Statistical Analysis Plan

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Statistical Analysis Plan (SAP) Text Version Number: v2.0
SAP Text Date: 07-FEB-2025

Sponsor Name: Laboratoires Théa

Clinical Investigation Plan Number: LT2769-004
Clinical Investigation Plan Title: Comparison of the performance and safety of T2769 versus Hylo-Forte® in the treatment of moderate to severe Dry Eye Syndrome.

Clinical Investigation Plan Version and Date: v2.0 09-Apr-2024

[redacted]

Trial registry number: NCT06375499

Authors: [redacted]

Notice of Confidential and Proprietary Information:

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

Approvals

[redacted], Pr Biostatistician	[redacted]	
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
[redacted], Assoc. Dir. Biostatisticis, [redacted] [redacted], Sr Biostatistician	[redacted]	[redacted]
Name, Title Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)

Laboratoires Théa Approval

[redacted], Medical Director	[redacted]	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
[redacted], Biometrics Manager	[redacted]	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
[redacted], Biostatistician	[redacted]	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

Table of Contents

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[redacted]

[redacted]

1. Glossary of Abbreviations

Abbreviation	Description
[redacted]	[redacted]
AE	Adverse Event
[redacted]	[redacted]
ATC	Anatomic Therapeutic Chemical
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence Interval
CIP	Clinical Investigational Plan
CIR	Clinical Investigation Report
[redacted]	[redacted]
CRF	Case Report Form
[redacted]	[redacted]
[redacted]	[redacted]
DED	Dry Eye Disease
DES	Dry Eye Syndrome
eCRF	Electronic Case Report Form
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
IMD	Investigational Medical Device
ITT	Intent-To-Treat
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MAR	Missing At Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model for Repeated Measures
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
PP	Per Protocol
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
[redacted]	[redacted]
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SOC	System Organ Class
SOP	Standard Operating Procedure
STEAE	Serious Treatment Emergent Adverse Event
[redacted]	[redacted]
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figure, and Listing
WHO	World Health Organization
[redacted]	[redacted]

2. Introduction

This SAP is based on Clinical Investigation Plan (CIP) No. LT2769-004, Version 2.0 dated 09 APR 2024 and the electronic Case Report Form (eCRF) Version 1.0 dated 12 AUG 2024. The analyses follow the guidelines from the International Organization for Standardization (ISO) described in ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice**Error! Reference source not found.**.

The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Investigation Report (CIR).

The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced, as well as the statistical methodologies that will be used, are complete and appropriate as per study design and objectives.

3. Study Objectives and Endpoints

The aim of this investigation is the comparison of T2769 with Hylo-Forte®.

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the investigation is to demonstrate the non-inferiority of T2769 compared to Hylo-Forte® in terms of total ocular surface staining (Oxford score) in patients with moderate to severe dry eye syndrome (DES).

3.1.2 Secondary Objective

[redacted]

- [redacted]
- [redacted] evaluate the safety of T2769.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary performance endpoint is the change from baseline (D1) in total ocular surface staining grade according to Oxford 0-15 grading scheme at D36 in the study eye.

[redacted]

[redacted]

3.2.3 Safety Endpoints

The safety endpoints are:

- Treatment-Emergent Adverse Event (TEAE) by System Organ Class (SOC) and Preferred Term (PT) (separately for ocular and systemic TEAE).

[redacted]

[redacted]

4. Study Design

This is a 5-week, international, multicentre, randomised, investigator-masked, 2 parallel groups (T2769 versus Hylo-Forte®) investigation. The clinical investigation design is confirmatory.

- Multicentre

The investigation will be performed in different sites in European Union (EU).

- Randomised

Eligible patients will be randomised on a 1:1 basis to T2769 or Hylo-Forte® respectively at the Randomisation Visit on Day 1 (Visit #2 - D1).

- Run-in period

Patients meeting the screening criteria will undergo a 7-10-days run-in period. During this period, all patients will substitute their current dry eye treatment with Hydrabak®, ophthalmic solution containing NaCl 0.9%. This period will allow to verify signs and symptoms of DES, and to facilitate the washout from the ocular surface of previous artificial tears treatment. Patients will instil 1 drop in each eye, from 3 to 6 times daily.

- Investigator-masked

A double-masked investigation design is not possible due to different commercial packaging between T2769 – Hylo-Forte®. However, the identity of the Investigational Medical Device (IMD) given to each patient will not be known for the masked investigator who is independently in charge of the ophthalmic examination. To this aim, the masked investigator will differ from the person who will record the used/unused IMDs. The masked investigator should not receive the returned IMDs from the patients and returned IMD must be stored in a different place from the IMD that have not yet been dispensed. Patients will also be trained to not report any information that could lead to unblinding in the diary and to the masked investigator.

- Exposure to the IMD

IMD will be administered by the patient every day from D1 until Visit 4 (included), one drop in each eye 3 to 6 times daily into the lower conjunctival sac of each eye.

No IMD instillation must be done at least 2 hours before Visit#3 and 4. However, the first instillation can be done any time after the patient has completed the randomisation visit.

There will be two treatment groups:

- T2769 (test medical device)
- Hylo-Forte® (comparative medical device)

The chosen comparator, Hylo-Forte®, of which performance has been demonstrated in the treatment of DES, is considered as a reference product.

- Investigation population

The study population will consist of patients with moderate to severe DES who have been treated with artificial tears for at least the last month prior to screening visit. It corresponds to the IMD target population.

- Treatment period

A 5-week treatment period allows to evaluate the therapeutic effect and to observe any potential safety issues.

- Primary [redacted] endpoint

The primary [redacted] endpoint of this clinical investigation (Section 3.2) have been taken into consideration based on the clinical literature review. Consequently, these endpoints were designed to provide adequate and sufficient clinical evidence on the performance, safety and clinical benefit of T2769 in its intended use.

Four visits are scheduled during the course of the clinical investigation as presented below:

Visit#1 (Screening Visit): Day 1-10 to Day 1-7 (Run-in Period)

Visit#2 – D1 (Randomisation Visit): Day 1

Visit#3 – D15: Day 15 (±1 day)

Visit#4 – D36 (Final Visit): Day 36 (±3 days) or Premature Discontinuation Visit.

Visits should be performed at the same hour (±2 hours) in the morning.

5. Analysis Sets

The following analysis sets will be considered:

- Enrolled set:

Enrolled set are all patients who have signed the informed consent form and had completed the screening visit (has been recorded in the eCRF).

- Safety (SAF) set:

All enrolled patients, having received at least one dose of IMD. Patients will be analysed according to the treatment received. Safety set will be the primary population for safety analysis.

- Intent-to-Treat (ITT) set:

All randomised patients. Patients will be analysed according to the treatment they were assigned to at randomisation.

- Full Analysis Set (FAS):

All randomised patients having received at least one dose of IMD, with at least one baseline and one post-randomisation performance assessment. Patients will be analysed according to the treatment they were assigned to at randomisation. The FAS will be the primary population for performance analysis.

- Per protocol (PP) set:

Subset of the FAS including patients without any major CIP deviations likely to seriously affect the primary outcome of the study. Patients will be analysed according to the treatment received. [redacted] The PP set will be considered as the secondary population and will be used for sensitivity analyses of the primary [redacted] performance endpoint.

6. Statistical Methodology

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

Statistical analyses will be performed [redacted]. All data will be listed, and summary tables and figures will be provided. Table, Figure, and Listing (TFL) mock shells will be provided for all analyses.

Statistical descriptions will be performed by treatment groups. For disposition and demography, description will also be presented overall. Variables recorded for each eye will be described separately for the study eye and for the contralateral eye (if applicable).

Baseline is defined as the assessment at randomisation/D1 visit before the first IMD instillation. Missing values at randomisation visit will not be replaced. Change from baseline at any time point is defined as the value at the timepoint minus the baseline value and is calculated only for the post-baseline visits.

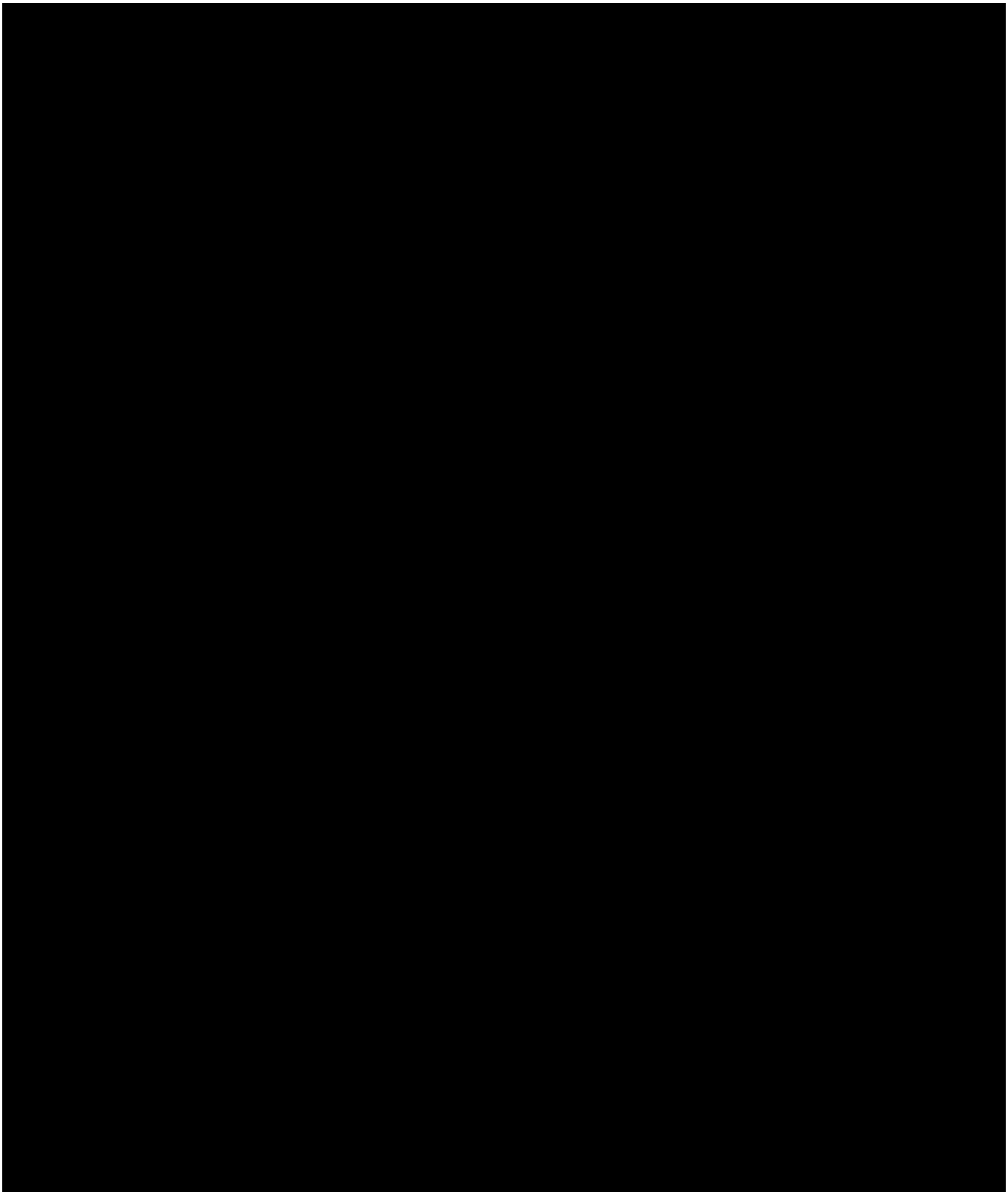
For endpoints defined as change from baseline, the descriptive statistics by visit (Screening, D1, D15 and D36) and the change from baseline at D15 and D36 will be presented. For endpoints defined in classes, the descriptive statistics by visit and change from baseline will be presented for the original assessments and in the pre-defined classes.

Disposition, demographics, exposure, history of dry eye, medical/surgical history, will be summarised by treatment group and overall, for the FAS, PP set and SAF set [redacted]. Disposition, demographics and history of dry-eye will also be presented for the ITT set. Previous and concomitant ocular/non-ocular treatments will be listed.

Quantitative variables (Continuous data) will be summarised in summary tables indicating the number of non-missing/missing observations (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum.

Qualitative variables (Categorical data) will be summarised in summary tables indicating the number of non-missing/missing observations (n), count and percentage of each modality. For all performance and safety analyses, percentages will be calculated based on the non-missing patient count (n) for each column for the patients in the respective analysis set. For all rest analyses, percentages will be calculated based on total patient count (N) for each column for the patients in the respective analysis set (missing counts will be included).

[redacted]



6.1.3 Handling of Dropouts and Missing Data

For primary analysis performed on FAS, Mixed Model for Repeated Measures (MMRM) and [redacted] method will be applied in case of missing value. [redacted] method assume missing data satisfy the conditions of Missing At Random (MAR). Missing values at randomisation visit will not be imputed.

[redacted]

6.1.4 Determination of Sample Size

The sample size is driven by the statistical hypothesis on the primary objective: to demonstrate the non-inferiority of T2769 compared to Hylo-Forte® in terms of the change from baseline (D1) in total ocular surface staining score assessed on Oxford 0-15 scale, in the study eye at the D36 visit.

[redacted]

[redacted]

6.2 Patient Characteristics

6.2.1 Patient Disposition

Patient disposition will be summarized in tables, by treatment group and overall, for the FAS, ITT, SAF [redacted], and PP sets. Moreover, a listing will be provided in all enrolled patients per site and patient.

Information will include:

- Number of patients that met all eligibility criteria
- Number of patients enrolled and patients per analysis set (see section 5)
- Number of patients who completed the clinical investigation
- Number of patients who discontinued the investigation and any primary reason for study discontinuation
- Number of patients per site
- Number of patients attended visits as considered in the analysis

[redacted]

6.2.3 Background and Demographic Characteristics

The demographic and background characteristics to be collected are:

- Age (in years)
- Sex

Similarly to patient disposition, gender, age as continuous and in three classes (<65 / ≥ 65 and <85 / ≥85, as well as age by gender will be summarized in tables, by treatment group and overall, for the FAS, SAF [redacted], ITT and PP sets. Moreover, a listing will be provided in ITT per patient for all the demographic data.

6.2.4 Prior and Concomitant Medications and Therapies

Prior medications are medications or non-medicinal therapies that were stopped prior to initiation of the IMD. Concomitant medications are any medications or non-medicinal therapies given concurrently with the IMD, either are ongoing at or began after the initiation of the IMD and before end-of-[redacted] Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHO-DD) version Sep 2024.

[redacted]

6.2.5 History of Dry eye

Medical history of dry eye will be collected and summarized separately from the rest of the medical and surgical history.

Dry-eye history will be summarized in table as per collected information in the eCRF, while time from first diagnosis to first IMD intake will also be calculated and summarized in the FAS, PP, ITT and SAF sets [redacted].

Variables to be summarised in tables are:

- Localisation (one eye, both eyes)
- Time from diagnosis of dry eye disease (years) [redacted]

[redacted]

[redacted]

6.2.6 Ocular and Systemic Medical and Surgical History (other than dry eye)

All ocular and systemic medical and surgical history (other than dry eye) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 27.1.

The history will be assumed as ocular or systemic, [redacted]. In addition, category will be validated based on the SOC. [redacted]

Medical and surgical history will be summarized separately for ocular and systemic history by the number and percent of patients within each SOC and PT in the FAS, PP and SAF sets [redacted]. Conditions that are reported more than once for a given SOC and PT will be counted only once per patient on the PT level for each SOC. Medical and surgical history will be sorted by descending overall frequency, by SOC and PT in the summary table.

All above data will also be listed separately for ocular and systemic history, sorted by patient number, onset date, SOC, and PT in the SAF set.

6.2.7 Treatment Exposure and Compliance

Exposure and compliance as described in the eCRF will be assessed by summarising the below, separately for Hydrabak® (run-in period) and IMDs (active treatment period), by treatment group, for the FAS, PP set, and SAF set[redacted]:

- Treated eye (One / Both)
- Treatment duration (in days) for the whole time period for both Hydrabak® and IMDs
- Treatment duration (in days) per period (from D1 to D15 and from D16 to D36) for IMDs only
- Mean Daily Dose Regimen (per day with intake) for the whole time period
- Mean Daily Dose Regimen (per day with intake) per period (from D1 to D15 and from D16 to D36)
- Number of days without treatment intake
- Overall compliance (%)

[redacted]

[redacted]

6.3 Statistical Analysis

6.3.1 Primary Performance Analysis

The primary performance endpoint is the change from baseline (D1) in total ocular surface staining grade according to Oxford 0-15 grading scheme at D36 in the study eye. [redacted]

[redacted] he primary analysis will be performed following original Oxford scale [redacted]

The inferential analyses of the primary performance endpoint will aim to assess the non-inferiority of T2769 to Hylo-Forte®. [redacted] The non-inferiority will be primarily tested using a MMRM approach.

The model will include treatment and scheduled visit time points (D15 and D36) as fixed factors, patient as random factor, and baseline total ocular surface staining (Oxford score) as continuous covariate. Treatment by scheduled visit time point and baseline total ocular surface staining (Oxford score) by scheduled visit time point will be included as an interaction term in the model.

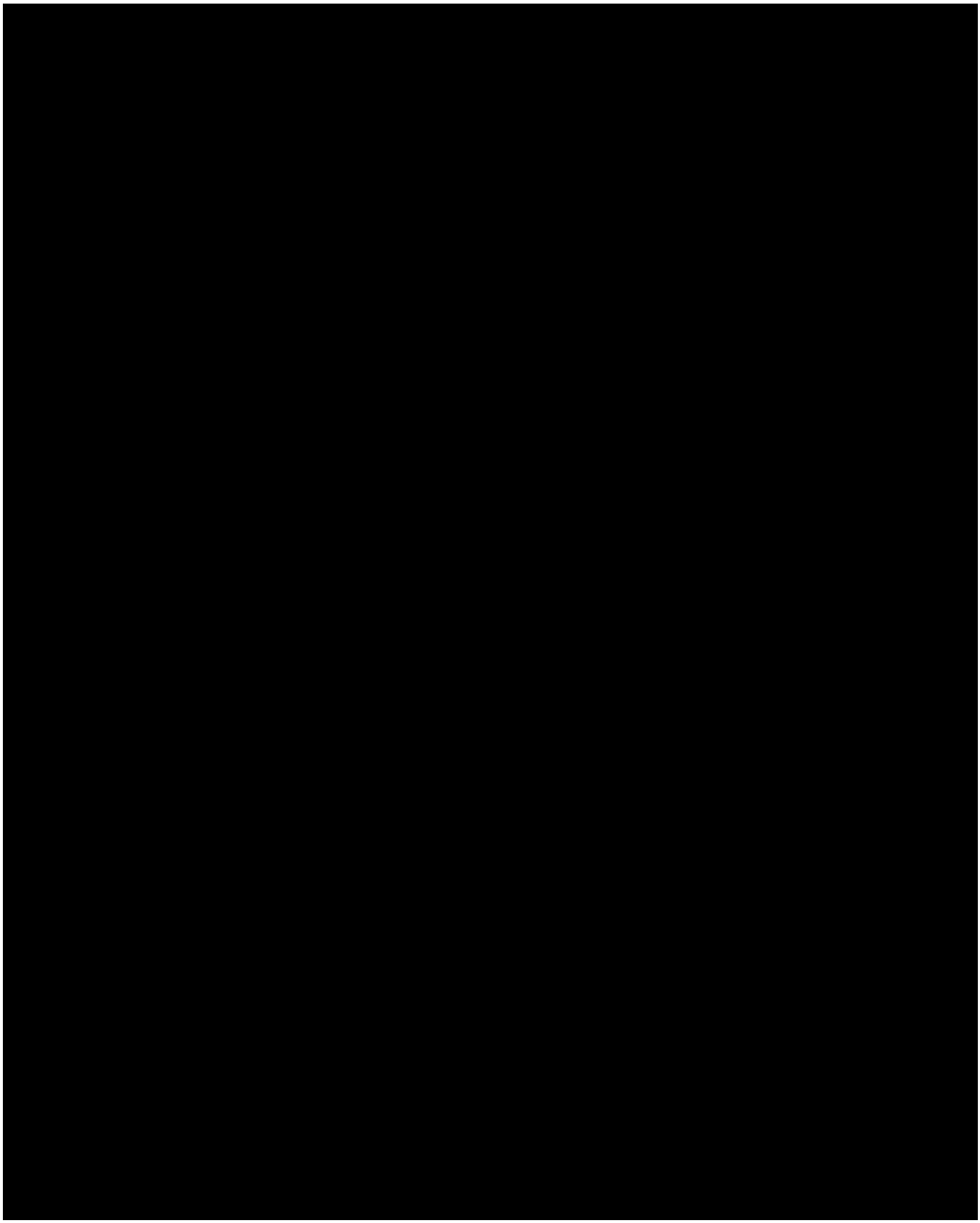
[redacted]

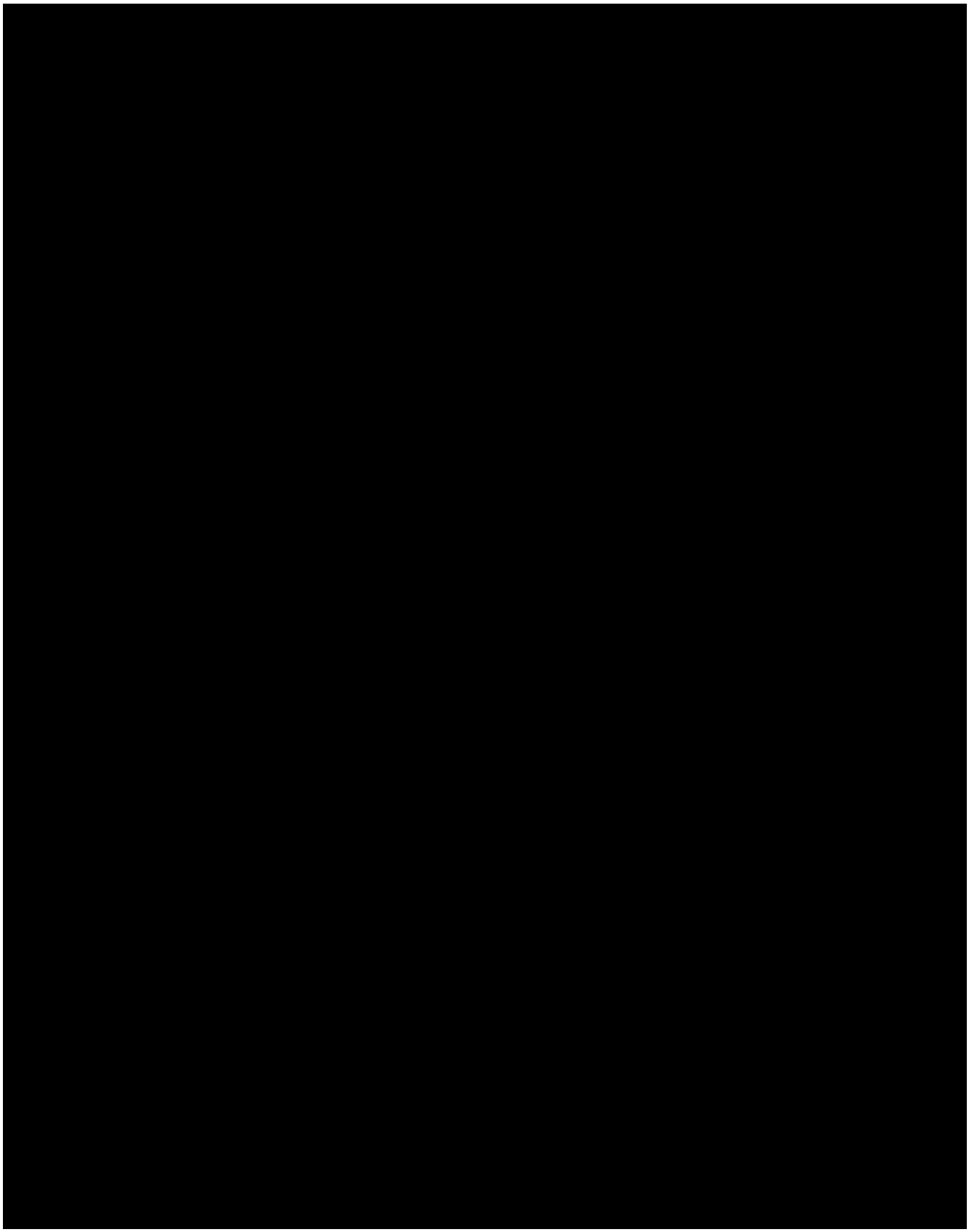
Descriptive tables will also be produced presenting data for total ocular surface staining values and change from baseline at each visit to support the MMRM analysis tables.

The mean and associated SD of the Oxford score on the study eye for each treatment will be graphically displayed by analysis visit for the FAS.

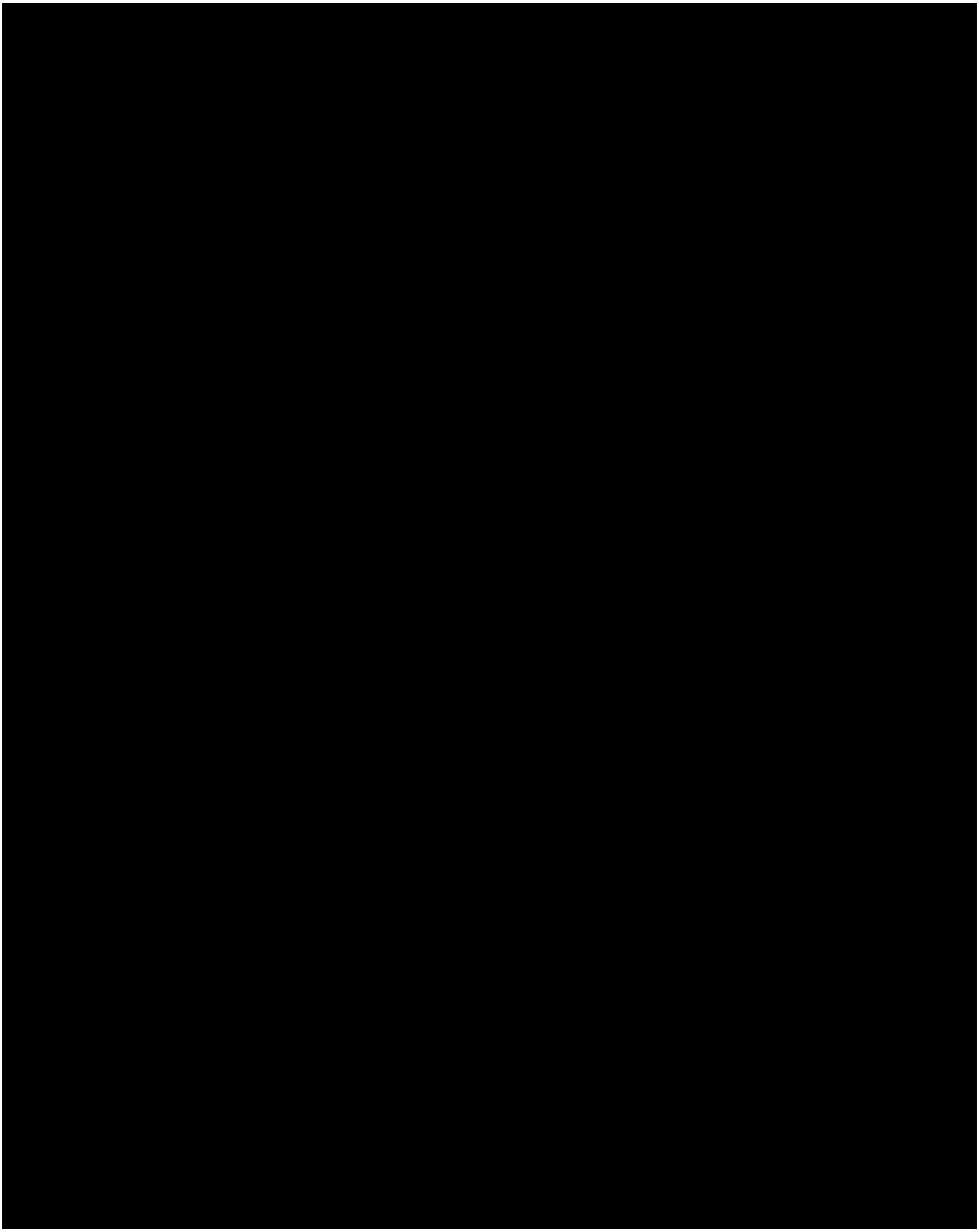
Primary performance endpoint will be primarily analysed on the FAS. [redacted]

[redacted]





[redacted]



[redacted]

[redacted]

6.3.4 Safety Analysis

6.3.4.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient participating in clinical research. [redacted]

Ocular and systemic AEs will be collected by the investigator (or authorised assessor/delegate) at each visit. In case of appearance of a new clinically significant sign or symptom, it should be reported as an AE. In case of clinically significant worsening of a pre-existing sign or symptom, it should be reported as an AE.

Both ocular and systemic AEs will be reported during the investigation and will be coded using MedDRA Version 27.1. Summary tables will be created for TEAEs. Ocular and systemic TEAEs will be analysed separately on the basis System Organ Class (SOC), by treatment group and overall, [redacted]

The summary tables will include the number of patients and the number of events, where applicable. Percentages will be based on the number of patients in the SAF. For summaries by SOC and Preferred Term (PT), a patient will be counted once at the SOC level and once at each PT level within the 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 overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

All AEs will be assessed for the relationship of the AE to IMD. [redacted]

Summary tables that will be provided are:

- An overall summary of the number and percentage of patients experiencing at least one TEAE, serious TEAE, IMD-related TEAE, IMD-related serious TEAE, TEAE leading to premature IMD discontinuation – and separately for ocular and systemic AEs.
- Number and percentage of patients with TEAEs, by SOC, PT and severity – separately for ocular and systemic AEs.
- Number and percentage of patients with TEAEs, by SOC, PT and relationship to IMD – separately for ocular and systemic AEs.
- Number and percentage of patients experiencing at least one serious TEAE, as well as the number of serious TEAEs, by SOC, PT and relationship to IMD – separately for ocular and systemic.
- Number and percentage of patients experiencing at least one TEAE leading to premature IMD discontinuation, by SOC and PT – separately for ocular and systemic AEs.
- Number and percentage of patients experiencing at least one serious TEAE, as well as the number of serious TEAEs, by SOC and PT – ocular and systemic AEs together.
- Number and percentage of patients experiencing at least one non-serious TEAE, as well as the number of non-serious TEAEs, by SOC and PT– ocular and systemic AEs.
- Number and percentage of patients experiencing at least one non-serious TEAE with PT occurring for at least 5% of the patients, as well as the number of non-serious TEAEs, by SOC and PT– ocular and systemic AEs.

Individual data listings will include all collected information, i.e. brief description of the event (diagnosis, localisation etc.), date and time of onset, time to AE occurrence, duration (days), intensity of symptoms (severity), treatment required, relationship with IMD and CIP procedure, action taken with the IMD, outcome, date and time of resolution and whether the event is classified as serious. [redacted]

Individual data listings that will be provided are:

- TEAEs – separately the ocular and systemic
- Non-TEAEs
- STEAEs
- TEAE leading to premature IMD discontinuation

All aforementioned analyses will be performed in the SAF set, apart from the non-TEAEs listing which will be created in the Enrolled set.

[redacted]

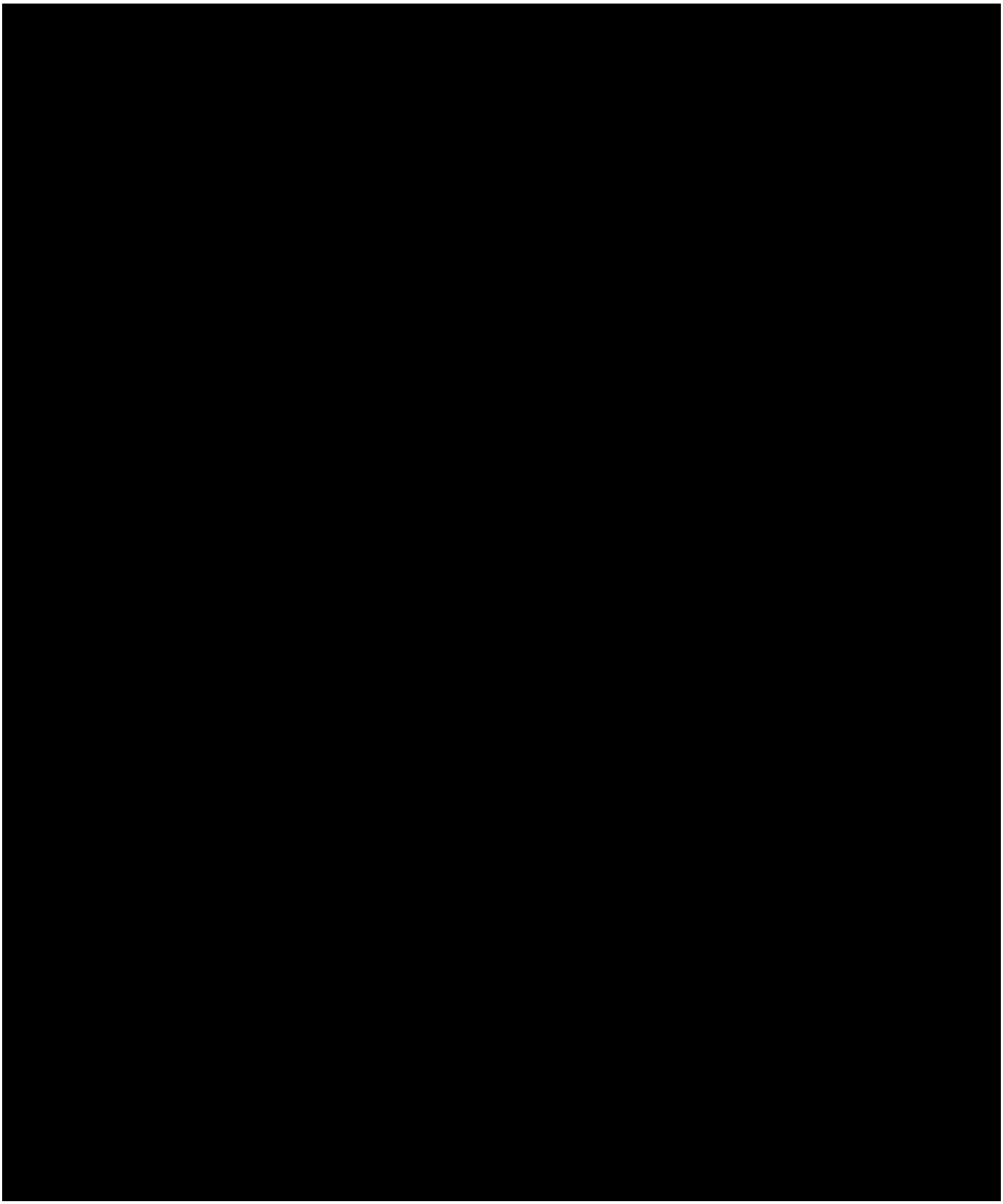
6.4 Interim Analysis

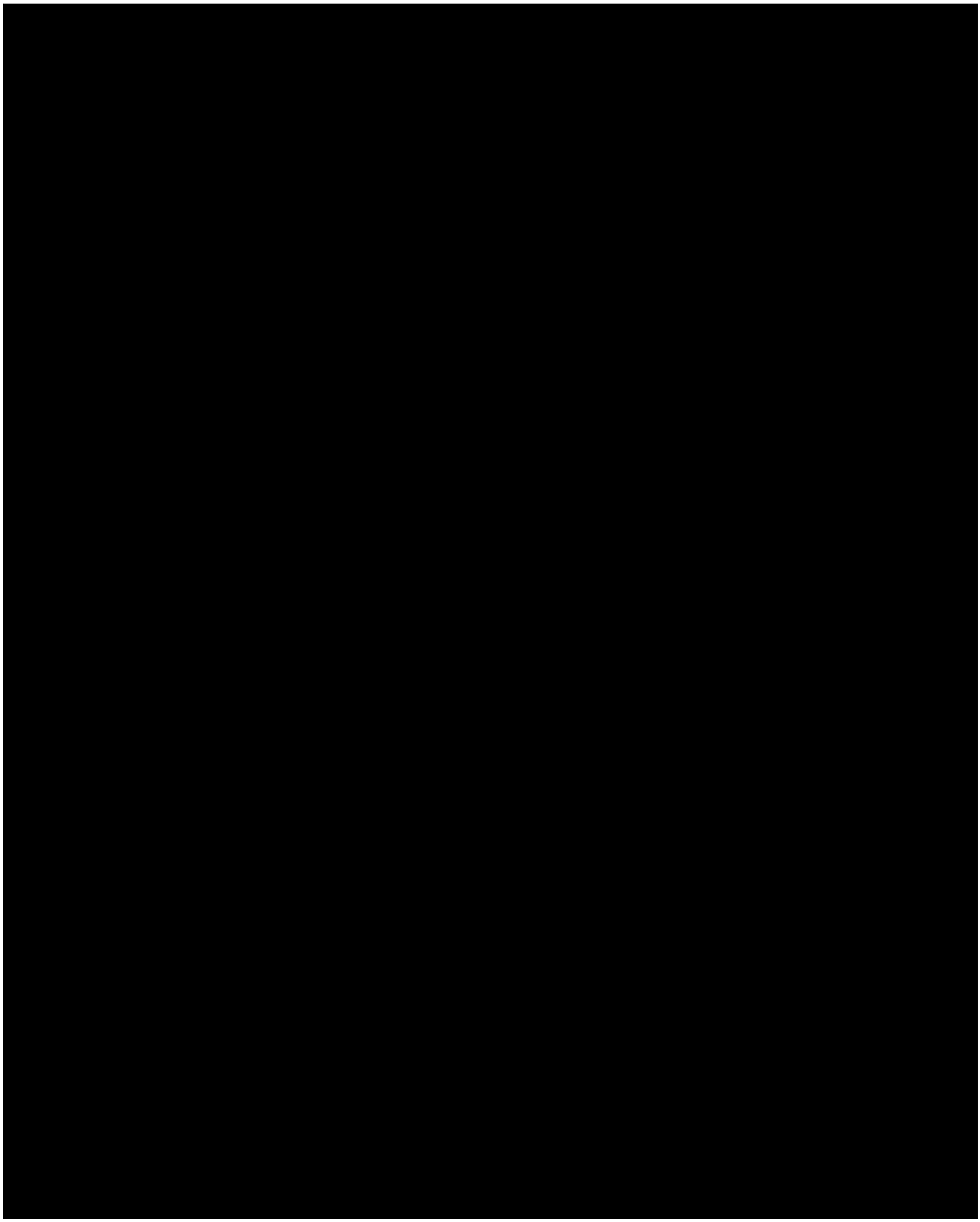
Not applicable. No interim analysis is planned for this investigation.

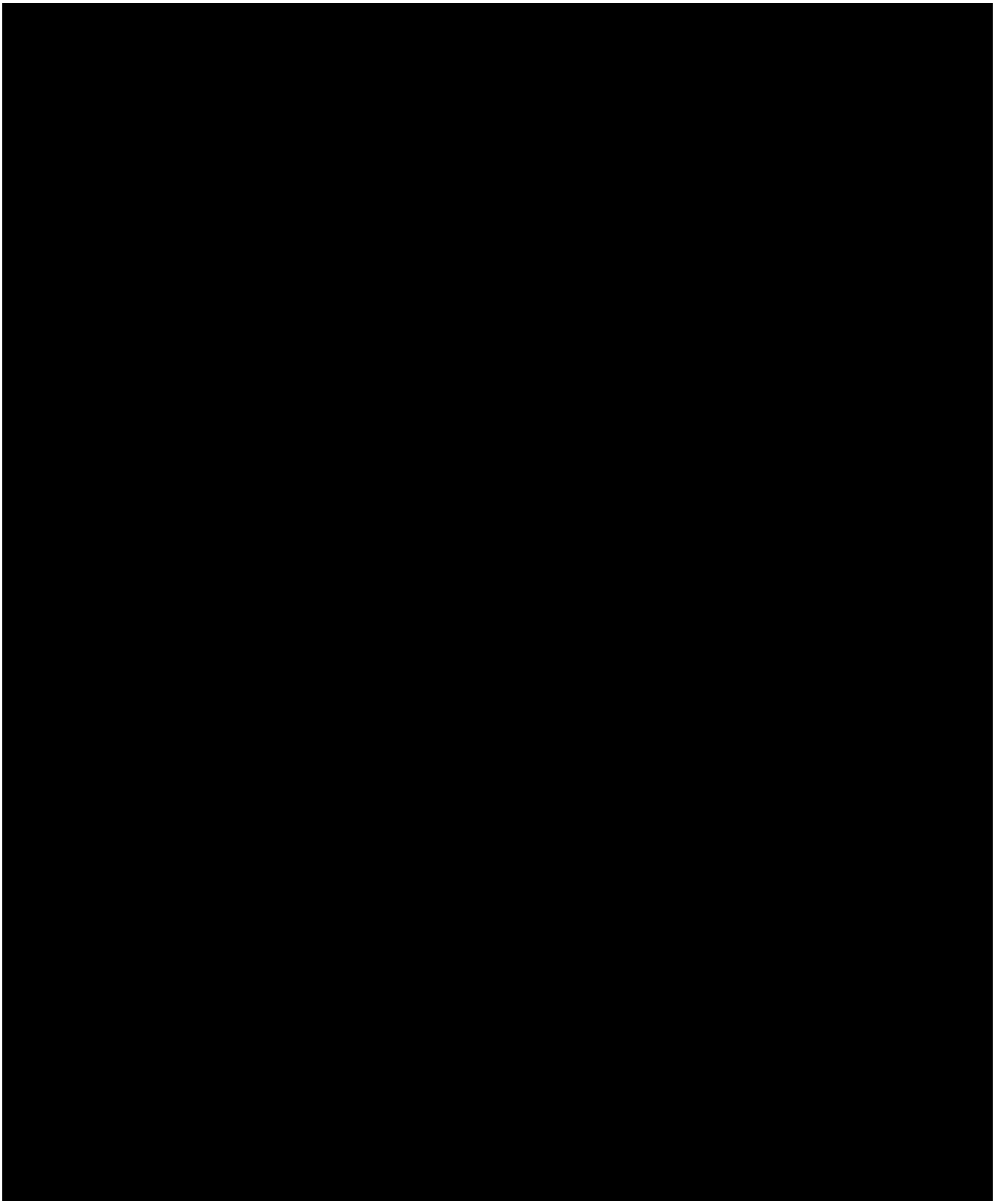
7. Tables, Figures and Listings

Mock tables, listings, and figures will be provided in an external document that accompanies this SAP. [redacted]

[redacted]







11. Deviations of the SAP from the CIP

[redacted]

[redacted] deviations from the CIP are the following:

[redacted]

- In the CIP it was stated that the summary tables would include the 95% CI for the mean/median (continuous variables) and the 95% CI of the percentages (categorical variables). However, this was removed from the SAP as it was found to not add any extra value while was increasing the complexity of the outputs.

[redacted]

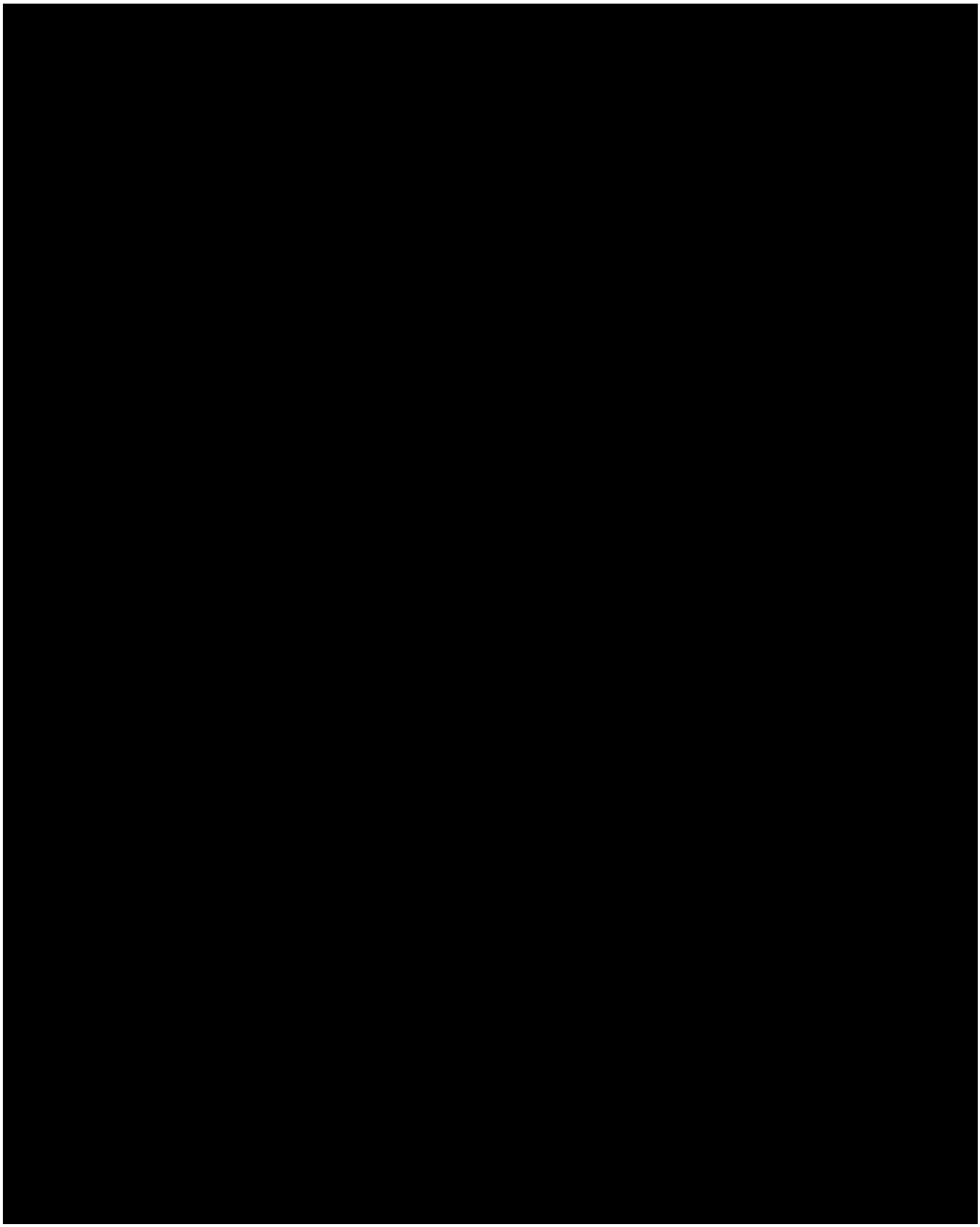
- For Adverse event reporting, more summary tables and details on listings to be provided are outlined in the SAP section 6.3.4.1 in comparison with the CIP.

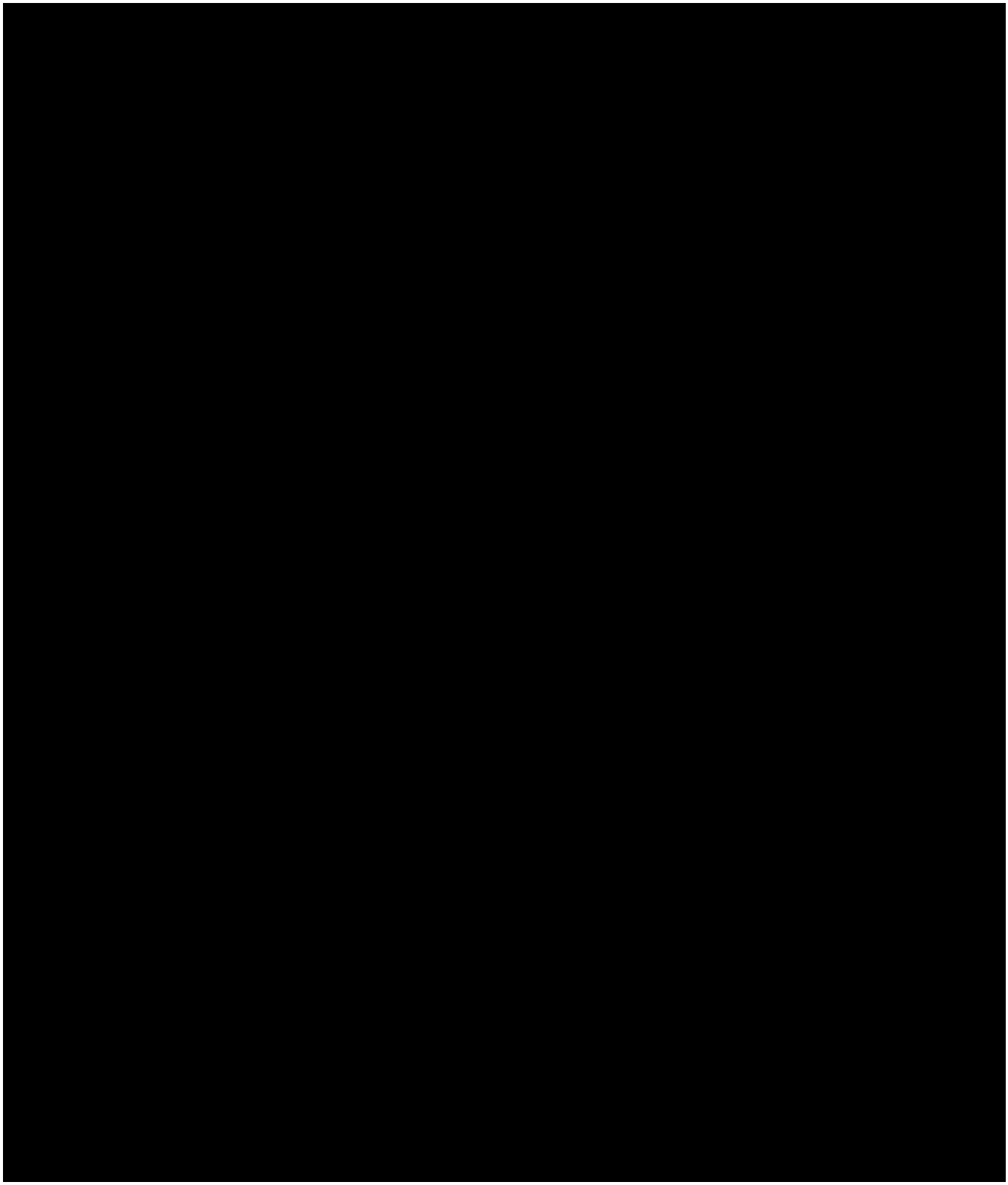
[redacted]

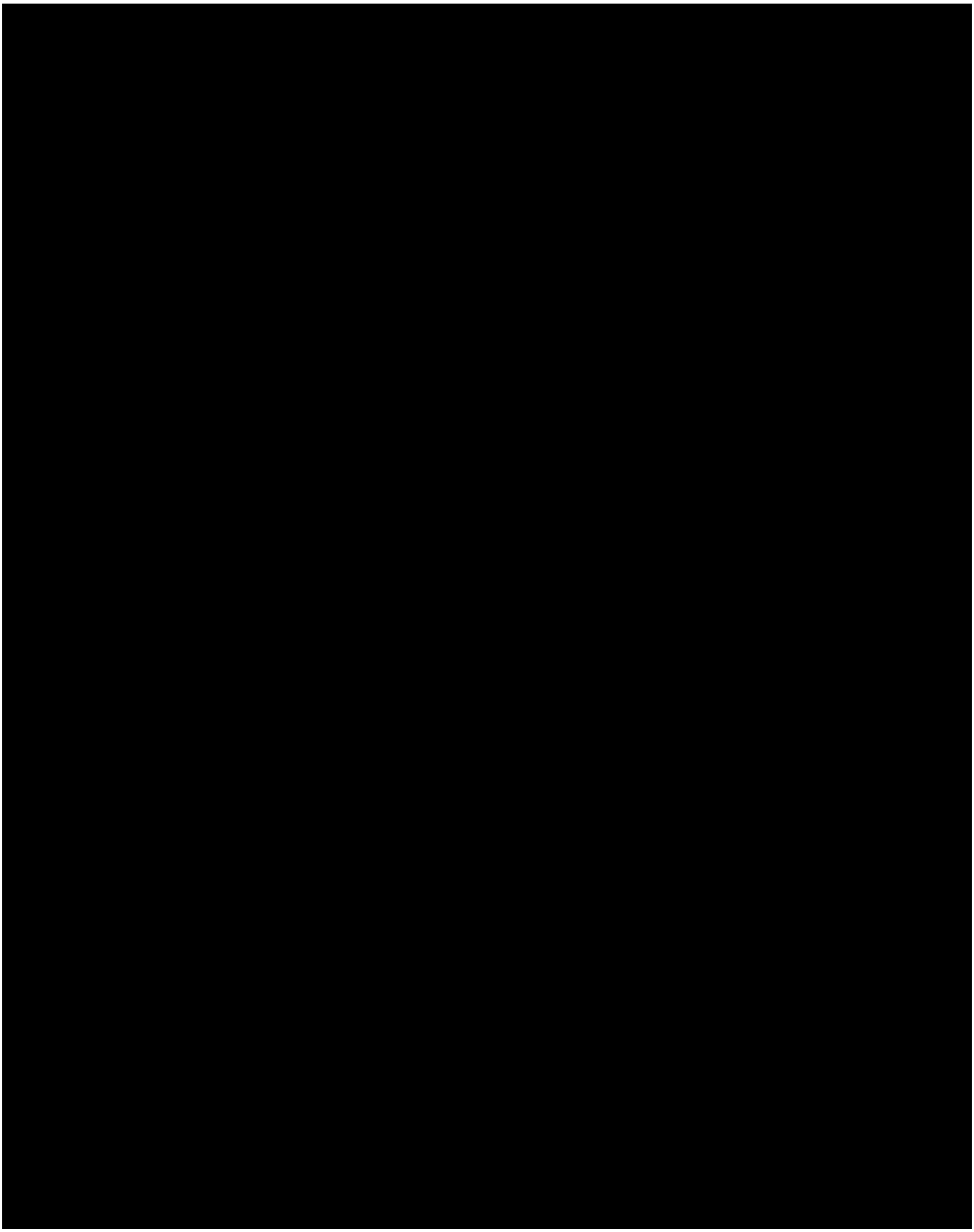
[redacted]

[redacted]

[redacted]







[redacted]

[redacted]