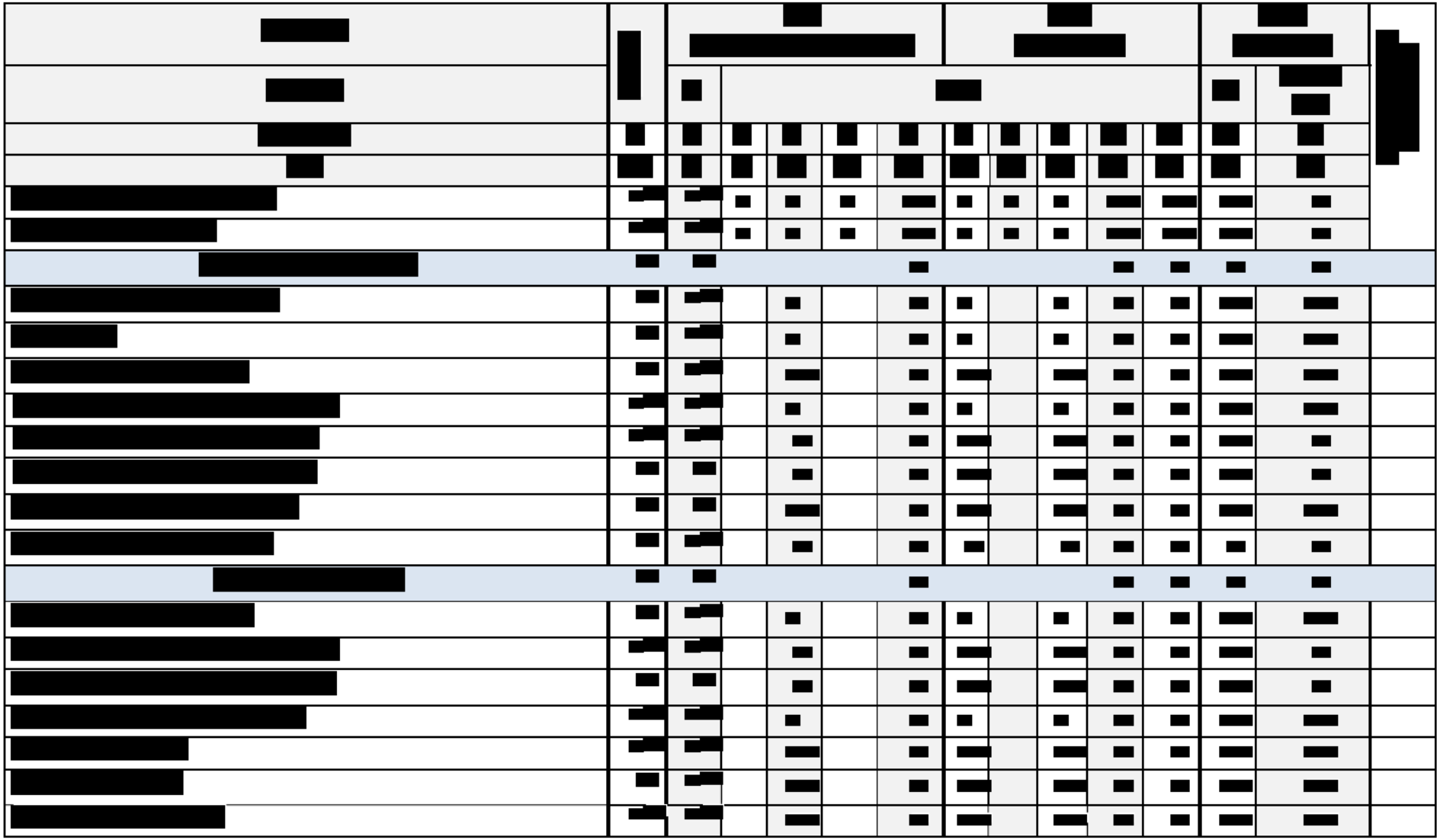
1. Study protocol: "A Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Efficacy and Safety of AS012 in Subjects with Non-Segmental Vitiligo", [redacted]

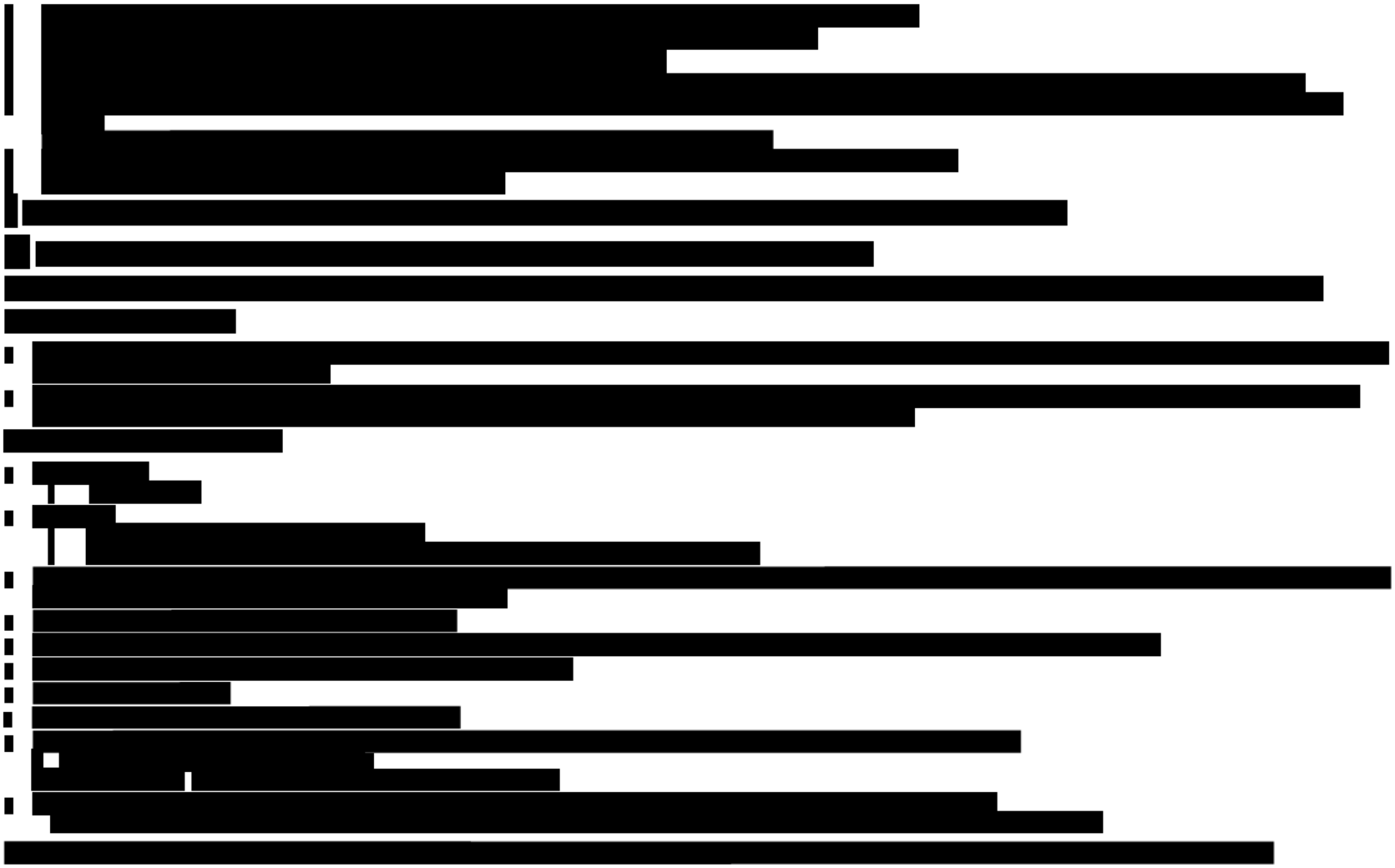
11. APPENDICES

[redacted]









11.2 Code Fragments

11.2.1 Primary analysis of the primary endpoint with multiple imputations

Step1. Efficacy data needs to be transposed to one record per subject structure with responses from Week 12 and Week 24 visits in different variables. In the examples below responses from Week12 and Week24 visits are denoted as CHG12 and CHG24.

Step 2. Impute intermittent missing values 50 times:

```
proc mi data=… out=… nimpute=50 seed=122001;
  var trtp disstab skinclass base chg12 chg24;
  class trtp disstab skinclass;
  fcs regpmm(chg12=trtp disstab skinclass base chg24);
  fcs regpmm(chg24=trtp disstab skinclass base chg12);
run;
```

Note: pre-specified seed is necessary to ensure results are repeatable and amenable to validation by double-programming. The value is chosen arbitrarily based on the protocol number.

Meaning of the variables:

- TRTP: treatment group
- DISSTAB: disease stability (stable/unstable)
- SKINCLASS: Skin type group (I-II, III-IV or V-VI)
- CHG12: response, i.e. VASI change from baseline, at Week 12
- CHG24: response, i.e. VASI change from baseline, at Week 24
- BASE: baseline value of VASI

Step 3. Analysis of imputed data. For each of the 50 imputations perform the primary analysis:

```
proc mixed data=… method=type3;
  by _imputation_;
  class trtp disstab skinclass;
  model chg24 = trtp disstab skinclass base;
  lsmeans trtp / diff=control('PLACEBO');
run;
```

Note: the input dataset is the output from the previous step. _Imputation_ variable is the imputation number from PROC MI output.

Step 4. Combine multiple imputation results:

```
proc mianalyze parms=…;
   by trtp;
   modeleffects trtp;
run;
```

Note: the input dataset (parms option) is LS Means or LS Means Differences (Diffs) dataset from the model from the previous step.

11.2.2 Sensitivity analysis of the primary endpoint with multiple imputations based on placebo scores

This analysis proceeds similar to the primary analysis in the previous section, except in Step 2 an additional statement is added to PROC MI to base the imputation on placebo scores only and consequently treatment group effect is removed from the imputations model:

```
proc mi data=… out=… nimpute=50 seed=122001;
  var disstab skinclass base chg12 chg24;
  class trtp disstab skinclass;
  fcs regpmm(chg12 chg24);
  mnar model (chg12 / modelobs = (trtp = 'PLACEBO'))
    model (chg24 / modelobs = (trtp = 'PLACEBO'));
run;
```