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Statistical Analysis Plan for Interventional Studies

SAP Version Number: 2.0
SAP Date: 13-Dec-2022

Sponsor Name: UNION therapeutics A/S

Protocol Number: UNI50001-203
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Dose-Ranging Study to Evaluate the Efficacy and Safety of Orismilast in Adults with Moderate-to-Severe Plaque-Type Psoriasis

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[redacted] **Project Code:** 7025422

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	09-Jun-2022	[redacted]	Initial Release Version
2.0	13-Dec-2022	[redacted]	Added carrying forward the baseline value to week 4 for those patients that don't have any post-baseline data for the MMRM. Added reassignment of Week 16/EOT, Week 20/Follow-up and unscheduled visits. Mantel-Haenszel test replaced with difference of proportions analyses.

I confirm that I have reviewed this document and agree with the content.

Approvals

[redacted] **Approval**

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Coviariance
ATC	Anatomical Therapeutic Chemical
bpm	beats per minute
BDRM	Blinded Data Review Meeting
BID	Twice a day
BMI	Body Mass Index
BSA	Body Surface Area
CFB	Change from Baseline
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
HADS	Hospital Anxiety and Depression scale
HBcAb	Antihepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IGA	Investigator Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board

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Abbreviation	Description
ITT	Intent-To-Treat
IEC	Independent Ethics Committee
MAR	Missing At Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model for Repeated Measures
N/A	Not Applicable
NCI	National Cancer Institute
NRS	Numeric Rating Scale
PASI	Psoriasis Activity and Severity Index
PASI50	50% reduction in PASI
PASI75	75% reduction in PASI
PASI90	90% reduction in PASI
PCFB	Percentage Change from Baseline
PD	Pharmacodynamics
PDE	Phosphodiesterase
pdf	Portable document format
PGA-F	Nail Psoriasis Physician Global Assessment
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PRO	Patient-Reported Outcome
PsA	Psoriatic Arthritis
PSS	Psoriasis Symptoms Scale
PT	Preferred Term
Q1	First quartile, 25th percentile of the data
Q3	Third quartile, 75th percentile of the data
QC	Quality Control
QoL	Quality of Life
QTc	Corrected QT Interval

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Abbreviation	Description
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
ss-IGA	Scalp-specific Investigator Global Assessment
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives based on Protocol v3.0.

2.1. Responsibilities

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety and efficacy and the pharmacokinetic analysis are planned after all patients complete the final study visit or terminate early from the study.

3. Study Objectives

3.1. Primary Objective

The primary objective is to evaluate the efficacy and safety of a modified-release orismilast tablet versus placebo in adults with moderate-to-severe plaque-type psoriasis.

3.2. Secondary Objective

Evaluate the dose response of orismilast and identify the dose with the best benefit/risk ratio to be evaluated in a Phase 3 program.

3.3. Exploratory Objectives

The exploratory objectives are to:

- [redacted].
- Evaluate the change in cardiovascular risk factors under orismilast treatment.
- [redacted]
- Evaluate the change in skin psoriasis at “difficult to treat” anatomical areas such as the scalp.
- Evaluate the change in psoriasis at “difficult to treat” anatomical areas such as nails.

4. Study Details/Design

4.1. Brief Description

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2b dose-ranging study is designed to assess the efficacy and safety of modified-release orismilast compared with placebo in adult patients with moderate-to-severe plaque-type psoriasis. Efficacy and safety endpoints will be evaluated to select an appropriate orismilast dose for subsequent Phase 3 studies. The study will be conducted in approximately 40 centers in Europe (Germany, Poland, UK) and US.

After a Screening visit up to 28 days before Baseline, approximately 200 patients will be assigned randomly in a 1:1:1:1 ratio to receive 1 of the 3 orismilast doses (20 mg, 30 mg, or 40 mg) or placebo twice daily (BID) for 16 weeks, with a 4-week Follow-up visit. Administration will begin at Baseline with a dose titration period of up to 14 days (for the orismilast arm only). The maximum duration of study participation is approximately 24 weeks.

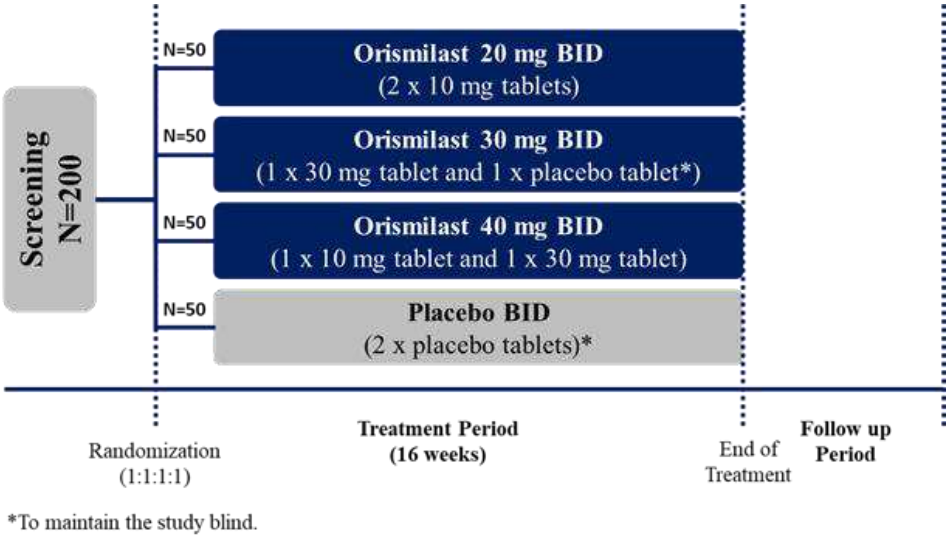
Patients will be seen at the site on Screening, Baseline (Day 1), and Weeks 1, 2, 4, 8, 12, 16 (End-of-Treatment [EOT] visit), and 20 (Follow-up visit, 4 weeks after treatment completion or discontinuation). Visits at Weeks 1 and 2 could be conducted via a telemedicine procedure at Investigator's discretion.

At Baseline and each visit from Week 4 onwards, Psoriasis Activity and Severity Index (PASI), body surface area (BSA), Investigator Global Assessment (IGA), and Psoriasis Symptoms Scale (PSS) will be assessed. Quality of life will be assessed by administration of Dermatology Life Quality Index (DLQI) at Baseline and at Weeks 16 and 20 visits. Additional efficacy parameters include: a Scalp-specific Investigator Global Assessment (ss-IGA), a nail psoriasis Physician Global Assessment (PGA-F), and [redacted]
These parameters will be assessed at Baseline and Weeks 16 and 20. Safety evaluations include adverse events (AEs), laboratory and vital sign assessments, physical examinations as well as mood change evaluation by patient (Hospital Anxiety and Depression Scale [HADS]) and suicidal ideation evaluation by Investigator (Columbia-Suicide Severity Rating Scale[C-SSRS]). A panel of cardiovascular risk factors will be assessed at Baseline and Week 16.

Before administration of the study drug at Baseline and on Weeks 4, 8, and 16, blood will be collected for orismilast concentration determination. In addition, [redacted] See

Figure 1 Study Design for the study design.

Figure 1 Study Design



Abbreviation: BID, twice a day

4.2. Patient Selection

4.2.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in the protocol.
2. Male and female patients ≥18 years of age at the time of signing the ICF.
3. Body weight of >40 kg at the time of signing the ICF.
4. Diagnosis of chronic, stable plaque-type psoriasis at least 2 months before the Screening visit. If the patient is diagnosed with psoriasis arthritis, the arthritis should be stable.
5. Moderate-to-severe plaque-type psoriasis as defined by PASI ≥12, BSA ≥10%, and IGA ≥3 at the screening and baseline visits..
6. Candidate for systemic antipsoriatic treatment or phototherapy.
7. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at the Baseline visit. In addition, sexually active WOCBP must agree to use a highly effective method of contraception until at least 4 weeks after the end of study treatment. Highly effective methods of contraception are those that have a failure rate of <1% (when implemented consistently and correctly) and include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implantable); progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable); intrauterine devices or systems; self or partner vasectomy; or bilateral tubal ligation. Patients must have been on a stable dose of hormonal contraceptives for at least 4 weeks before the Baseline visit. Abstinence from heterosexual intercourse is an accepted method of contraception if it is the patient's lifestyle and is practiced for the entire duration of the study. Note: A woman of nonchildbearing potential is defined as a

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woman with surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or a woman in a postmenopausal status defined as cessation of menses for at least 12 months without an alternative medical cause and a confirmatory follicle-stimulating hormone (FSH) test or as cessation of menses for at least 24 months without an alternative medical cause.

4.2.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Therapy-resistant psoriasis defined as ≥2 treatment failures due to inadequate efficacy within the past 5 years of any biologic therapies (including but not limited to etanercept, adalimumab, infliximab, certolizumab pegol, guselkumab, secukinumab, risankizumab, ixekizumab, tildrakizumab, or ustekinumab) administered in adequate dose and duration according to the label or local/national guidelines (patients who stopped systemic treatment for reasons not related to lack of efficacy are not excluded).
2. Unstable psoriasis or PsA with acute deterioration within 4 weeks of the Screening visit.
3. History of allergy or hypersensitivity to any component of the study treatment.
4. Active infection (eg, bacteria, viral, fungal) requiring treatment with systemic antibiotics within 4 weeks of the Screening visit.
5. Malignancy or history of malignancy except for treated (ie, cured) basal cell skin carcinomas.
6. Current diagnosis of predominant guttate, erythrodermic, exfoliative, or pustular psoriasis, or of drug-induced psoriasis, or other skin conditions that might confound the evaluation of psoriasis vulgaris, as judged by the Investigator (eg, atopic dermatitis, lupus).
7. Any recurrent medical condition associated with serious GI diseases, such as inflammatory bowel disease.
8. Any medical or psychiatric condition (eg, current major depression with a score for depressive symptoms ≥15 of HADS at Baseline, schizophrenia, suicidal behavior, psychiatric hospitalization within the prior year) which, in the Investigator's opinion, would preclude the patient from adhering to the protocol, completing the study per protocol, and/or would place the patient at unacceptable risk for receiving the investigational therapy.
9. Any therapies and systemic treatments as described in Protocol Section 9.5.2 which do not comply with the indicated washout interval[redacted].
10. Any previous treatment with orismilast or failure of treatment with apremilast or any other systemic PDE4 inhibitor as described in Protocol Section 9.5.2.
11. Any condition, including laboratory or ECG abnormalities, that places the patient at an unacceptable risk to participate in the study or confounds the ability to interpret data from the study.
12. Severe hepatic impairment based upon medical history and laboratory abnormalities (eg, low albumin and abnormal bilirubin).
13. Any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
    a. Absolute neutrophil count of <3.0 × 109/L (<3000/mm^3)

b. Hemoglobin of <10.0 g /dL or hematocrit <30%
c. Platelet count of <100 × 10^3 cells/mm^3 (SI: <100 × 10^9 cells/L).
d. Absolute lymphocyte count of <1.0 × 109/L (<1000/mm^3)
e. Total bilirubin >1.5 × the upper limit of normal (ULN); patients with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ULN
f. Alanine aminotransferase or aspartate aminotransferase >2.5 × the ULN;
g. Serum creatinine ≥1.5 mg/dL. For a patient with a value of ≥1.5 mg/dL, a creatinine clearance of ≥60 mL/min (calculated using the CKD-EPI Creatinine Equation) is allowed.

14. History or evidence of hepatitis B virus (HBV) infection at Screening. Patients with positive hepatitis B surface antigen (HBsAg) are excluded. For patients with isolated positive antihepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb) result must also be positive to be considered for this study.
15. History or positive test result for hepatitis C virus (HCV) antibody, indicating ongoing infection, at Screening. Confirmatory testing for HCV RNA will be conducted for patients who have a positive test result. Patients who have a negative result for HCV RNA will be eligible to participate in the study.
16. History of positive HIV, or have congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease). Patients who are positive for HIV antibodies (HIV-1 or HIV-2) at Screening are excluded from the study.
17. Suicidal ideation or behavior in the past 12 months as indicated by a positive response (yes) to questions 4 or 5 on the C-SSRS completed at the Screening visit or the C-SSRS completed at the Baseline visit.
18. Pregnant or breastfeeding.
19. History of alcohol or substance abuse within 6 months before Baseline that, in the opinion of the Investigator, will preclude participation in the study.
20. Institutionalized by court order or by local authority.

4.3. Determination of Sample Size

Approximately 200 patients will be enrolled to ensure approximately 50 patients per arm. This sample size is based on assumptions that the percentage change from Baseline in PASI is -32.2% and -50.9% for placebo and each orismilast dose group, respectively, and the standard deviation is 33% (1, 2). Using a 2-sided 2-sample t-test, 50 patients in each treatment arm can achieve a power of 80% at the significance level of 5%.

4.4. Treatment Assignment and Blinding

Randomization will occur prior to first study treatment administration, at the Baseline visit. Patients will be assigned randomly in a 1:1:1:1 ratio to 1 of 3 orismilast dose groups (20 mg, 30 mg, or 40 mg) or placebo. The randomization is stratified by site.

A randomization list will be used to assign the treatments to each patient. The randomization list will be kept secured with access restricted to only the designated personnel directly responsible for labeling and handling the study drug until the study blind is broken at the end of study (database lock).

To facilitate the double blind, the tablets will be packaged in the same type of blister and the active and placebo tablets will have the same appearance (in terms of size, form, weight, and color). One dose consists of 2 identical tablets (a 10 mg or 30 mg orismilast tablet or a matching placebo).

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Blinding codes should only be broken in emergency situations for reasons of patient safety. The patient for whom the blind has been broken will be discontinued from the study and undergo the early termination procedures. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded.

All patients will be centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS).

Sponsor safety staff may unblind the study drug assignment for any patient with a serious adverse event (SAE). If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's study drug assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

4.5. Administration of Study Medication

The patients will receive the study drug at the site directly from the investigator or designee, who will also give instruction for dose administration. The date of study drug dispensed to the patientswill be recorded. At all site visits, patients will return all study drug, including packaging, dispensed at the previous visit.

The dose of study drug and study patient identification will be confirmed at the time of administration by a member of the study site staff other than the person administering the study drug.

When patients self-administer the study drug at home, compliance with the protocol will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and relevant form. Deviation from the prescribed dosage regimen should be recorded.

A record of the quantity of study drug dispensed to and administered by each patient must be maintained and reconciled with study drug and compliance records. Study drug administration dates, including dates for administration delays and/or dose reductions will also be recorded.

4.6. Study Procedures and Flowchart

The Schedule of assessments is in Protocol Section 10.

5. Endpoints

5.1. Primary Efficacy Endpoint

- Percentage change in PASI score from Baseline to Week 16.

5.2. Secondary Efficacy Endpoints

Key Secondary Efficacy Endpoints:

- Patients achieving 75% reduction in PASI (PASI75) response at Week 16.
- Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in IGA at Week 16.

Other Secondary Efficacy Endpoints:

- Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in IGA at Weeks 4, 8, 12, and 20.
- Patients achieving PASI75 response at Weeks 4, 8, 12, and 20.
- Patients achieving 50% reduction in PASI (PASI50) and 90% reduction in PASI (PASI90) response at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in PASI at Weeks 4, 8, 12, and 20.
- Change from Baseline in total PSS score at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in each individual item of the PSS at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in the affected BSA at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in DLQI score at Weeks 16 and 20.
- Patients experiencing psoriasis rebound by Week 20, defined as PASI ≥125% of Baseline or new generalized pustular, erythrodermic, or more inflammatory psoriasis.

5.3. Exploratory Endpoints

- Change from Baseline in PGA-F at Week 16.
- Change in ss-IGA from Baseline at Week 16 in the subgroup of patients with Baseline score of at least 2 (mild scalp psoriasis).
- Change from Baseline of scalp itch NRS at Week 16 in the subgroup of patients with Baseline score of at least 4 on the 11-point NRS.
- [redacted]
- Change in cardiovascular risk factors at Week 16. The following parameters will be collected: weight, body mass index, waist and hip circumferences, blood pressure, fasting serum glucose, triglycerides, cholesterol (total and HDL/LDL fractions), and C-reactive protein.

5.4. Pharmacokinetic Endpoint

- Plasma levels of the drug and its metabolites

5.5. Safety Endpoints

- The occurrence, severity, and seriousness of treatment-emergent adverse events (TEAEs) reported over the 16-week Treatment Period and the 4-week Follow-up Period.

- Changes from Baseline in physical examination; vital sign measurements (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements); and body weight over the 16-week Treatment Period and the 4-week Follow-up Period.
- Changes from Baseline in electrocardiogram (ECG) findings over the 16-week Treatment Period and the 4-week Follow-up Period.
- Changes from Baseline in safety laboratory values (hematology, serum chemistry, and urinalysis) over the 16-week Treatment Period and the 4-week Follow-up Period.
- HADS at each visit except Week 2.
- C-SSRS at each visit except Weeks 1 and 2.

5.6. Pharmacodynamic Endpoint

- [redacted]

6. Analysis Populations

6.1. Randomized Population

The randomized population will include all patients randomized. Unless specified otherwise, this population will be used for patient listings and for summaries of patient disposition.

6.2. Safety Population

The safety population will include all randomized patients who receive at least 1 dose of the study drug. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

6.3. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized patients who receive at least 1 dose of study drug. The treatment group assignment will be designated according to initial randomization. The ITT population will serve as the basis for the analysis of efficacy.

6.4. Per-Protocol Population

The Per-protocol (PP) population includes all randomized patients who receive at least 1 dose of study drug, have at least 1 post-Baseline PASI assessment, and without major protocol deviations (PD) affecting efficacy analysis. The treatment group assignment in this population will be designated according to initial randomization. Efficacy analysis for primary and secondary endpoints will be repeated on the PP Population.

6.5. Protocol Deviations

Protocol deviation management at [redacted] Health is detailed in Protocol Deviation and Non-compliance Management [redacted]. For details on the process for defining analysis datasets refer to [redacted]. The Protocol deviation criteria are graded as minor and major.

Patients with a major protocol deviation affecting efficacy analysis will be excluded from the PP population. The list of major protocol deviations potentially leading to PP population exclusion includes at least the following deviations:

- Violations of inclusion or exclusion criteria.
- Use of disallowed medication (that may influence the interpretation of efficacy results).
- Non-compliance with study medication intake: less than 80% of total number of tablets during entire treatment period or during the last 4 weeks
- Major deviation from study specific instructions/procedures

The final list of patients who are to be included in the PP population will be determined at the Blinded Data Review Meeting (BDRM). The BDRM will occur when all or nearly all queries have been resolved and the database is near to final. For the BDRM meeting, a BDRM Preparation Plan will be prepared. This plan will detail further the types of protocol deviation criteria and will include, as a minimum: 1) the exact criteria which will be used to determine if a patient will be excluded from the PP population; 2) the listings which will be prepared for sponsor review in order to determine which patients to exclude from the PP population. Details of patient specific exclusions from the PP population will be detailed in the BDRM Report.

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7. General Aspects for Statistical Analysis

7.1. General Methods

- All statistical analyses will be conducted using SAS® for Windows® Version 9.4 or higher.
- All data will be listed, and summary tables will be provided.
- In general, unscheduled visit data will be listed, but not included in the summary tables by visit. Unscheduled data will be included to identify the worst-case post-baseline for safety shift tables. Unscheduled data will be used to avoid missing data.
- Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of patients (N), mean, standard deviation, median, Q1, Q3, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of patients for each category by treatment group.
- There will be no adjustment for multiplicity, thus all p-values reported will be nominal.
- All relevant patient data will be included in listings. All patients entered into the database will be included in patient data listings. Screen failure data will be included at the end of the appropriate listings and labelled 'Screen Failures'.
- Unless otherwise specified, listings will be sorted by randomized treatment, subject number and chronologically by assessment date and time.
- Missing records will be omitted from the listings, and missing data within a record will be left blank.
- Unless otherwise specified, baseline summaries will be presented for each treatment (Placebo, Orismilast 20 mg BID, Orismilast 30 mg BID, Orismilast 40 mg BID) and for Total. Safety summaries will be presented for each treatment (Placebo, Orismilast 20 mg BID, Orismilast 30 mg BID, Orismilast 40 mg BID) and for Orismilast Total. Efficacy summaries will be presented for each treatment (Placebo, Orismilast 20 mg BID, Orismilast 30 mg BID, Orismilast 40 mg BID).

7.2. Key Definitions

Treatment period
The Treatment Period for this study is 16 weeks, from Day 1 to Week 16 (112 ± 3 days).

Study day
If the event date ≥ date of first dose of IP, study day = event date – date of first dose of IP + 1.
If the event date < date of first dose of IP, study day = event date – date of first dose of IP.

Baseline Value
Baseline value will be defined as the last non-missing value recorded prior to the first intake of study treatment.

Change from Baseline (CFB)
CFB = Post-baseline value – Value at baseline

Percentage change from baseline (PCFB)
PCFB = ((Post-baseline value – Value at baseline) / Value at baseline)*100%.

7.3. Missing Data

Missing data will be treated as missing, except in the following cases.

Efficacy
Missing data for the primary analysis of primary and secondary binary endpoints will be handled with the multiple imputation method, assuming Missing At Random (MAR) within arm.
For categorical efficacy endpoint based on a continuous variable, the multiple imputation will be first done for the continuous variable, then determine the category using the imputed values.
Secondary continuous endpoints will be analyzed based on observed data using an MMRM, thus using a modelling approach assuming MAR for missing data.
For a supportive analysis of key secondary efficacy endpoints missing data will be handled as non-response.

Safety
• Missing AE relationship will be imputed by 'definitely'.
• Missing AE severity will be imputed by 'Grade 3'.
• Missing or incomplete dates in safety data:
In all listings, missing or incomplete dates will be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

I. The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing or incomplete, it is assumed to have occurred during the treatment period (i.e. a TEAE for AEs) except if the partial onset date indicates differently).
II. A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

7.4. Visit Windows

If there are multiple planned assessments for any study procedure at a given time point, the latest non-missing value will be used for summarization. Unscheduled assessments will be listed and will be used to flag baseline visit if this is the last non-missing assessment before the first dose of study drug, but unscheduled assessments will not be included in the summarization, unless to be used to avoid missing data at Week 4, 8, 12, 16 and 20.

Visits in RAVE captured as 'Week 16 / EoT and 'Week 20 / Follow-up' will be reassigned to either 'Week 16' or another scheduled post-baseline visit or 'EoT' and 'Week 20' or 'Follow-up' as follows: If a patient completed the study treatment (based on the End-of-Treatment form information), data captured in RAVE as 'Week 16 / EoT', will be presented as 'Week 16' irrespectively of violation of visit window. If a patient discontinued the study treatment, provided that no data are available from a certain scheduled post-baseline visit (Week 4, 8, 12, 16) for a subject, data captured on the 'Week 16 / EoT' visit have the potential to be assigned to a particular scheduled visit in data summaries and analyses, provided the data are collected between 13 days before and 14 days after the planned time point for the scheduled visit, as displayed in table below:

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Visit (target day)	Visit window (day is date of assessment minus date of first dose)
Week 4 (day 28)	Day 15 to 42
Week 8 (day 56)	Day 43 to 70
Week 12 (day 84)	Day 71 to 98
Week 16 (day 112)	Day 99 to Day 139 *

* Week 16 uses a broader visit window.

If the 'Week16/EoT' visit falls outside the visit schedule in the trial procedure it will be present as 'EoT'.

If the subject completed study treatment, data captured in RAVE as 'Week 20 / Follow-up' will be presented as 'Week 20' irrespectively of violation of visit window. If the subject did not complete study treatment, data captured in RAVE as 'Week 20 / Follow-up' will be presented as 'Follow-up'.

7.5. Pooling of Centers

Not Applicable since no adjustment for center or by center analyses are planned.

7.6. Subgroups

Subgroup analyses only apply to some of the exploratory endpoints and are described in section 9.2.3.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Patient Disposition and Withdrawals

Listings of treatment assignments, including the subject's identification, date of randomization, and assignment to treatment, will be presented.

The following frequencies (number and percent) will be displayed for all patients in the screened population: patients screened, patients randomized, screen failures, and reasons for screen failure.

The analysis populations will be summarized with counts and percentages by treatment. This table will include the following: number of patients in screened population, patients in safety population, reasons for exclusion from the safety population, patients in Intent-to-Treat population, reasons for exclusion from the Intent-to-Treat population, patients in Per-Protocol population, and reasons for exclusion from the Per-Protocol population.

The following frequencies (number and percent) will be displayed for all patients in the randomized population: randomized patients, patients in the safety population, patients in Intent-to-Treat population, patients in Per-Protocol population, patients who completed the study (including follow-up), patients who discontinued early, patients who completed study treatment, patients who discontinued study treatment early also presented by reason for early discontinuation and study duration in days. The denominators will be the number of randomized patients. A Kaplan-Meier plot of time to discontinuation of study treatment will be presented by treatment for the ITT population.

Completion/discontinuation status, inclusion/exclusion criteria definitions and Inclusion/exclusion criteria violations will be listed by patient.

8.2. Protocol Deviations

All protocol deviations (minor and major) observed during the conduct of the study will be listed. Major protocol deviations (patients with at least one major PD overall and split by PD category, patients with at least one minor PD overall and split by PD categorywill be summarized by treatment group for all randomized patients.

8.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, sex, child-bearing potential, race, ethnicity, PsA, disease duration, height, body weight and body mass index (BMI) will be summarized for the ITT population using standard descriptive statistics. This table will be repeated for the PP population.

A summary table will be provided for previous psoriasis treatments (e.g. prior systemics, biologics). Previous psoriasis treatments and reasons for stopping previous psoriaisis treatments will be summarized for the ITT population. Baseline efficacy assessments: PASI, IGA, PSS, BSA, DLQI score, PGA-F, ss-IGA, scalp itch NRS and [redacted] will be summarized for the ITT population, No formal statistical comparisons between populations will be performed. Demographics will be listed for all patients in the randomized population.

8.4. Smoking and Alcohol History

Smoking and alcohol history will be summarized for the ITT population using standard descriptive statistics and listed for all patients in the randomized population.

8.5. Medical History

Medical history, including surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 24.0.Past Medical history and ongoing conditions will be summarized in separate tables for the ITT population presenting the number and percentages of patients within each preferred term (PT) grouped by the system organ class (SOC). A patient with multiple occurrences of an event in a PT is counted only once. Medical history will be listed for all patients in the randomized population.

8.6. Medication

The WHO Drug, March 2021, B3 will be used to classify prior and concomitant medications by therapeutic class and drug name.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment.

The use of prior medications, concomitant medications and concomitant disallowed medications will be summarized by the number and percentage of patients for the ITT population. If a patient takes a specific medication multiple times or takes multiple medications within a specific therapeutic class, that patient would be counted only once for the coded drug name or therapeutic class.

Prior and concomitant medications will be listed for all patients in the randomized population.

8.7. Extent of Exposure

Study drug administration data including dates for administration, dispensing and dose interruption details will be listed for all patients in the ITT population.

8.8. Treatment Compliance

When patients receive the study drug at the site, they will receive it directly from the investigator or designee who will also give instruction for dose administration. The date of study drug dispensed to the patientswill be recorded. At all site visits, patients will return all study drug, including packaging, dispensed at the previous visit.

The dose of study drug and study patient identification will be confirmed at the time of administration by a member of the study site staff other than the person administering the study drug.

When patients self-administer the study drug at home, compliance with the protocol will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits. Deviation from the prescribed dosage regimen should be recorded..

A record of the quantity of study drug dispensed to and administered by each patient must be maintained and reconciled with study drug and compliance records. Study drug administration dates, including dates for administration delays and/or dose reductions will also be recorded.

Number of patients with missed doses, number of missed doses, days of dosing, reasons doses were missed and compliance rate will be summarized overall by treatment for the ITT population and separately for the titration period..

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9. Efficacy

For inferential analyses of primary and secondary efficacy endpoints, each active treatment group will be compared with the placebo group.

Primary and secondary efficacy endpoints are to be assessed in the ITT Population. Missing data for the primary analysis of primary and secondary binary endpoints will be handled with the following multiple imputation method: Intermittent missing data will first be imputed using the MCMC method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data. Data missing after patients discontinue treatment early will then be multiply imputed with the SAS MI procedure using a regression statement (number of imputations: 50, seed: 5863781). At each time point, missing data will be assumed to be MAR and to follow a distribution similar to scores for patients who are still in the study and randomized to the same treatment group.

For categorical efficacy endpoints based on a continuous variable, the multiple imputation will be first done for the continuous variable, then determine the category using the imputed values. Efficacy analyses will be repeated on the PP Population for primary and secondary endpoints.

When appropriate, the raw parameter, its change from Baseline, and percentage change from Baseline will be summarized.

9.1. Primary Efficacy Endpoint and Analysis

The primary endpoint in this study is the percentage change in PASI score from Baseline at Week 16.

The primary endpoint (primary analysis) will be analyzed using analysis of covariance (ANCOVA) with treatment group as factor and Baseline PASI as covariate. Each active treatment dose will be compared with placebo. No adjustment for multiplicity will be made and the 0.05 level of significance will be used to claim efficacy compared with placebo. Least square means and the 95% confidence interval of the difference between each active treatment and placebo will be calculated.

The primary analysis set will be the ITT population with multiple imputation approach to handle missing values. The same analyses will be repeated for Weeks 20, 12, 8 and 4. These analyses will be repeated on the PP population.

LSMean (+/-SE) percentage change of PASI score will be presented graphically over time from Baseline to Week 4, 8, 12, 16 and 20.

Actual values, change from baseline values and percentage change from baseline of PASI will be summarized by visit using descriptive statistics and presented graphically over time.

The mixed model for repeated measures (MMRM) will be used as a supportive analysis. To ensure that all patients are included in the analysis, the baseline value for patients with no post-baseline data should be carried forward as the first post-baseline assessment, corresponding to imputing a change of 0 at the first post-baseline assessment. The MMRM model will be implemented using SAS PROC MIXED with treatment group, visit and treatment-by-visit interaction as factors and baseline PASI score by-visit interaction as a covariate. A restricted maximum likelihood (REML) will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors. Least Squares Means Estimates and 95% confidence intervals will be given for each treatment group and for the difference between treatment groups (here also p-values will be presented).

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PASI (including change from baseline values, percentage change from baseline values, PASI50, PASI75, and PASI90) will be listed.

9.2. Secondary Efficacy Endpoints and Analyses

Continuous secondary efficacy endpoints will be analyzed based on observed data using MMRM, using a modelling approach assuming MAR for missing data. These analyses will be repeated on the PP population.

The binary secondary efficacy endpoints will be analyzed using differences in proportions, comparing each active treatment group to placebo in the ITT population with handling of missing data as specified in Section 9. Response by treatment group and difference in response rate and p-values compared to placebo will be presented.

The secondary endpoints and the percentage change of BSA will be presented graphically over time from Baseline to Week 20. In addition, shift tables will be provided between Baseline and each visit for the IGA distribution. The PASI percentage changes from Baseline will be plotted to identify where the best separation between treatments occur. These figures and tables are based on observed cases, thus purely descriptive.

9.2.1. Key Secondary Endpoints

- Patients achieving 75% reduction in PASI (PASI75) response at Week 16.
- Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in IGA at Week 16.

In addition to absolute PASI scores, response to treatment is presented as a percentage response rate: PASI50, PASI75 and PASI90. PASI75 represents the percentage of patients who have achieved a 75% or more reduction in their PASI score from baseline.

The key secondary endpoints (primary analysis) will be analyzed using differences in proportions, comparing each active treatment group to placebo in the ITT population. Response by treatment group and difference in response rate and p-values compared to placebo will be presented. As supportive analysis, this analysis will be repeated, with handling of missing data as non-response. In case of baseline imbalance in baseline disease severity between treatment groups an additional supportive analysis stratifying for baseline disease severity using a Cochran-Mantel-Haenszel (CMH) test will be performed.Actual values of IGA will be summarized by visit using descriptive statistics and presented graphically over time.The percentage of patients with PASI75 and the percentage of patients achieving clear (0) or almost clear(1) will be presented graphically over time. These tables and figures are based on observed cases, thus purely descriptive.

9.2.2. Other Secondary Endpoints

- Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in IGA at Weeks 4, 8, 12, and 20.
- Patients achieving PASI75 response at Weeks 4, 8, 12, and 20.

- Patients achieving 50% reduction in PASI (PASI50) and 90% reduction in PASI (PASI90) response at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in PASI at Weeks 4, 8, 12, and 20.
- Change from Baseline in total Psoriasis Symptoms Scale (PSS) score at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in each individual item of the PSS at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in the affected body surface area (BSA) at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in Dermatology Life Quality Index (DLQI) score at Weeks 16 and 20.
- Patients experiencing psoriasis rebound by Week 20, defined as PASI ≥125% of Baseline or new generalized pustular, erythrodermic, or more inflammatory psoriasis.

PASI50 represents the percentage of patients who have achieved a 50% or more reduction in their PASI score from baseline.PASI90 represents the percentage of patients who have achieved a 90% or more reduction in their PASI score from baseline.

Continuous secondary efficacy endpoints will be analyzed using MMRM, similar to the supportive MMRM for the primary endpoint.The same analyses will be repeated on the PP population.

The analysis on categorical secondary efficacy endpoints will be performed using differences in proportions, comparing each active treatment group to placebo in the ITT population with handling of missing data as specified in Section 9. Response by treatment group and difference in response rate and p-values compared to placebo will be presented.

Actual values and change from baseline values of PSS will be summarized by visit using descriptive statistics and presented graphically over time. Actual values, change from baseline values and percentage change from baseline of BSA and DLQI will be summarized by visit using descriptive statistics and presented graphically over time. The percentage of patients with PASI50 and PASI90 will be presented graphically over time. These tables and figures are based on observed cases, thus purely descriptive.

PSS (including change from baseline values) will be listed. BSA and DLQI (including change from baseline and percentage change from baseline values) will be listed.

9.2.3. Exploratory Endpoints

- Change from Baseline in PGA-F at Week 16.
- Change in ss-IGA from Baseline at Week 16 in the subgroup of patients with Baseline score of at least 2 (mild scalp psoriasis).
- Change from Baseline of scalp itch NRS at Week 16 in the subgroup of patients with a Baseline score of at least 4 on the 11-point NRS.

- [redacted]

- Change in cardiovascular risk factors at Week 16. The following parameters will be collected: weight, BMI, waist and hip circumferences, blood pressure, fasting serum glucose, triglycerides, cholesterol (total and HDL/LDL fractions), and C-reactive protein.

The cardiovascular risk factors that will be collected are as follows: weight, body mass index, waist and hip circumferences, blood pressure, fasting serum glucose, triglycerides, cholesterol (total and HDL/LDL fractions), and C-reactive protein.

All exploratory endpoints will be summarized descriptively in the ITT Population.

PGA-F, ss-IGA, scalp itch NRS, [redacted], and cardiovascular risk factors (including change from baseline values) will be listed.

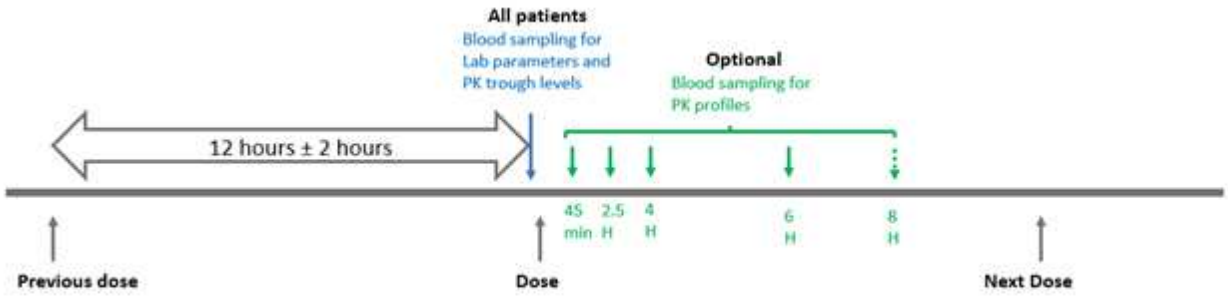
10. Pharmacokinetics

Exploratory endpoint: Plasma levels of the drug and its metabolites at scheduled visits.

Blood samples will be collected for measurement of concentrations of orismilast and its major metabolites (LEO 40815 and LEO 32728) as specified in the SoA in Protocol Section 10 before the morning dose of the study drug. The concentration of study drug will be determined from the plasma samples using a validated analytical method.

Blood sampling for measuring trough levels: The patients will be instructed to self-administer the study drug approximately [redacted] hours prior to the planned blood collection for PK analysis. The date and time of the dose taken prior to the PK blood sampling will be collected and registered. It is recommended to have date and time of last subject's drug intake before PK sampling recorded in subject's source and in the eCRF as well.

Blood sampling for calculation of PK profiles: In addition to the sample collected for measuring trough levels, patients will be offered optional participation in specific blood sampling for calculation of PK profiles. This additional procedure is voluntary for patients and patient's consent will be obtained before collection of the blood samples. For PK profiling, [redacted] additional blood samples will be collected during each visit at [redacted] and [redacted]. The patient will be instructed to take the next dose of the study drug in the clinic and blood samples will be taken at the following timepoints: [redacted] (estimated C_{max}), [redacted] after intake of the study drug, as shown in the figure below. An additional [redacted] blood sample will be collected if the patient accepts. The actual date and time of the study drug administration in the clinic and each blood sample collection will be recorded.



Abbreviations: Lab, laboratory; PK, pharmacokinetics

The plasma levels of the drug and its metabolites will be summarized descriptively by visit and hour.

A listing of PK levels will be presented by treatment group, subject number, and collection date and time.

11. Pharmacodynamics

12. Safety

All safety analyses will be conducted using the safety population.

Safety will be assessed based on adverse event (AE) reports, physical examination, vital signs, ECGs, clinical laboratory data, HADS and C-SSRS using descriptive statistics.

No inferential statistical analyses are planned on the safety parameters of this study.

12.1. Adverse Events

AEs for all patients in the safety population will be included in the AE summaries.

Adverse events will be summarized by system organ class (SOC) and preferred term (PT) for each treatment and Orismilast total, based on the MedDRA dictionary version 24.0. Severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Any AEs that occur before dosing on study Baseline will be categorized as pretreatment events. TEAEs will be defined as those AEs that occur or worsen in severity after initial dosing and up to 7 days after the last dose of study drug.

Duration will be calculated for AEs that resolve as the difference between the resolution date and onset date plus 1 and expressed in days.

The summary tables will include the number of patients and the number of events. Percentages will be based on the number of patients in the safety population. For summaries by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level.

For summaries by SOC, PT, and maximum severity, a patient will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by Orismilast total descending frequency of SOC and then, within a SOC, by Orismilast total descending frequency of PT.

The following tables will be provided:

- An overall summary of the number of events and number and percentage of patients reporting TEAEs, related TEAEs (TEAEs recorded as “Relationship to study drug” = “Possibly” or Probably” or “Definitely”), serious TEAEs (TESAEs), TEAEs resulting in death, TEAEs of special interest, TEAEs leading to study drug discontinuation, TESAEs leading to study drug discontinuation, TEAEs by relationship and TEAEs by toxicity grade;
- TEAEs overall by system organ class and preferred term;
- An overall summary of the number of events and number and percentage of patients reporting TEAEs, related TEAEs (TEAEs recorded as “Relationship to study drug” = “Possibly” or Probably” or “Definitely”), serious TEAEs (TESAEs), TEAEs resulting in death, TEAEs of special interest, TEAEs leading to study drug discontinuation, TESAEs leading to study drug discontinuation, TEAEs by relationship and TEAEs by toxicity grade starting within the dose titration period (initial 3 weeks)

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- TEAEs overall by system organ class and preferred term starting within the dose titration period (initial 3 weeks)
- TEAEs by maximum toxicity grade, overall and by system organ class and preferred term;
- TEAEs by toxicity grade, overall and by system organ class and preferred term;
- TEAEs by maximum relationship to study medication, overall and by system organ class and preferred term;
- TEAEs by relationship to study medication, overall and by system organ class and preferred term;
- TESAEs, overall and by system organ class and preferred term;
- TESAEs by maximum toxicity grade, overall and by system organ class and preferred term;
- TESAEs by toxicity grade, overall and by system organ class and preferred term;
- TESAEs by maximum relationship to study medication, overall and by system organ class and preferred term;
- TESAEs by relationship to study medication, overall and by system organ class and preferred term;
- TEAEs leading to study drug discontinuation, overall and by system organ class and preferred term;
- TEAEs leading to death, overall and by system organ class and preferred term;
- TEAEs of special interest, overall and by system organ class and preferred term;
- AEs starting in the 4-week Follow-up period overall by system organ class and preferred term;
- SAEs starting in the 4-week Follow-up period overall and by system organ class and preferred term;

Only TEAEs will be included in the summary tables, however separate listings for treatment-emergent AEs, non-treatment-emergent AEs, AEs starting within the dose titration period (initial 3 weeks) and AEs starting in the 4-week Follow-up period will be generated. Additional listings will be provided for deaths, AESIs, serious AEs and Adverse Events Leading to Study Drug Discontinuation.

12.2. Laboratory Evaluations

Safety laboratory samples for chemistry, hematology and urinalysis will be collected at various visits. Refer to Section 10 of the Protocol for the schedule of activities indicating when the respective samples are taken.

The following parameters will be included:

Chemistry: Albumin, Alanine aminotransferase, Alkaline phosphatase, Aspartate aminotransferase, Blood urea nitrogen or urea, Creatinine, Electrolytes (sodium, potassium, chloride, calcium, phosphorus), Gamma glutamyltransferase, Lactate dehydrogenase, Total bilirubin, Direct bilirubin.

Hematology: Full and differential blood count, Hematocrit, Hemoglobin, Mean cell hemoglobin, Mean cell hemoglobin concentration, Mean cell volume, Platelet count, Red blood cell count (% reticulocytes), White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

Urinalysis: Appearance, pH, Protein, Glucose, Ketone bodies, Indicators of blood and white blood cells, Specific gravity, Urine human chorionic gonadotropin (premenopausal females only), Urobilinogen.

Cardiovascular risk factors (fasting condition and at Baseline and Week 16 only): C-reactive protein, Glucose, Total cholesterol, High-density lipoprotein, Low-density lipoprotein, Triglycerides. Patients should be in fasting condition (no food or fluids other than water for 8 hours) before sample collection at Baseline and Week 16.

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Serology: HIV antibody, Hepatitis B virus, Hepatitis C virus, Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis B surface antibody, Follicle-stimulating hormone (confirmatory test for female patients in a postmenopausal status defined as cessation of menses for at least 12 months without an alternative medical cause).

Pregnancy test: A serum pregnancy test will be performed on all women of childbearing potential at Screening, and a urine pregnancy test will be performed at all other visits.

All summaries will be based on results in SI (standard international system of units) units and will be output in the order listed above.

Actual values and changes from baseline in chemistry and hematology will be summarized by visit using descriptive statistics.

Shift tables, showing shifts from baseline to week 16 relative to the normal ranges for chemistry and hematology will be provided. These summaries of normal range category changes illustrate the number and percentage of patients who fall into specified categories (Decrease to Low, Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the overall worst-case normal range category. The worst-case post-baseline row will be used to summarize the patients' overall worst-case normal range category change. The determination of the worst-case takes into account both planned and unscheduled assessments.

Patients with missing baseline value are to be assumed to have a normal baseline value. Worst-case can be either High or Low. If a patient has a Decrease to Low and an Increase to High during the same time interval, then the patient is counted in both the 'Decrease to Low' and 'Increase to High' categories. If a patient was high at baseline and decreases to Low during the time interval, then the patient is counted in the 'Decrease to Low' category. Likewise, if a patient was Low at baseline and increases to High during the time interval, then the patient is counted in the 'Increase to High' category. Patients are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range High and no normal range Low values during the time interval
- High at baseline and do not change to Low during the time interval
- Low at baseline and do not change to High during the time interval

All laboratory results will be included in data listings. Abnormal results for chemistry, hematology and urinalysis will be listed separately. Laboratory results for serology and pregnancy tests will be listed only.

12.3. Vital Signs

Heart rate (beats per minute [bpm]), respiratory rate (breaths per minute), systolic and diastolic blood pressure (mmHg) and body temperature (degree Celsius) will be measured at different visits as per the SoA in Protocol Section 10.

The conversion for temperature is as follows: Temperature (in °C) = 5/9 (Temperature [in °F]-32).

Actual values and changes from baseline in vital sign measurements will be summarized by visit using descriptive statistics.

All vital signs will be provided in data listings.

12.4. ECG

A 12-lead, resting ECG will be obtained at the visits indicated in the SoA in Protocol Section 10.

Actual values and changes from baseline in ECG parameters (heart rate [bpm], PR Interval [msec], QRS Interval [msec], RR Interval [msec], QT Interval [msec], and QTc [msec]) will be summarized by visit using descriptive statistics. An outlier analysis will be performed that will summarize by treatment the frequency and percentage of participants who meet any of the following outlier criteria at each visit:

- QTc interval > 450 msec
- QTc interval > 480 msec
- QTc interval > 500 msec
- QTc interval increases from baseline > 30 msec
- QTc interval increases from baseline > 60 msec

This outlier analysis will be repeated summarizing frequency and percentage of participants by treatment who meet any of these outlier criteria at at any time during the trial.

All ECG parameters, including overall ECG evaluation will be provided in data listings.

12.5. Physical Examination

A complete physical examination will be performed at Screening and Week 16. A limited physical examination will be conducted at Day 1 and Week 20.

A shift table to demonstrate changes in physical examination from baseline to all post-baseline visits by treatment will be generated.

Physical examination data will be listed.

12.6. The Hospital Anxiety and Depression Scale

The HADS is a patient reported outcome (PRO), comprises 7 questions for anxiety and 7 questions for depression with each answer being graded from 0 to 3 with a higher score indicating a worse conditionand. For each group of questions, scores of less than 7 indicate noncases, whereas 8 to 10, 11 to 14, and 15 to 21, indicate mild, moderate, or severe anxiety or depression, respectively. HADS will be collected at different time points as per the SoA in Protocol Section 10.

Actual values and changes from baseline in HADS scores (depression, anxiety and total) will be summarized by treatment. A summary table presenting the frequency and percentage of participants by treatment within categories (< 7, 8 – 10, 11 – 14 and 15 – 20) for anxiety and depression at each visit will be generated. A shift table to demonstrate changes in anxiety total score and depression total score from baseline to all post-baseline visits by treatment will be generated.

HADS scores, questions and answers will be provided in data listings.

12.7. The Columbia-Suicide Severity Rating Scale

The C-SSRS, investigator administered version, was designed to provide a prospective, standardized measure of suicidality. The scale allows clinicians and researchers alike to assess the severity and

lethality of suicidal behaviors and ideations and can be used to monitor treatment outcomes and establish suicide risk in a variety of research and clinical settings. Requiring approximately 5 min for completion, the C-SSRS is administered in the form of a clinical interview. This C-SSRS is available in 2 versions: 1 for use at screening referring to the past year and 1 for use throughout the rest of the study referring to the time since the prior visit.

C-SSRS will be collected at different time points as per the SoA in Protocol Section 10.

The C-SSRS categories have been re-ordered from the actual scale to facilitate the definitions of the endpoints, and to enable clarity in the presentation of the results: category 1 – Wish to be Dead, category 2 – Non-specific Active Suicidal Thoughts, category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan, category 5 – Active Suicidal Ideation with Specific Plan and Intent, category 6 – Preparatory Acts or Behavior, category 7 – Aborted Attempt, category 8 – Interrupted Attempt, category 9 – Actual Attempt (non-fatal), category 10 – Completed Suicide.

Suicidal ideation is defined as a “yes” answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS. Suicidal behavior is defined as a “yes” answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS. Suicidal ideation or behavior is defined as a “yes” answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

A summary table presenting number of patients with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be generated, as well as a shift table to demonstrate changes in C-SSRS suicidal ideation scores from baseline to all post-baseline visits by treatment. Patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent based on the C-SSRS will be listed.

13. Interim Analyses

No interim analysis is planned in this study.

14. Changes from Analysis Planned in Protocol

The randomized population is not specified in protocol, but this population is added for listings and disposition summaries.

15. Reference List

1. K. Reich, M. Gooderham, L. Green, A. Bewley, Z. Zhang, I. Khanskaya, R.M. Day, J. Goncalves, K. Shah, V. Piguet,J. Soung. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). J Eur Acad Dermatol Venereol. 2017,31, 507-517. doi: 10.1111/jdv.14015.

2. C. Paul, J. Cather, M. Gooderham, Y. Poulin, U. Mrowietz, C. Ferrandiz, J. Crowley, C. Hu, R.M. Stevens, K. Shah, R.M. Day, G. Girolomoni and A.B. Gottlieb. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2).Br J Dermatol 2015; 173, 1387-1399.

3. Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat. 2015 Feb;26(1):23-31. doi: 10.3109/09546634.2013.865009.

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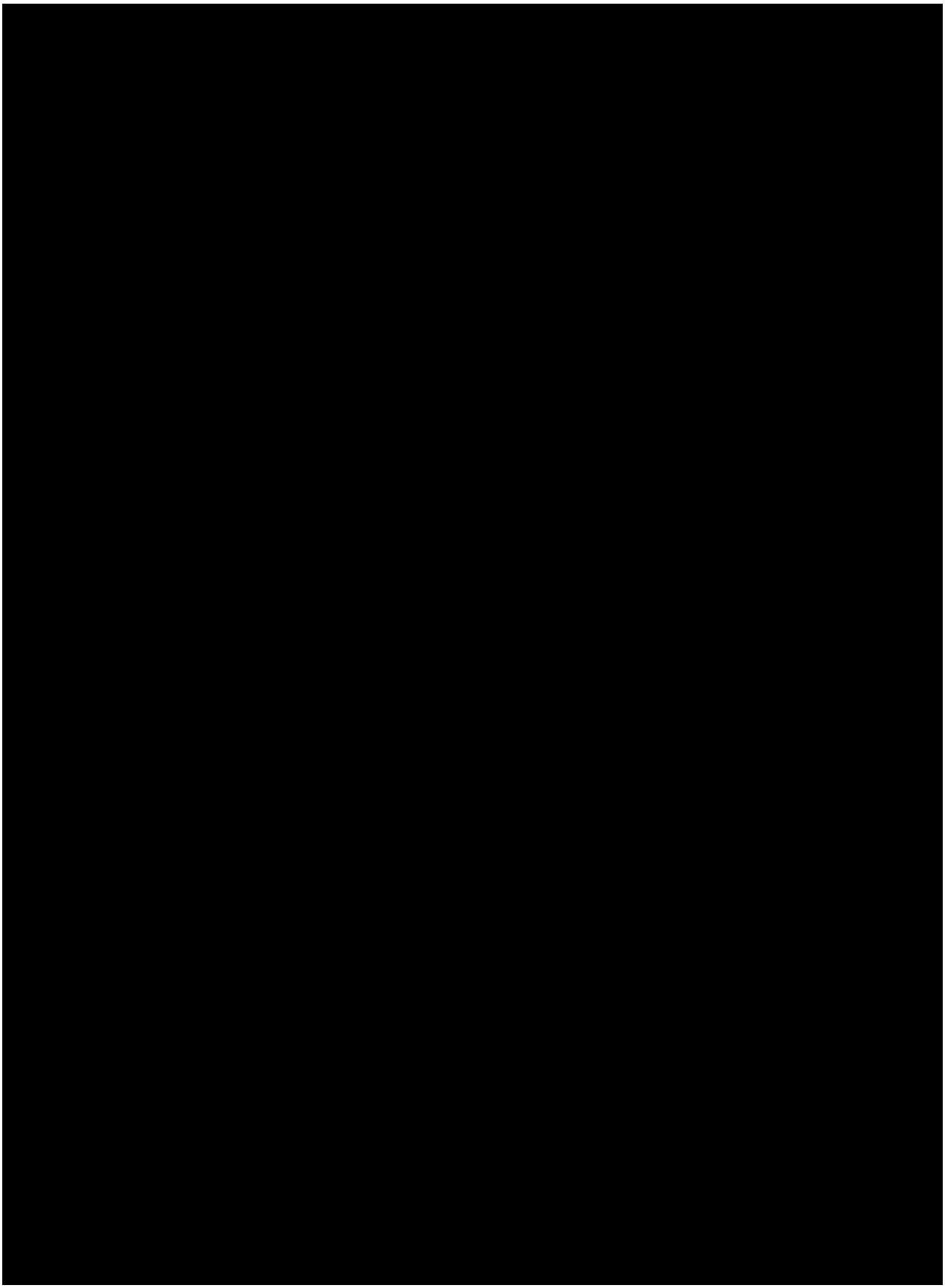

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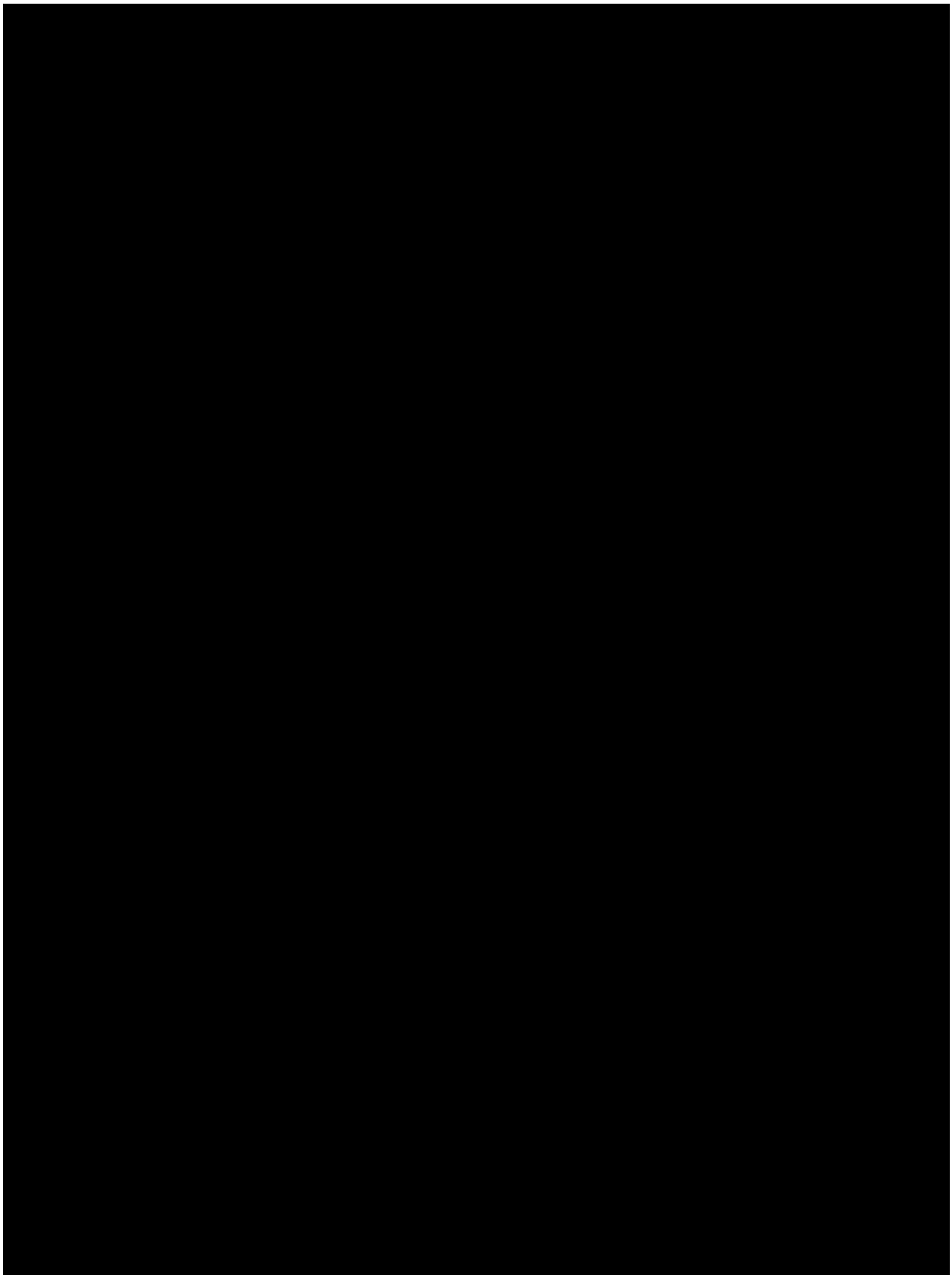

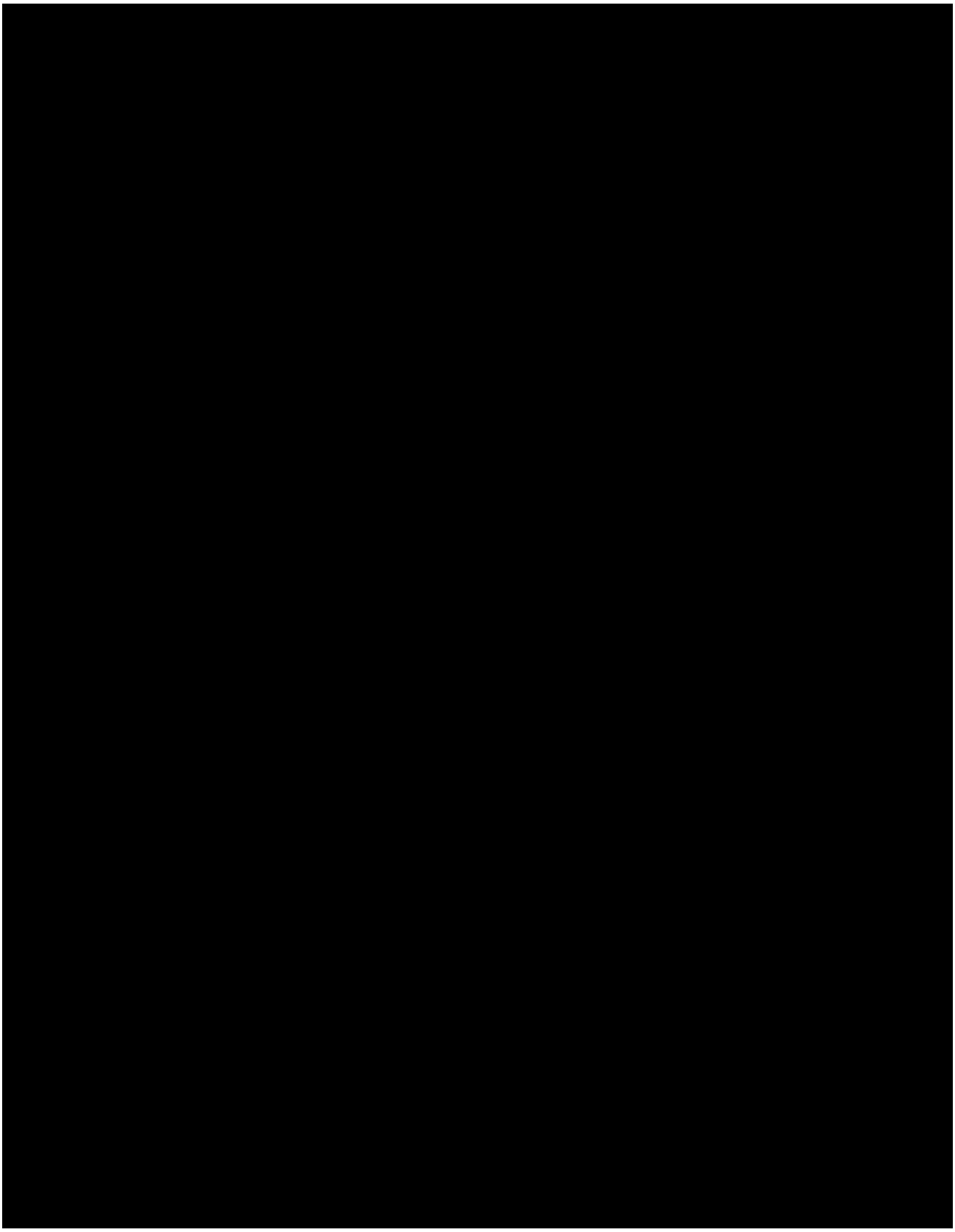

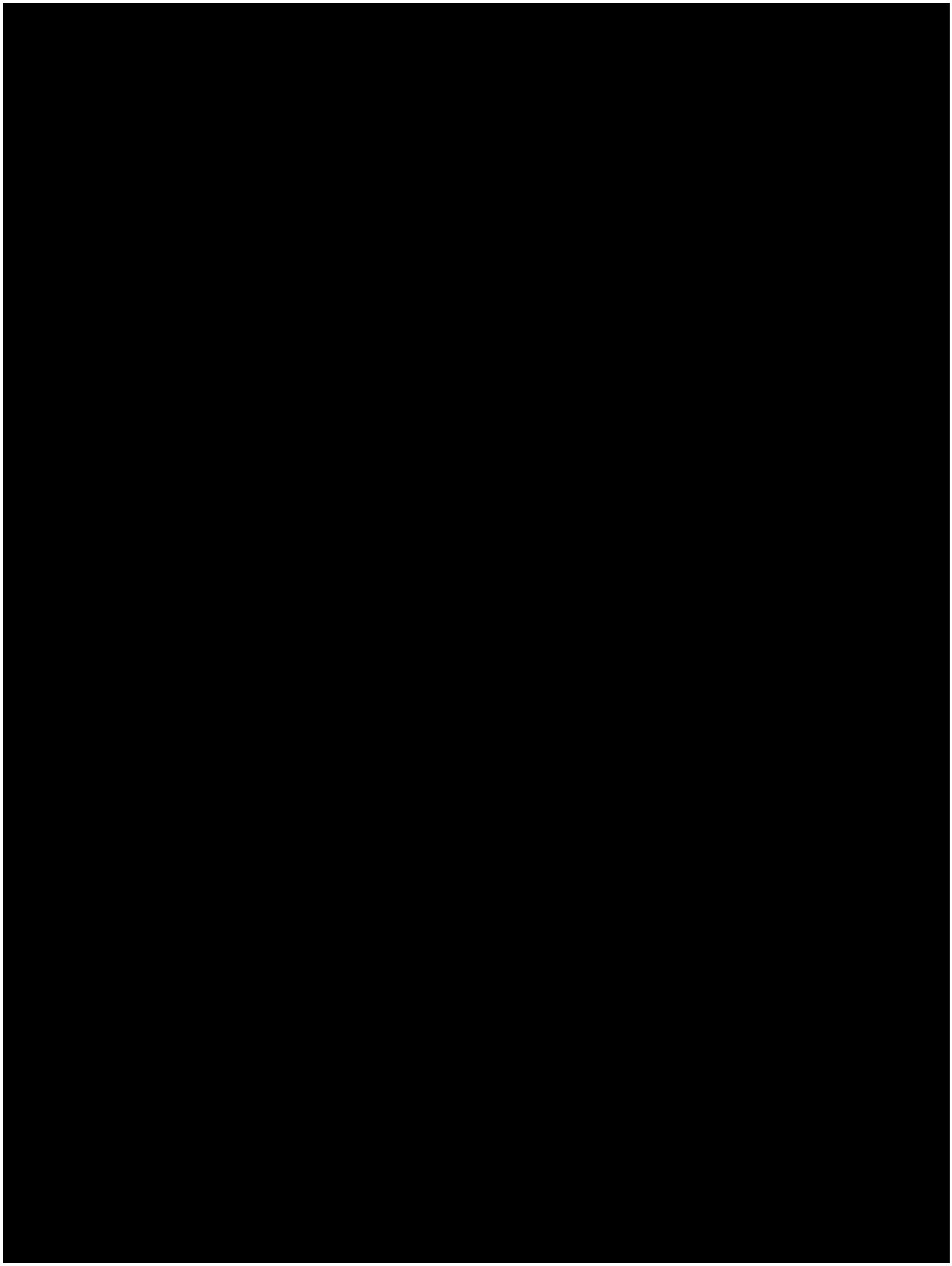

17. Quality Control

SAS programs are developed to produce output such as analysis data populations, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in [redacted]

[redacted] describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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Header	Table Number	Name	Analysis Population
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Header	Table Number	Name	Analysis Population
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Header	Table Number	Name	Analysis Population
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21. Shells

The TFL shells will be provided as a separate document.

22. Appendices

Not Applicable.