TRIAL STATISTICAL ANALYSIS PLAN

Global ID_Version:	**228892_92500_3.0**
BI Trial No.:	1305-0023 (FIBRONEER™ – ILD)
Title:	A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)
Investigational Product(s):	Nerandomilast
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	30 Dec 2024
Version:	3.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Antifibrotic
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BMI	Body Mass Index
C_{max}	Maximum Concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CQM	Clinical Quality Monitoring
DILI	Drug Induced Liver Injury
DLCO	Diffusion capacity of the lung for carbon monoxide
ECG	Electrocardiogram
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EoT	End of Treatment
EoS	End of Study
ESR	Erythrocyte Sedimentation Rate
ES	Entered Set
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastro Intestinal

Term	Definition / description
GMP	Good Manufacturing Practice
HLGT	High Level Group Term
HLT	High Level Term
HR	Heart Rate
HRCT	High Resolution Computed Tomography Scan
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
iPD	Important Protocol Deviation
IPF	Idiopathic Pulmonary Fibrosis
L-PF	Living with Pulmonary Fibrosis
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed effect Model Repeat Measurement
PN	Preferred Name
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PRO	Patient Reported Outcome
QoL	Quality of Life
REP	Residual Effect Period
RMP	Risk Management Program
RS	Randomised Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoC	Standard of Care
SOP	Standard Operating Procedure
t_{max}	Timepoint of Maximum Plasma Concentration
TEAE	Treatment Emergent Adverse Events
TS	Treated Set
TOM	Trial Oversight Meeting
TSAP	Trial Statistical Analysis Plan

Term	Definition / description
ULN	Upper Level of Normal
UIP	usual interstitial pneumonia
WHO	World Health Organisation

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

The main analysis of this study will be performed once the last randomized patient reaches the Week 52 visit (Visit 10). At that time, a first database lock (DBL1) will occur and sponsor will be unblinded to randomization assignment. All planned efficacy and safety analyses will be performed to assess the benefit-risk of Nerandomilast 9mg bid and 18mg bid over 52 weeks.

A final database lock (DBL2) will then occur after all patients have completed the EOT visit and the EOS visit as applicable. Analyses defined over the whole trial will be repeated to include newly emerging data including, but not limit to, time-to-event efficacy endpoints and selected safety outputs over the whole trial.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

- Due to Health Authority feedback and shifting trial timelines with fast recruitment, the Sponsor has decided to not perform an Interim Analysis (IA) for efficacy as outlined in Section 7.2.8 in Versions 1-3 of the Clinical Trial Protocol (included in signed off TSAP version 1.0). This decision has been reflected in Clinical Trial Protocol (CTP) version 4 as of Sept. 21st, 2023.
- In CTP Table 7.3.1:1 the following statement was made for missing FVC replacement due to death in primary and sensitivity analyses: "*impute based on 10th percentile of all observed values (change from baseline) in each treatment arm at each visit*".

  In this TSAP, we clarify in Section 7.4 the derivation rule for missing FVC replacement due to death be:

  "…for patients who died before end of Week 52 analysis period (i.e. day 393 inclusive) without lung transplantation, their missing FVC change from baseline values at visit(s) on or after death event date will be replaced based on 10th percentile of observed values (change from baseline) across all treatment arms at each visit, see Table 7.4.2.1: 1. Missing FVC value or measured FVC value prior to death date will not be replaced."

- Re-categorized several sensitivity analyses on alternative intercurrent event handling rules as supplementary analyses per guidance in ICH E9 R1 on differences between sensitivity analysis and supplementary analysis.
- Added supplementary analyses for primary and key secondary endpoints on alternative handling strategies with respect to protocol defined ICEs. Details can be found in Section 7.4.4 and Section 7.5.1.4.
- Added sensitivity analysis for primary endpoint:
    - a ranked ANCOVA is planned to assign poorest outcome (rank) for patients who died. Details can be found in Section 7.4.2.3.
    - analysis to exclude highly influential FVC changes, that with more than 1000mL absolute change (increase or decrease) from baseline value at Week 52. Details can be found in Section 7.4.2.7

Added further endpoints of:

- Absolute change from baseline in FVC [mL] over the whole trial
- Absolute change from baseline in FVC % predicted over the whole trial
- Absolute change from baseline in DLCO % predicted (corrected for hemoglobin) over the whole trial
- Absolute change from baseline in L-PF scores (including symptom domain scores for fatigue, cough and dyspnea, impact score and total score) over the whole trial, as well as absolute change from baseline in L-PF Symptoms Dyspnea, Symptoms Cough, and Symptoms Fatigue domain scores at Week 26
- Time to first dyspnea symptom deterioration or death
- Time to first cough symptom deterioration or death
- Time to first fatigue symptom deterioration or death
- Time to first use of supplemental oxygen
- Time to increase of supplemental oxygen use
- Absolute change from baseline in supplemental oxygen flow rate [L/min] over the whole trial
- Time to absolute decline in FVC % predicted of >15% from baseline or death over the whole trial

5. ENDPOINTS(S)

In this section, more details on definition and derivation of endpoints are given. Note that for all endpoints and analyses, Section 6.8 should be consulted for baseline value definition.

For endpoints where the “date of last contact” is utilised, the following will apply:

- The last contact date when the patient was known to be alive is defined as the latest date recorded in the electronic Case Report Form (eCRF) from the dates listed below

(in case a date is planned to be imputed for the analysis, the imputed date will also be used for the definition of "date of last contact"):

- Date of last visit (e.g. for spirometry), date of last reported Adverse Event (AE) (excluding censored dates), date of last reported concomitant treatment, date of last laboratory sample, date of last drug intake, date of last reported dose change / interruption, date of last non-elective hospitalization admission and date of concomitant non-drug therapy, last vital status date as documented on Vital Status eCRF page when the patient is known to be alive and last successful contact date as documented on the End of Study eCRF page if the patient was lost to follow-up.

5.1 PRIMARY ENDPOINT(S)

As is defined in Section 2.1.2 of CTP, the primary endpoint is the absolute change from baseline in Forced Vital Capacity (FVC) [mL] at Week 52. The analysis will be based on FVC values obtained at pre-specified visits over 52 weeks.

Details of FVC measurement collection are specified in Section 5.1.1 of CTP.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint

As is defined in Section 2.1.3 of CTP, the key secondary endpoint is time to the first occurrence of any components of the composite endpoint: time to first acute ILD exacerbation, first hospitalization for respiratory cause, or death (whichever occurs first) over the duration of the trial.

Acute ILD exacerbations defined in CTP Section 5.1.2 are collected in the adverse event page under the category of "acute exacerbation of disease under investigation" or the category of "Suspected Acute Exacerbation of Disease Under Investigation" and the specific eCRF page for ILD acute exacerbation. Events that are clinically considered as acute ILD exacerbation on the AE page and fulfilled the protocol defined acute ILD exacerbation criteria based on responses in the exacerbation page (Table 5.2.1: 1) will be considered as acute exacerbation for analysis.

Both confirmed and suspected (missing CT data) cases will be considered for the endpoint evaluation. A sensitivity analysis including only confirmed acute exacerbations as events will be performed as well. Details can be found in Section 7.5.1.2.

Table 5.2.1: 1 Derivation rules for protocol defined acute/suspected acute ILD exacerbation based on responses from acute exacerbation eCRF page

eCRF questions	(confirmed) acute ILD exacerbation	Suspected acute ILD exacerbation
Acute respiratory deterioration within the last month?	Yes	Yes

eCRF questions	**(confirmed) acute ILD exacerbation**	**Suspected acute ILD exacerbation**
Extra-parenchymal cause identified (e.g. Pneumothorax, pleural effusion, pulmonary embolism)?	No	No
New, bilateral GGO/consolidation on Chest CT (not fully explained by cardiac failure or fluid overload)?	Yes	Chest CT not performed

Hospitalization due to respiratory cause defined in CTP Section 5.1.4 will be collected in a specific non-elective hospitalization eCRF page, which captures the date of hospitalization, whether the non-elective hospitalization was due to respiratory cause, and the primary admission diagnosis. Admission diagnosis entered in the non-elective hospitalization eCRF page will be blinded reviewed to determine the respiratory relatedness before DBL1 and continue to be reviewed before DBL2.

Date of death for an individual patient will be obtained from either the AE page for patients with AEs leading to death, End of Study or from the vital status eCRF page.

5.2.1.1 Calculations for time to event endpoints

For a time to event endpoint with single component and component within a composite time to event endpoint, time in days will be derived as:

Situation	Time (in Days)	Rule
Event	Event time	date of first event - date of first drug intake + 1
Event-free	Censoring time	latest known event-free date - date of first drug intake + 1

Based on the definition of the event and planned data collection scheme, event date and last known event-free date for time to event endpoints or a component within a composite time to event endpoint are defined in Table 5.2.1.1: 1.

Table 5.2.1.1: 1 Definition of first event date and latest known event-free date

Event name	**Date of first event**	**Last known event-free date**
ILD exacerbation	Earliest AE start date of documented (suspected) acute exacerbation fulfils the protocol defined criteria	Last contact date

Event name	Date of first event	Last known event-free date
Hospitalization due to respiratory cause	Earliest start date of documented respiratory related hospitalization on non-elective hospitalization eCRF	Last contact date
Hospitalization due to any cause	Earliest start date of documented non-elective hospitalization eCRF	Last contact date
Absolute/relative decline in FVC % predicted > 5/10/15%	Earliest date of documented absolute/relative decline in FVC % predicted>5/10/15%	Last FVC measurement date
Absolute decline in DLCO % predicted > 15%	Earliest date of documented absolute decrease in DLCO % predicted > 15%	Last DLCO measurement date
Dyspnea symptom deterioration	Earliest date of documented absolute increase from baseline in L-PF symptom dyspnea domain score > 9	Last L-PF symptom dyspnea domain questionnaire completion date
Cough symptom deterioration	Earliest date of documented absolute increase from baseline in L-PF symptom cough domain score > 16	Last L-PF symptom cough domain questionnaire completion date
Fatigue symptom deterioration	Earliest date of documented absolute increase from baseline in L-PF symptom fatigue domain score > 13	Last L-PF symptom fatigue domain questionnaire completion date
Use of supplemental oxygen	Earliest date of documented first supplemental oxygen use indicated on L-PF oxygen questionnaire	Last L-PF oxygen questionnaire completion date
Increase of supplemental oxygen use	Earliest date of documented first increase of supplemental oxygen use	Last L-PF oxygen questionnaire completion date
Initiation of antifibrotic treatment	Earliest date of documented antifibrotic treatment on concomitant medication page	Last contact date
Initiation of immunosuppressive (rescue) therapy	Earliest date of documented immunosuppressive (rescue)	Last contact date

Event name	Date of first event	Last known event-free date
	therapy on concomitant medication page	
Death	Date of death documented on vital status page, EoS page or AE page	Last contact date

For composite time to event endpoints, patient with at least one event in any of the components of the composite will be considered to have an event and the date of the first event will be used for the composite endpoint. A patient without an event will be considered censored at the earliest of all censoring dates of the component endpoints, see Table 5.2.1.1: 2.

Table 5.2.1.1: 2 Censoring rules for composite time to event endpoint

Rule	Situation	Outcome (event or censored)	Date of event or censoring
1	Patient is free of event from any component	Censored	Earliest censoring time
2	Patient has event(s) from at least one of the components	Event	Earliest event time

5.2.2 Secondary endpoint(s)

Other secondary endpoints are defined in Section 2.1.4 of CTP.

For other secondary time to event endpoints, calculations as specified in Section 5.2.1.1 will be followed for event, censoring time, and censoring mechanism.

Absolute changes from baseline in FVC % predicted at Week 52 will be computed and evaluated as secondary endpoint of this trial.

DLCO

Details of DLCO measurement collection are specified in Section 5.1.6 of CTP.

Absolute changes from baseline in DLCO % predicted corrected for hemoglobin at Week 52 will be evaluated as secondary endpoint of this trial.

DLCO % predicted will be computed as

$$\frac{mean\ DLCO}{DLCO\ predicted\ corr.\ for\ Hb} \times 100\%$$

where mean DLCO is the average of two acceptable DLCO measurements collected at each prespecified visit indicated in the study protocol. In case there is only one acceptable DLCO

measurement collected, the only measurement will be used. Investigator reported DLCO predicted values will be used in analysis.

Notice that when presenting DLCO % predicted value, DLCO predicted value will be corrected for hemoglobin using the most recent hemoglobin values:

$$DLCO_{pred\ for\ Hb}(male) = DLCO_{pred} \times \frac{1.7Hb}{10.22 + Hb}$$

$$DLCO_{pred\ for\ Hb}(female) = DLCO_{pred} \times \frac{1.7Hb}{9.38 + Hb}$$

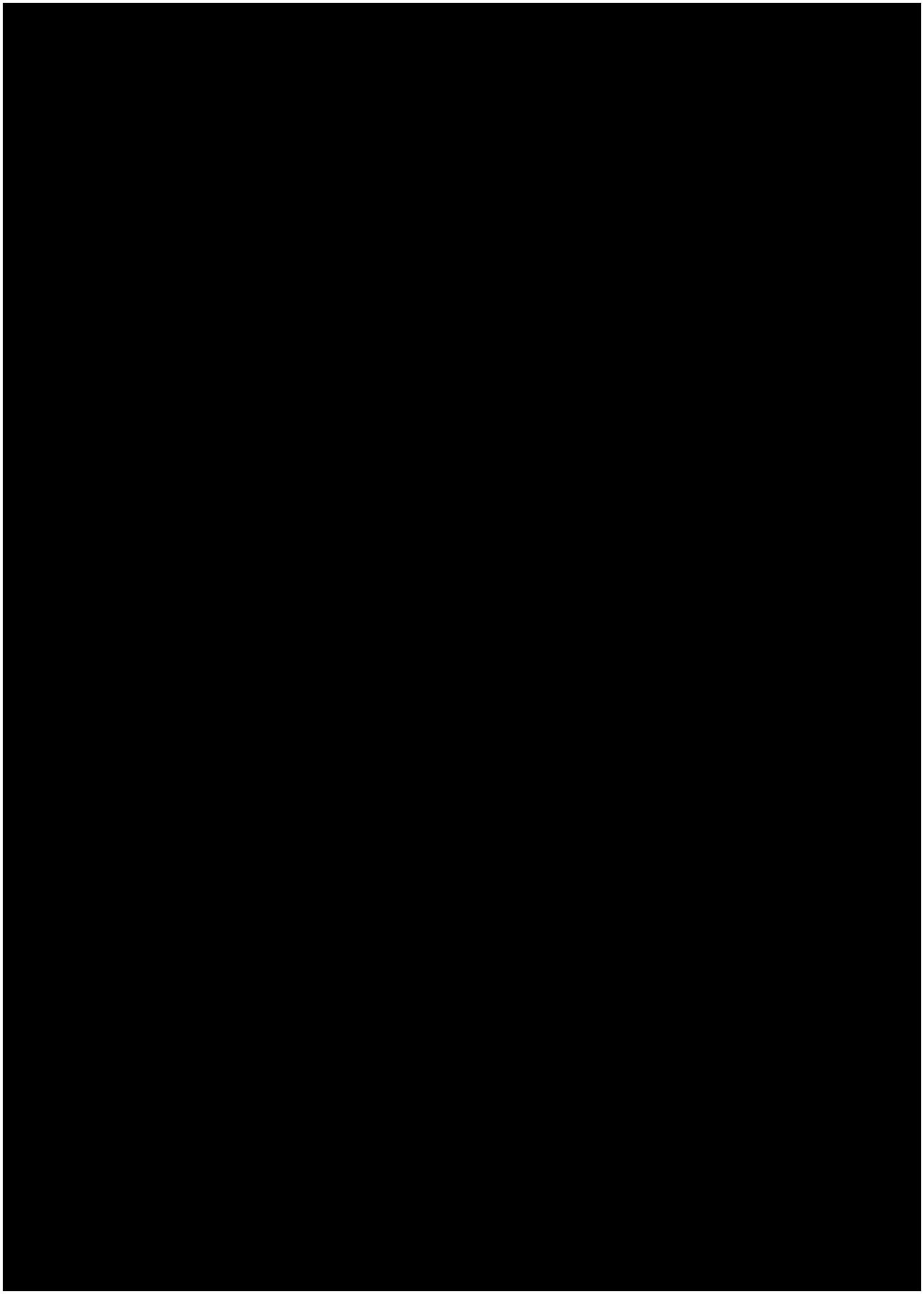
Live with Pulmonary Fibrosis (L-PF) Symptom domain scores

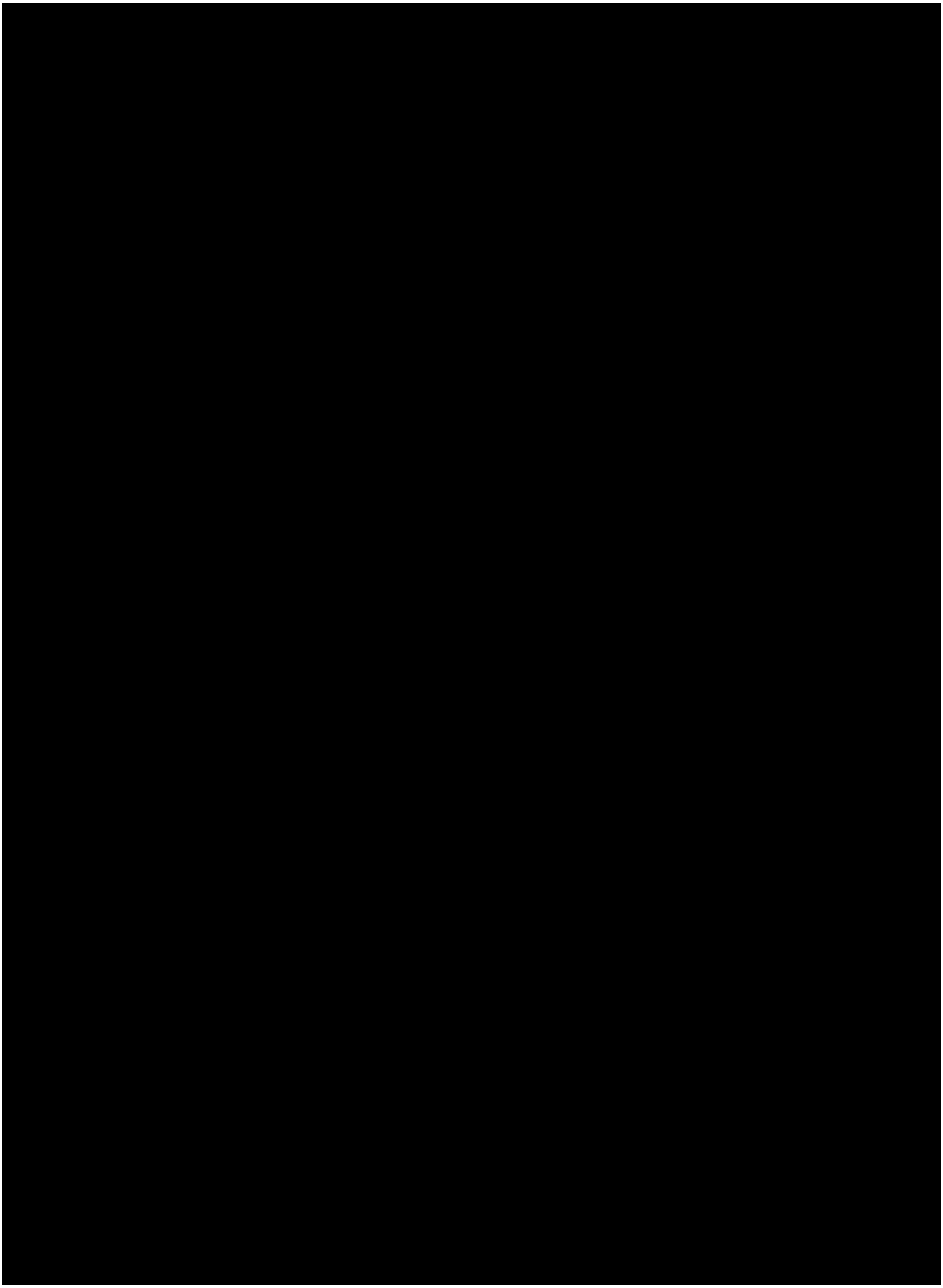
The Living with Pulmonary Fibrosis (L-PF) questionnaire is a 44-item questionnaire with two modules: 1) symptoms (23 items) and 2) impacts (21 items). L-PF was developed with the input of patients with pulmonary fibrosis (PF) and thus is intended to capture perceptions specific to PF patients. The Symptoms module yields three domain scores: 1) dyspnea, 2) cough and 3) fatigue as well as a total Symptoms score. Scoring is performed as a summary score, the mean of the dimension ratings multiplied by 100. Summary score ranges from 0-100, the higher the score, the greater the impairment.

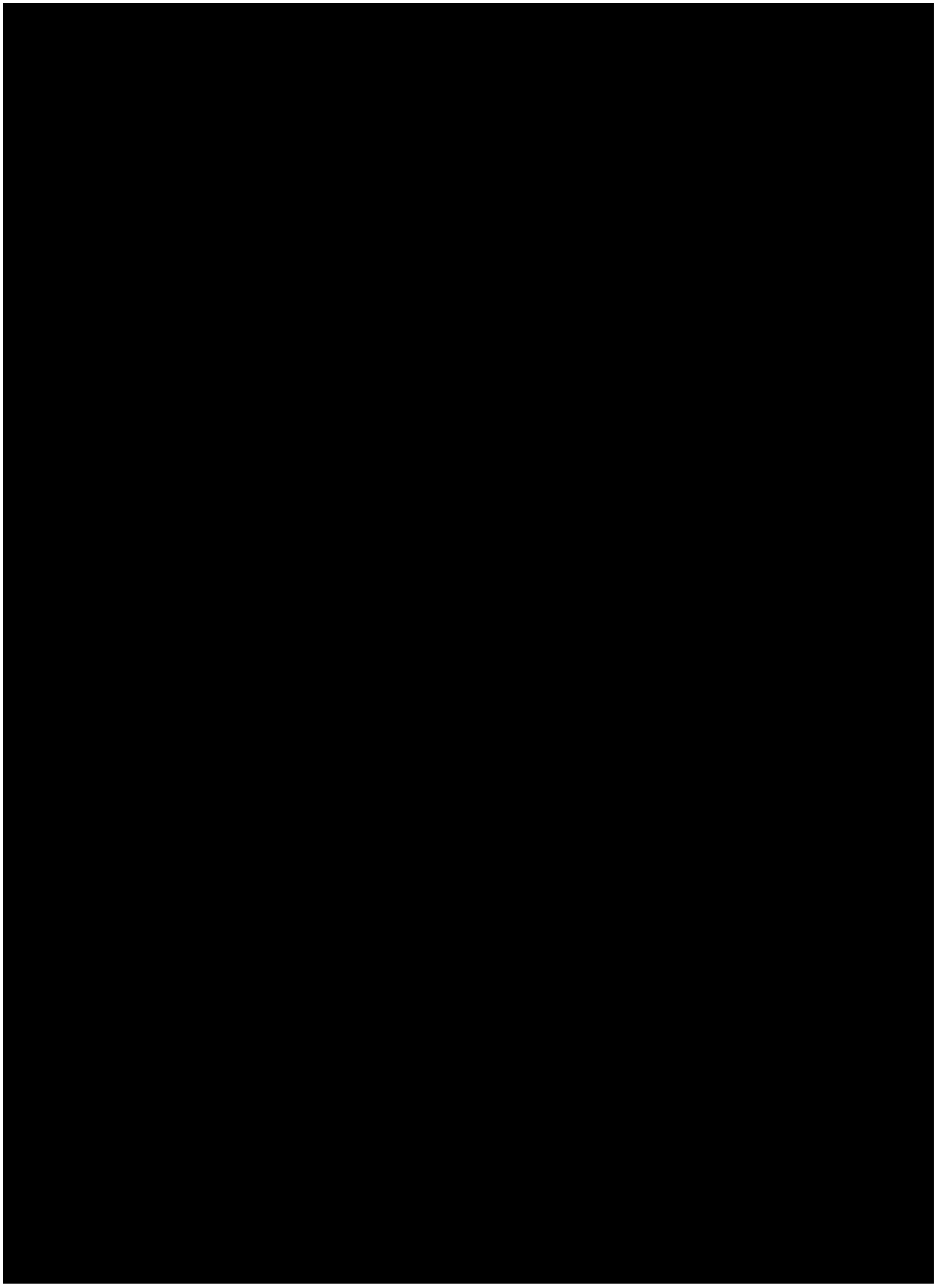
Absolute changes from baseline in domain scores including Symptoms Dyspnea, Symptoms Cough, and Symptoms Fatigue at Week 52 will be computed and evaluated as secondary endpoint.

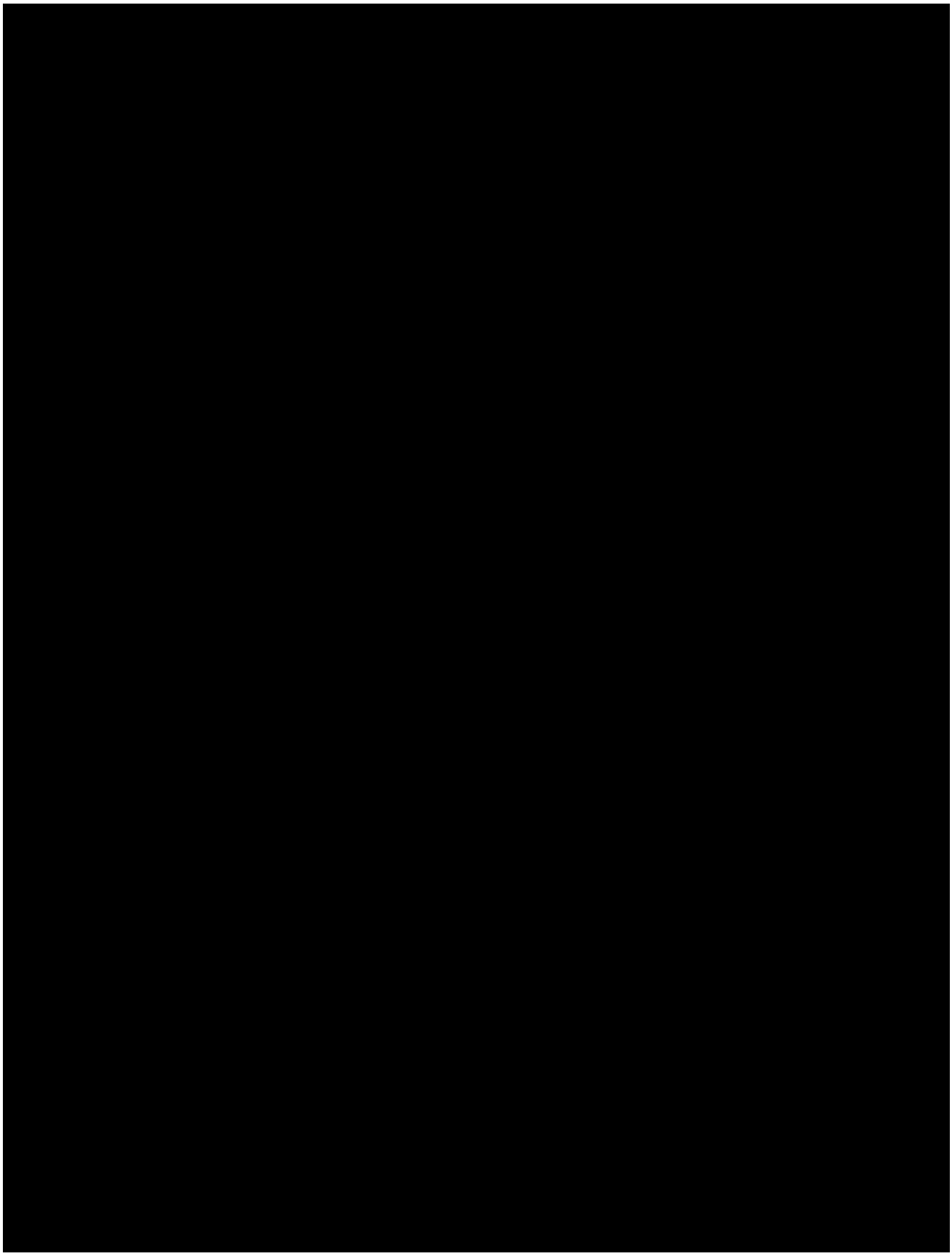
Scoring instructions for L-PF are described in Section 10.2. Specific rules of handling of missing items are detained in Section 6.7.2.

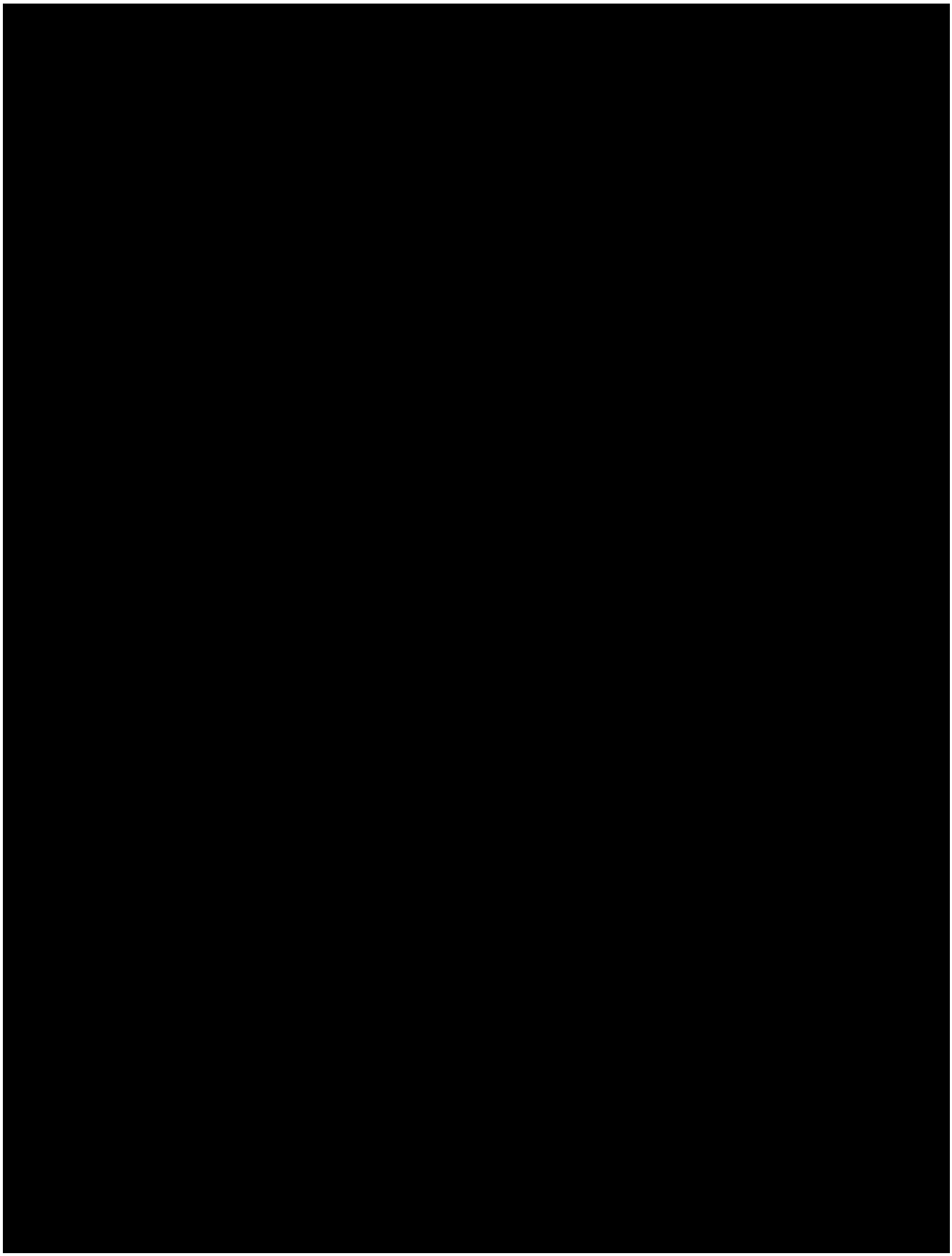
Details of L-PF measurement collection are specified in Section 5.1.5.1 of CTP.











6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For reporting purposes, all randomized patients will be classified into one of the following:

- Nera 18 mg bid
- Nera 9 mg bid
- Placebo

For efficacy analyses, patients will be analyzed as randomized based on Full Analysis Set (FAS).

For safety analyses, patients will be analyzed as treated based on Treated Set (TS).

The study periods based on actual start and stop dates of study medication administration are defined in Table 6.1: 1.

Table 6.1: 1 Flow Chart of analysis phases

Study analysis phase	Label	Start date (inclusive)	End date (exclusive)
Screening	Screening	Date of informed consent	Date/time of first drug intake
On-treatment	Placebo	Date/time of first drug intake	12:00 am on the day after last drug intake + 7 days or to date of first trial drug intake in extension trial, whichever occurs earlier
	Nera 18 mg bid		
	Nera 9 mg bid		
Follow-up	Follow-up	12:00 a.m. on the day after last drug intake + REP	12:00 a.m. on the day after patient's trial termination date

For AE listing, "off-treatment" period is defined with start date of "start date of treatment interruption + 7 days" and end with "re-start date of treatment"

As a summary:

- For primary efficacy analyses, data from first drug intake date up to week 52 will be considered. For efficacy descriptive analyses over the whole trial period, all data collected after first drug intake date will be considered.
- For safety analyses, data from the treatment period, possible off-treatment periods and residual effect period will be considered as on-treatment.

For the main analysis only data collected over the whole trial available at the time of data cut off for DBL1 will be considered, whereas all data collected within the trial will be considered and reported for the final analysis at DBL2.

Table 6.1: 2 Summary of analysis periods according to the type of endpoint or analysis

Type of analysis	**Analyses / Endpoints**	**Studied period**	
		Start date[1]	**End date [2]**
Efficacy analyses over 52 weeks	Analyses on all efficacy endpoints listed in CTP Sections 2.1 and 2.2 defined over 52 weeks	Date of first drug intake	Date of last measurement before or at 52 Weeks (≤ 393 days after first drug intake)
On-treatment efficacy analyses over 52 weeks	While on treatment supplementary analysis for primary endpoint	Date of first drug intake	Date of last trial drug intake +7 days before or at 52 Week (≤ 393 days after first drug intake), whichever occurs first
Efficacy analyses over the whole trial	Analyses on time-to-event endpoints specified in Sections 2.1.3, 2.1.4 and 2.2.2 of the CTP and Section 4, including key secondary endpoint Annualized rate of hospitalization for respiratory cause Absolute change from baseline in: • FVC (ml) • FVC (% of predicted) • DLCO (% of predicted) • L-PF scores	Date of first drug intake	Date of last measurement up to the last follow-up visit (included) or last contact date
On-treatment efficacy analyses over the whole trial	While on treatment supplementary analysis for key secondary endpoint	Date of first drug intake	Date of last trial drug intake +7 days

Type of analysis	**Analyses / Endpoints**	**Studied period**	
		Start date[1]	**End date** [2]
Efficacy time to event analysis over 52 weeks	Estimated cumulative incidence rates for time-to-event endpoints at Week 52	Date of first drug intake	If FVC %pred, DLCO% pred or L-PF scores are in the endpoint: Date of first drug intake + 372 days Else, date of first drug intake + 365 days
Extent of exposure analysis	See Section 7.7	Date of first drug intake	See Section 7.7
Safety analysis over the whole trial	• Time to first onset of adverse events listed in Section 7.8.1.9 • Adverse events • Laboratory data • Vital signs • Other (C-SSRS, HADS)	Date of first drug intake	Date of last drug intake + 7 days or last contact date, whichever occurs first
Safety analysis over 52 weeks	• Adverse events • Laboratory data • Vital signs	Date of first drug intake	If day of last drug intake ≤ 372 days after first drug intake: Date of last drug intake + 7 days If day of last drug intake ≥ 373: Date of first drug intake + 372 days

[1] Date of randomisation and date of first drug intake should be identical. If there are discordances between these dates on patient level, date of first drug intake will be used.
[2] End date is included.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Although all treated patients will be included in the safety analyses and all randomized patients will be included in the efficacy analyses, patients with important protocol deviations (iPDs) will be documented.

Definitions of iPDs are included in the DV domain specifications and are stored within the trial master file (TMF) in the electronic document management system (EDMS). Listings for

data consistency checks and a list of protocol deviations will be provided at each CQM / TOM meeting to help identify iPDs. During these meetings, it will be decided whether a protocol deviation is an iPD. Confirmed iPDs will be documented in either the DV domain specifications (for manual iPDs) or iPD-for-reconciliation spreadsheet (for automatic iPDs), which will be used as source files for SDTM DV domain generation.

Regardless of manual or automatic iPDs, different iPD categories are defined in the tab of "iPD Def and Handling" of the DV domain specification spreadsheet. The final list of iPDs will be confirmed at the last blinded report planning meeting (BRPM)/trial oversight meeting (TOM) before the database lock. A summary table and listings for iPD incidents will be provided in the Clinical Trial Report (CTR).

6.3 INTERCURRENT EVENT

Intercurrent Events (ICEs) are events occurring after treatment initiation which affect the existence or interpretation of the outcomes associated with the clinical objectives. The expected intercurrent events of interest in this trial are listed in Table 6.3: 1 together with the sources they are identified from. Note that in addition to the ICEs specified by the CTP, several iPDs are also considered as ICEs in this study. Details can be found in Section 7.4.4.3.

Table 6.3: 1 Intercurrent events and their corresponding documentary sources

Intercurrent event	Documentary source
Change of background antifibrotic therapy	Concomitant medication page in eCRF
Start of a restricted medication	Concomitant medication page in eCRF
Treatment discontinuation or interruption (any cause)	• Study medication interruption page in eCRF ("Study Medication Interruption or Re-start of Study Medication" = "Interruption") • End of treatment page in eCRF ("Did the subject complete the planned treatment period?" = 'No')
Death	Adverse event page in eCRF ("Outcome" = "Fatal") or, Vital Status page in eCRF ("Subject Status" = "Dead") or, End of study page (vital status) in eCRF ("Did the subject complete the planned observation period?" = 'No' and "primary reason" = 'Death')
Lung transplant	Concomitant Non-drug therapies page in eCRF ("Procedure/Non-Drug Therapy" = "Lung transplant")
iPD related	DV domain specification, iPD for reconciliation sheet, and Table 7.4.4.3: 1.

According to the study protocol, all intercurrent events will be primarily handled by the treatment policy as defined in ICH E9(R1) except for death and lung transplants. Thus, all available data from baseline (excluded) up to Week 52 or EOS for respective efficacy endpoints, including visits after EOT and follow up visit, will be included in the primary analyses, except for death and lung transplant.

Specifically, data collected after

- change of treatment (premature treatment discontinuation or interruption),
- change of background antifibrotic (rescue) therapy usage,

will all be included.

Lung transplants are assumed to be random events, rather than indicators for treatment failure, as it depends on whether a patient is on a transplant registry and whether they can be accepted for lung transplant due to be neither too sick nor too well. In addition, assessments after lung transplantation are no longer reflective of diseased lung(s). Therefore, the treatment effect of interest is in the hypothetical scenario that lung transplantations are unavailable, and data collected after lung transplant will be excluded. Specifically, death after lung transplant will be ignored too, as it is unlikely related to the disease under investigation, but rather complications of the transplant. This data handling rule will be applied in all the efficacy analyses described in this TSAP unless otherwise specified.

Death events of any cause are considered as treatment failure in this trial. Therefore, the treatment effect of interest takes death as a composite variable with a penalty in the outcome. Details on timing and value for death replacement can be found in Section 7.4.

The treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug (including treatment discontinuation), changes to standard of care, and the use of prohibited medication. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis.

Additional supplementary analyses for primary and key secondary endpoints under alternative strategy are specified in Section 7.4.4 and Section 7.5.1.4.

Summary of the number and timings of each ICE in each treatment group will be reported. For ICE related to important protocol deviations, only summary of iPD incidences will be reported (refer Section 6.2). For other ICEs specified in Table 6.3: 1, summary of frequencies and timing will be reported. Timing of such an event is defined as the time from a patient's treatment initiation to the event start date. Summary of change background antifibrotic therapies and use of restricted medications will be included in the summary of concomitant medication. Treatment discontinuation and interruption will be reported together with patients' exposure results. Death will be summarized and be included in the efficacy analyses for secondary endpoint (refer Section 7.5.1). Lung transplant will be summarized in the patient disposition table (refer Section 7.2.2).

6.4 SUBJECT SETS ANALYSED

The following analysis sets have been defined in Section 7.2.1 of CTP for statistical analyses:

- Entered Set (ES):

This patient set includes all patients who signed informed consent.

The ES will be used for the analyses of patient disposition.

- Randomised Set (RS):

  This patient set includes all randomised patients, whether treated or not.

- Full Analysis Set (FAS):

  This patient set includes all randomized patients who received at least one dose of study drug. The FAS will be used for baseline demographics and characteristics, protocol deviations, and all efficacy analyses, in which patients will be analyzed as their randomized treatment group.

- Treated Set (TS):

  This patient set includes all randomized patients who received at least one dose of study drug. The TS will be used for all safety analyses, in which patients will be analyzed according to the actual treatment they received.

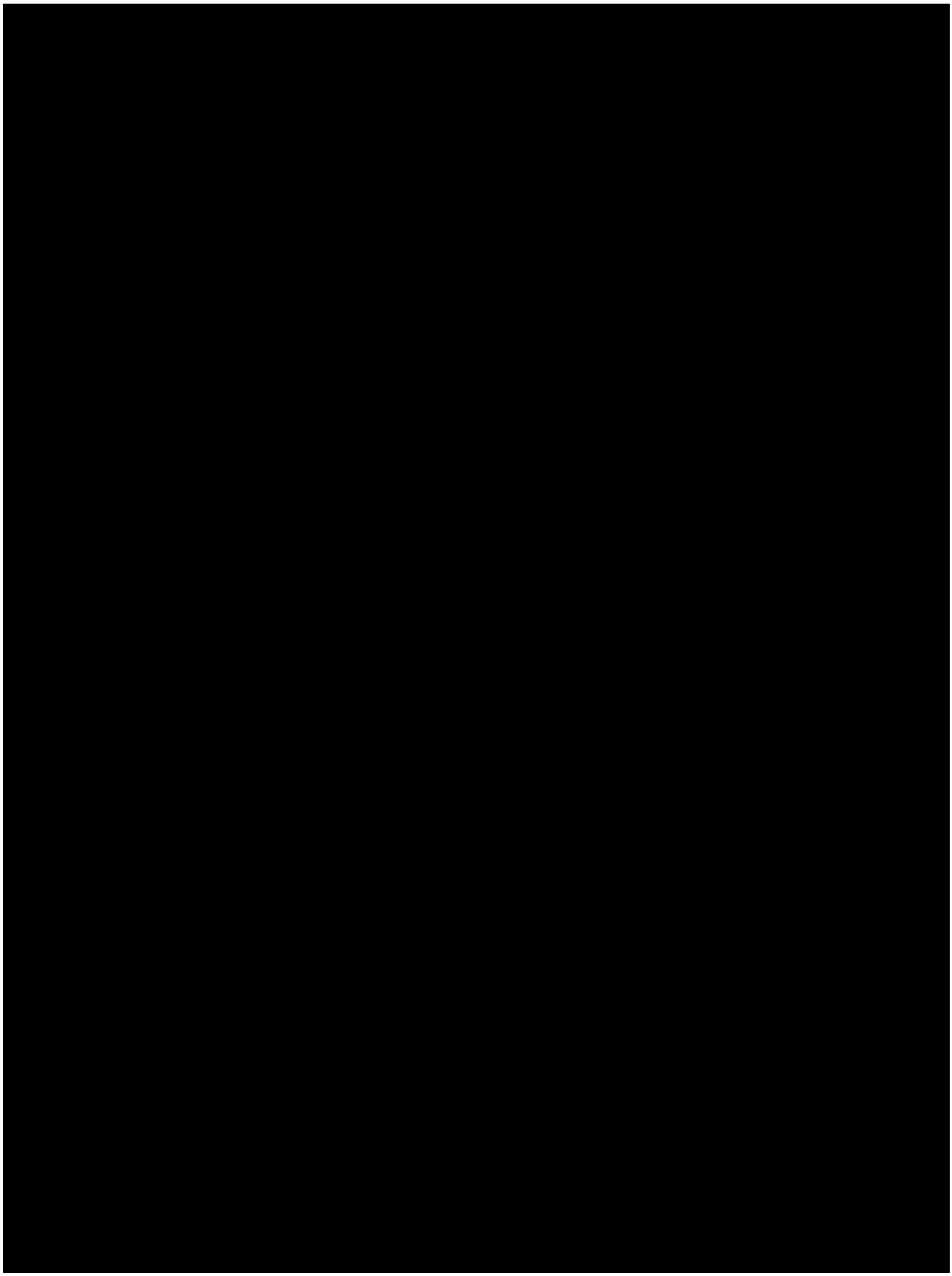
- PK parameter analysis set (PKS):

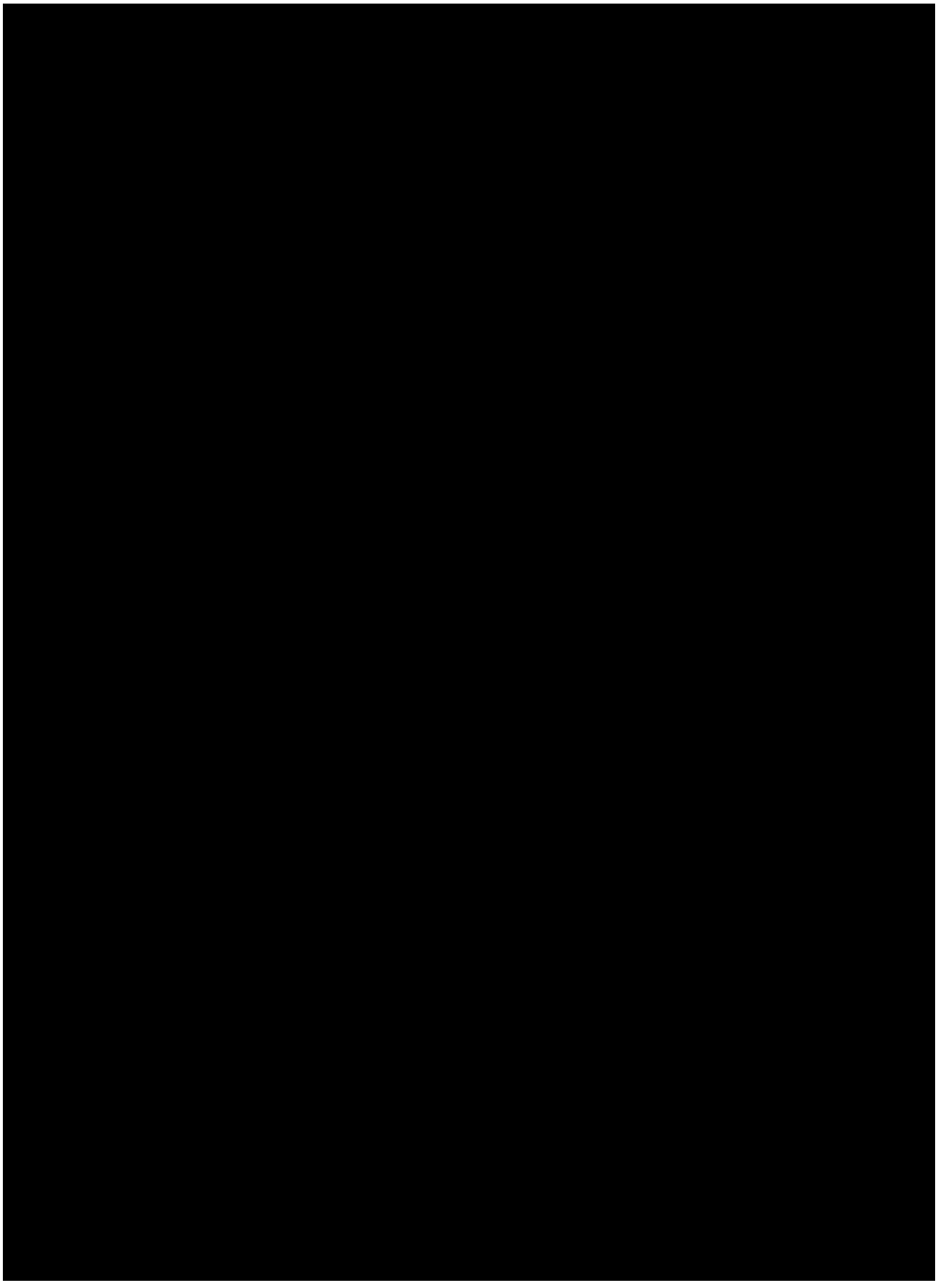
  This patient set includes those patients in the TS with at least one valid plasma concentration available.

Actual treatment received is defined as the treatment with maximum exposure according to actual treatment dispensation.

For both the Full Analysis Set and Treated Set, the displayed treatment groupings will be: “Nera 9mg bid”, “Nera 18mg bid”, and “Placebo”.

Patients without informed consent signed will be removed from all analysis sets.





6.6 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.7 HANDLING OF MISSING DATA AND OUTLIERS

6.7.1 Primary endpoint

Missing data for non-death reasons were not imputed. The statistical model used for primary analysis (see Section 7.3.1 of CTP) allows for missing data, assuming they are missing at random (MAR). Even patients with baseline and only one post-baseline assessment can be included in the model and can therefore participate in variance estimation. The statistical model assumes that patients who prematurely discontinue study participation would have behaved similarly to those who remained in the study.

Missing data due to death will be assigned with a poor outcome under composite variable strategy (See Section 7.4).

Sensitivity analyses using alternative assumptions and tipping point analysis will be conducted to investigate the potential effect of missing data on the results of the primary analysis (see Section 7.4.2.1 and Section 7.4.2.2).

A sensitivity analysis to exclude FVC outliers, defined as absolute change from baseline > 1000mL or <-1000mL, will be planned (See Section 7.4.2.7).

6.7.2 Secondary and further endpoints

Time-to-event endpoints

In the primary analysis of time-to-event endpoints, missing or incomplete data will be handled using standard survival analysis techniques (i.e., censoring).

Continuous endpoints

In the model-based analysis of all other continuous endpoints, missing data will not be imputed except for death. The mixed effect model will handle missing data based on a likelihood method under the “missing at random assumption”.

Missing data due to death will be assigned with a poor outcome under composite variable strategy (See Section 7.4).

PRO questionnaires

Item-level data for the PRO measures will be handled according to the instructions provided by the instrument developer, with details provided in Section 10.2.

The L-PF scores represent means. Missing items are generally not counted in both the numerator and the denominator. If the missing items are ≥50% within a score, then the corresponding score is set to missing.

6.8 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Selection of baseline

In general, the last assessments observed prior to the first study medication intake at Visit 2 are considered as the baseline measurements. If the data at Visit 2 are missing, then the last assessments collected prior to Visit 2, i.e., at screening, will be used as the baseline.

Since the protocol specifies, that all measurements shall be taken at visit 2 before any intake of study medication, all measurements, except for safety lab and vital signs, at the first day of study medication intake are analysed as before any intake of trial medication. For safety lab and vital signs, the actual measurement time will be compared with first study medication intake time to determine the baseline. For C-SSRS, if only assessment at Visit 1 is available prior to first study medication intake date, then answers based on recall period for past 3 months will be considered as baseline.

Given height is a relatively stable measurement over time, to reduce missing baseline data, height measurements, as early as -110 days prior to first study medication intake date will be considered for baseline value.

Time windows and calculated study visit

Time windows will be used for assignment of measurements to the scheduled visits. For different types of assessments, their collection plans as well as the visit windows are defined in Table 6.8: 1, Table 6.8: 2, Table 6.8: 3, and Table 6.8: 4. According to the definition, the data will be mapped to the planned study visits based on the actual date of data collection. The calculated study visits will be used in tables in Clinical Trial Report (CTR) to summarize data and to present analyses results. They will also be used together with the actual data collection dates (and days relative to the first drug intake) in the end-of-text listings.

For efficacy measurements, the measurement labelled under scheduled visit that is closest to the protocol planned visit day will be selected for analysis. If multiple measurements occur on the same day, the last measurement within that day will be used. If a measurement under

scheduled visit is not available, a measurement from unscheduled visits that is closest to the protocol planned visit day will be selected for analysis.

For safety measurements, if multiple measurements fall under the same analysis window, the one closest to the protocol planned visit day will be selected for analysis. If more than one records occur on the same day, the later one will be selected based on measurement time.

Table 6.8: 1 Collection plan and analysis time windows for spirometry (FVC), physical exam, C-SSRS, weights, pregnancy test, and vital signs

Visit name	Visit number (n)	Planned day of the visit* (V_n)	Start day* (S_n)	End day* (E_n)	Length of the window
Baseline	2	1	-84	1	85
Week 2	3	15	2	29	28
Week 6	4	43	30	64	35
Week 12	5	85	65	106	42
Week 18	6	127	107	155	49
Week 26	7	183	156	218	63
Week 36	8	253	219	281	63
Week 44	9	309	282	337	56
Week 52	10	365	338	393	56
Every 12 weeks thereafter	p	V_p	$S_p = E_{p-1} + 1$	$E_p = (V_p + V_{p+1})/2$	$E_p - S_p + 1$

* Relative to the day of first drug intake
** p=11,12,13,…

Table 6.8: 2 Collection plan and analysis time windows for L-PF, HADS

Visit name	Visit number (n)	Planned day of the visit* (V_n)	Start day* (S_n)	End day* (E_n)	Length of the window
Baseline	2	1	-84	1	86
Week 12	5	85	2	134	133
Week 26	7	183	135	218	84
Week 36	8	253	219	281	63
Week 44	9	309	282	337	56

Visit name	Visit number (n)	Planned day of the visit* (V_n)	Start day* (S_n)	End day* (E_n)	Length of the window
Week 52	10	365	338	393	56
Every 12 weeks thereafter	p	V_p	$S_p = E_{p-1} + 1$	$E_p = (V_p + V_{p+1})/2$	$E_p - S_p + 1$

*Relative to the day of first drug intake
** p=11,12,13,…

Table 6.8: 3 Collection plan and analysis time windows for DLCO and SpO2

Visit name	Visit number (n)	Planned day of the visit* (V_n)	Start day* (S_n)	End day* (E_n)	Length of the window
Baseline	2	1	-84	1	86
Week 12	5	85	2	134	133
Week 26	7	183	135	274	140
Week 52	10	365	275	393	119
Every 12 weeks thereafter	p	V_p	S_p	E_p	$E_p - S_p + 1$

* Relative to the day of first drug intake
** p=11,12,13,…

Table 6.8: 4 Collection plan and time windows for laboratory test

Visit name	Visit number (n)	Planned day of the visit* (V_n)	Start day* (S_n)	End day* (E_n)	Length of the window
Baseline	2	1	-84	1	86
Week 6	4	43	2	64	63
Week 12	5	85	65	134	70
Week 26	7	183	135	218	84
Week 36	8	253	219	281	63
Week 44	9	309	282	337	56
Week 52	10	365	338	407**	70**

Visit name	Visit number (n)	Planned day of the visit* (V_n)	Start day* (S_n)	End day* (E_n)	Length of the window
Every 12 weeks thereafter	p	V_p	$S_p = E_{p-1} + 1$	$E_p = (V_p + V_{p+1})/2$	$E_p - S_p + 1$

* Relative to the day of first drug intake
** Extended time window for safety / laboratory data
*** p=11,12,13,…

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1/Median/Q3 / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

In descriptive statistics tables, mean, standard error, standard deviation and median will be rounded to one additional digit than the raw individual value. In case extreme data outside of the expected range are observed, quartiles and percentiles will be presented additionally.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not).

Patients will be analysed according to the stratum to which they belong based on the antifibrotic background therapy information reflected on concomitant medication eCRF page at the time of randomization, which may not necessarily coincide with data used for randomisation. This principle also applies to HRCT pattern value, that is, HRCT pattern value reported in the eCRF page will be used for analysis. Such an error occurs before randomization and is therefore consistent with regulatory guidance.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the FAS.

A table in the CTR will present the number of patients screened, randomized and treated. The number of patients prematurely discontinuing their study treatment will be shown with the reasons for discontinuation, and the derivation algorithm for permanent treatment discontinuation reasons per data collected from EoT eCRF page can be found in appendix 10.4. The number and percent of patients completing the end of treatment visit and completing planned observation period, which includes patients who complete end of study visit and who have lung transplant or died, will be reported. When calculating percentages, the denominator will be the number of patients treated in each treatment group and displayed as randomized treatment assignment. As mentioned in CTP Section 3.1, “After review of the efficacy and safety data available at DBL1, the sponsor will communicate the end of the trial and all patients still on blinded study treatment will perform an End of Treatment (EOT) visit

and an End of Study (EOS) visit if applicable". The detailed date of sponsor's communicating the end of the trial will be documented in the decision log of final Report Planning Meeting (RPM) or final CTR.

For the demographic and baseline characteristics listed in Section 5.4.1, the CTR tables will show the relevant descriptive statistics (summary statistics for continuous variables; tabulations of frequencies and percentages for categorical variables) by treatment arm.

7.2 CONCOMITANT DISEASES AND MEDICATION

7.2.1 Baseline conditions

The baseline conditions will be included as coded items using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at BI at the time of database lock. They will be summarized by MedDRA system organ class (SOC) and Preferred Term. The CTR table will show the counts of patients with a baseline condition in each SOC in descending order of overall prevalence and then the conditions (preferred terms) under that SOC in descending order of overall prevalence.

7.2.2 Concomitant therapies

The concomitant therapies will be categorized as:

- Baseline therapies: treatments with a start date before first trial drug intake and an end date on or after the day of the first trial drug intake
- Concomitant therapies initiated on-treatment: treatments with a start date on or after the day of first trial drug intake and before or on the day of last trial drug intake

The following categories of concomitant therapies will be summarized by treatment over the whole trial:

- Baseline therapies
- Baseline and on-treatment concomitant therapies
- Baseline immunosuppressant use
- On-treatment immunosuppressant use
- On-treatment Restricted concomitant therapies
- On-treatment non-drug therapies (including lung transplant)

Time to first use of restricted medication by treatment group will also be presented by Kaplan-Meier curve. Definitions of restricted medications are depicted in Section 4.2.2.1 of the CTP.

Table 7.2.2: 1 summarizes the concomitant therapy outputs over the whole trial. Summaries by ATC and preferred name (PN) will use the ATC3 code, and will be sorted by descending frequency of first ATC class and then PN within each ATC class. The WHODrug Standardised Drug Groupings (SDGs) is an additional WHODrug resource with the purpose of harmonizing an unbiased search strategy for the most common groupings of medications based on joint properties that are not easily extracted using the ATC system. All SDGs allow

for modifications by the user, and when altered they are referred to as Customised Drug Groupings (CDGs). In clinical trials, the SDGs/CDGs can provide information on how a specific class of drugs may affect the study drug, causing unknown interactions, protocol deviations, and unreported adverse events.

Summaries by Standardized Drug Grouping (SDG) /Customized drug groupings (CDGs) of interest will be sorted by descending frequency of CDG and then PN within each CDG. CDGs can be found in Appendix Section 10.5 and 10.8.

Table 7.2.2: 1 Concomitant therapy outputs over the whole trial

	By ATC and PN	By CDG and PN
Baseline therapies	X	
Baseline and on-treatment concomitant therapies	X	
On-treatment Restricted concomitant therapies		X
Baseline immunosuppressant use		X
On-treatment immunosuppressant use		X

7.3 TREATMENT COMPLIANCE

Overall compliance (in percent), defined in in Section 5.4.2, will be summarized with relevant descriptive statistics (summary statistics for continuous variables; tabulations of frequencies and percentages for categorical variables) by treatment arm, based on FAS, both for over 52 weeks and for over the whole trial duration. Only IMP compliance data in CRF visits before and on {last treatment exposure day + 10 days } will be used for calculations.

7.4 PRIMARY ENDPOINT(S)

The primary endpoint is the absolute change from baseline in FVC (mL) at Week 52. The primary endpoint will be analysed using a mixed-effect model for repeated measures (MMRM). Please see Sections 7.1, 7.2, and 7.3.1 of the CTP for additional information on the underlying hypotheses, multiplicity adjustments strategy.

Adjusted mean estimate of the absolute change from baseline in FVC (mL) at Week 52 for each treatment group, its standard error and two-sided asymptotic 95% confidence interval, the difference in adjusted mean estimate between Nera18mg and placebo groups, Nera 9mg and placebo groups, their standard error, two-sided 95% confidence interval and the two-sided p-value will be presented in the table. The difference in adjusted mean estimates between BI Nera18mg and Nera 9mg, its standard error and two-sided asymptotic 95% confidence interval will also be shown separately.

Corresponding graphs (with adjusted mean estimate and standard error of the mean) for FVC change from baseline (mL) over time will also be presented for the estimated values.

Handling of death events

Event of death will be handled via composite variable strategy. Re-analysis, resampling analyses using historical Phase III data from INPULSIS and INBUILD trials and simulations were performed. Replacement strategies based on 1-15% percentiles of FVC change from baseline value as well as replacement of absolute FVC at Week 52 with values range from 0 to 1000mL were evaluated and compared. Operating characteristics on estimated treatment effect, Type-I error and statistical power, suggested that a replacement strategy on FVC change from baseline values with a poor, but not extreme value, e.g.10th observed percentile, would provide stable, robust estimates and maintaining reasonable statistical power, while impose adequate penalty for death events.

Therefore, for patients who died before end of Week 52 analysis period (i.e. day 393 inclusive) without lung transplantation, their missing FVC change from baseline values at visit(s) on or after death event date will be replaced based on 10th percentile of observed values (change from baseline) across all treatment arms at each visit, see Table 7.4.2.1: 1. Missing FVC value or measured FVC value prior to death date will not be replaced. Table 7.4: 1 lists several examples on analysis value derivation in scenarios when death and/or lung transplant is present.

Table 7.4: 1 Examples of analysis value derivations for primary endpoint (primary analysis) in presence of death and lung transplant

Study day and value of last FVC measurement	Study day of death	Study day of lung transplant	Analysis change from baseline value at Week 52	Rationale
365, 3000mL	385	NA	3000mL-baseline	Week 52 FVC data non-missing
310 (Week 44), 3000mL	385	NA	10th percentile change from baseline of observed 52 week FVC values	Week 52 FVC is missing and death event occurs within Week 52 analysis window
365, 3000mL	370	360	missing	Data (FVC or death) after lung transplant will be discarded
355, 3000mL	370	360	3000mL-baseline	FVC at Week 52 is available and is assessed before ICE of death and lung transplant

For subgroup analysis, replacement for death events will be calculated based on overall population, not within each subgroup.

7.4.1 Primary analysis of the primary endpoint(s)

The primary analysis is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline in FVC at Week 52 between treatment groups. The analysis will include the fixed, categorical effects of treatment at each visit, baseline intake of AF treatment at each visit, baseline HRCT pattern at each visit, and the fixed continuous effects of baseline FVC value at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The statistical model will be as follows:

$$y_{ijkmn} = \beta_j S_i + \tau_{kj} + f_{mj} + \omega_{jn} + e_{ij}$$

$$e_{ij} \sim N_Z(0, \boldsymbol{\Sigma})$$

- y_{ijkmn} change from baseline in FVC value [mL] for patient i in intake of AF treatment at baseline stratum m and HRCT pattern stratum n at visit j receiving treatment k,
- S_i = FVC baseline measurement (mL) of patient i, $i = 1,2, \ldots$
- β_j = coefficient of baseline effect at visit j
- τ_{jk} = the effect of treatment k at visit j, $j = 1, \ldots, Z$ and $k = 1, .., Y$,
- f_{mj} = the effect of baseline AF treatment stratum m at visit j, $m = 1,2$. Intake of AF treatment at baseline is used as reported in the CRF ("No" as the class of reference, regardless of any mis-assignment to treatment based on identification of the wrong stratum in IXRS)
- ω_{jn}= the effect of HRCT pattern stratum n at visit j, n=1,2. HRCT pattern is used as reported in the CRF ("Other fibrotic patterns" as the class of reference, regardless of any mis-assignment to treatment based on identification of the wrong stratum in IXRS)
- e_{ij} = the random error associated with the j^{th} visit of the i^{th} patient. Errors are independent between patients.
- $\boldsymbol{\Sigma}$ = an unstructured covariance matrix with dimension Z (where Z is the maximum value for the visit index j)

Graphs showing the distribution of absolute and relative FVC change from baseline, with and without death replacement will be provided in CTR Appendix 16.1.13.1.7.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided α according to the multiple testing strategy specified in Figure 7.4: 1. The primary treatment comparison will be the contrast between treatments at Week 52.

In the event of non-convergence, the following methods will be attempted (in order) to overcome it:

1. Add the 'singular=1e-10' option in the model statement – This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).
2. Set 'maxiter=100' in the Proc Mixed statement – This increases the number of convergence iterations used from a default of 50.

3. Set 'scoring=4' to specify use of the Fisher scoring algorithm in the first 4 iterations.
4. Include the statement 'performance nothread' – this removes multi-threading from the calculations.
5. Provide starting values for covariance parameters using a 'parms' statement.

The first model to converge will be used as the primary analysis on the analysis of absolute change from baseline in FVC at week 52. Please refer to Section 10.1 for more details concerning the statistical model and SAS code specifications.

Testing procedure:

The graphical testing procedure (17) as depicted in protocol Section 7.1 will be used to test the primary and key secondary endpoints for both dose levels. As the graphical testing procedure abides the closed test principle, it holds strong control of family-wise type I error rate at two-sided alpha level of 0.05.

Statistical hypotheses to be tested for the primary endpoint are:

- H_{01}: there is no difference in the mean change from baseline in FVC in mL at Week 52 between Nera 18 mg bid and placebo vs.

  H_{a1}: there is a difference in the mean change from baseline in FVC in mL at Week 52 between Nera 18 mg bid and placebo.

- H_{02}: there is no difference in the mean change from baseline in FVC in mL at Week 52 between Nera 9 mg bid and placebo vs.

  H_{a2}: there is a difference in the mean change from baseline in FVC in mL at Week 52 between Nera 9 mg bid and placebo.

Statistical hypotheses to be tested for the key secondary endpoint are:

- H_{03}: there is no difference in the time to first acute ILD exacerbation, first hospitalization for respiratory cause or death between Nera 18 mg bid and placebo vs

  H_{a3}: there is a difference in the time to first acute ILD exacerbation, first hospitalization for respiratory cause or death between Nera 18 mg bid and placebo.

- H_{04}: there is no difference in the time to first acute ILD exacerbation, first hospitalization for respiratory cause or death between Nera 9 mg bid and placebo vs.

  H_{a4}: there is a difference in the time to first acute ILD exacerbation, first hospitalization for respiratory cause or death between Nera 9 mg bid and placebo.

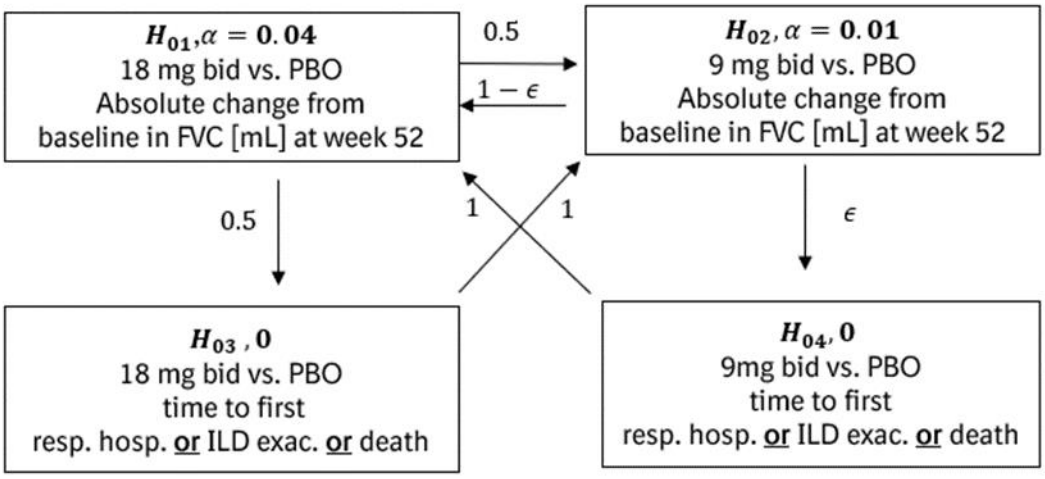


Figure 7.4: 1 Graphical testing procedure for hypothesis testing strategy

The testing procedure will start from testing of H_{01} and H_{02} for the primary endpoint. 4% level of the alpha level will be initially allocated to the comparison between 18 mg bid and placebo. 1% level of the alpha level will be initially allocated to the comparison between the 9 mg bid arm and placebo. At this step, no alpha is reserved for tests of the key secondary endpoint.

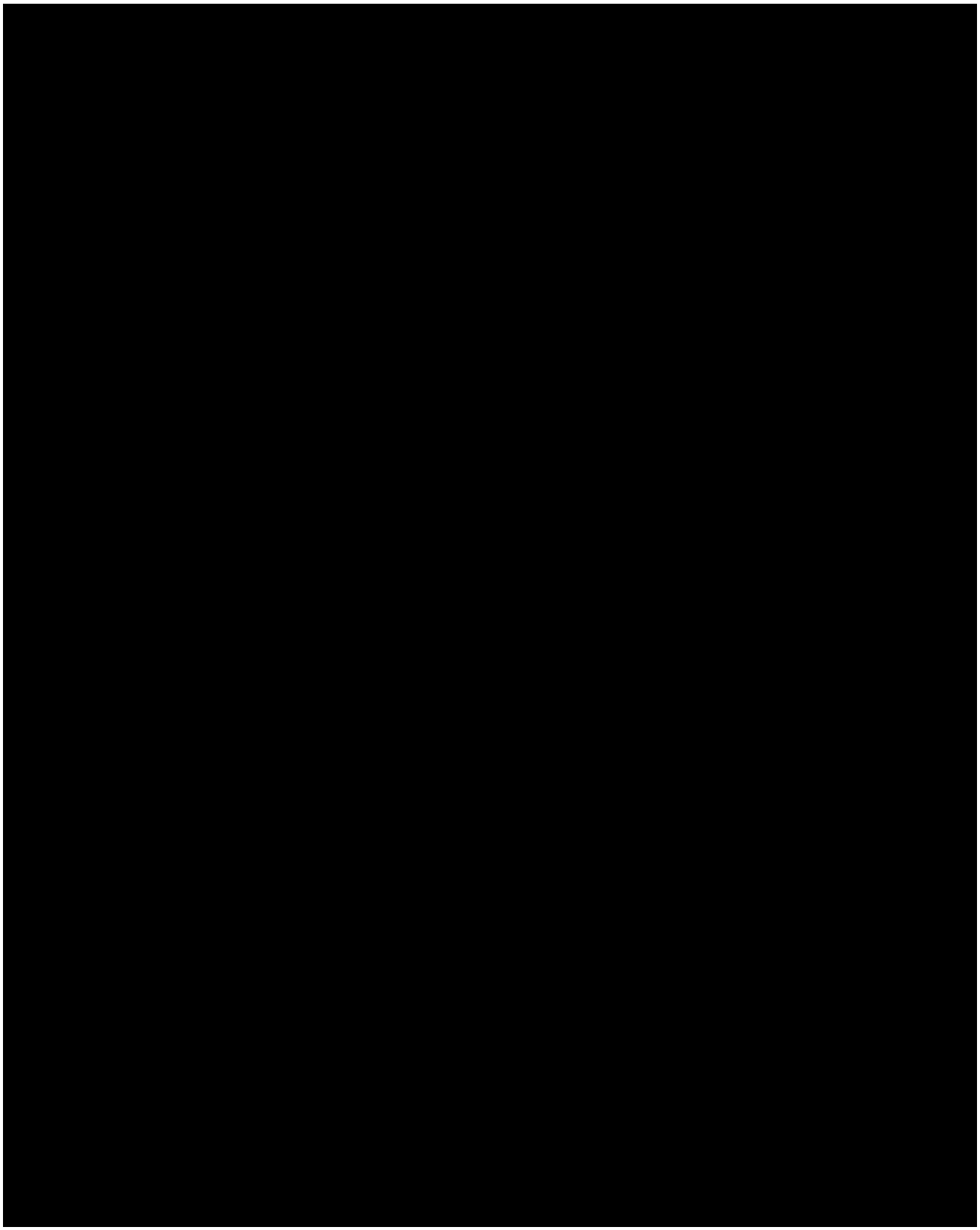
- If neither H_{01} nor H_{02} is rejected, all α is deemed as "spent" and no further testing will be performed.
- If at least one of H_{01} or H_{02} is rejected, the retained α from the successful hypothesis will be propagated according to the weights on the arrows leaving that hypothesis as depicted by the Figure 7.4: 1.

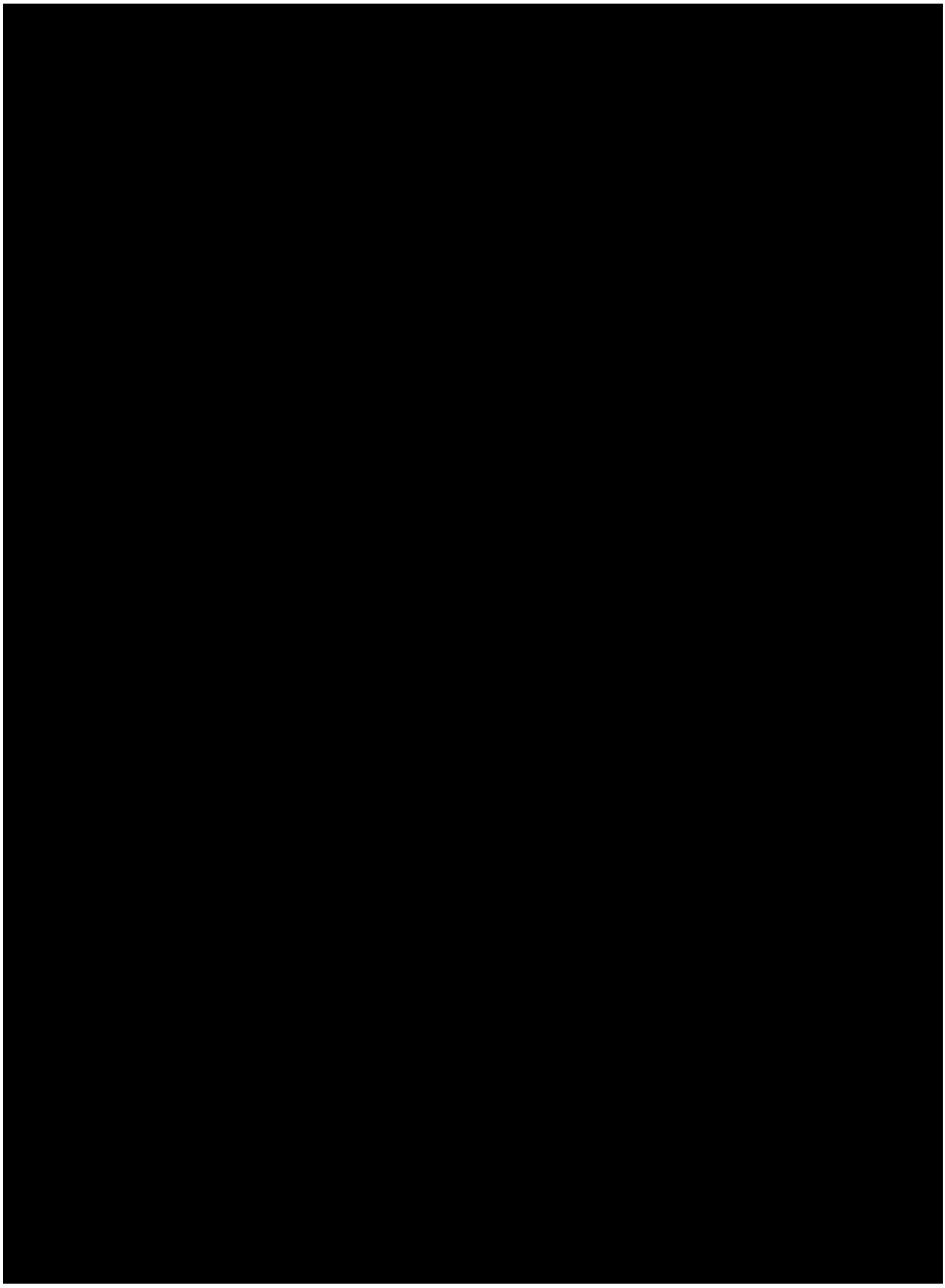
Note that ϵ is set to a negligible amount of 0.0001 at the start, to reflect the priority on hypotheses for 18 mg bid vs. placebo, namely H_{01} and H_{03}, over the 9 mg bid vs. placebo. The testing process continues if there is at least one hypothesis in the procedure that can be rejected at its allocated α level at that point. Each time a hypothesis is rejected, the graph is updated to reflect the reallocation of α. This iterative process of updating the graph and reallocating α is repeated until all hypotheses have been tested or when no remaining hypotheses can be rejected at their corresponding α levels at that point.

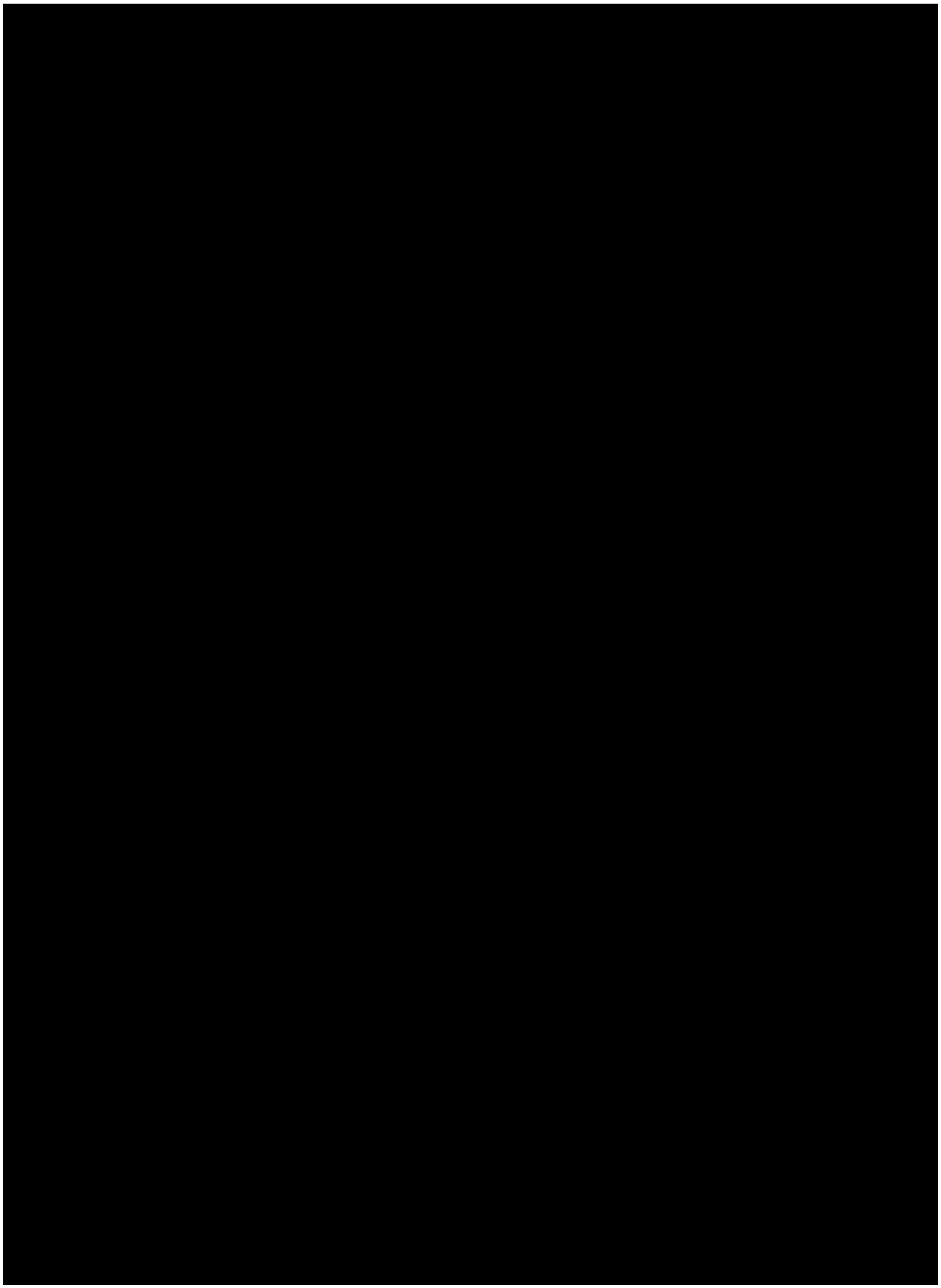
The primary objective of the trial will be achieved if either H_{01} or H_{02} is rejected and this trial is considered positive.

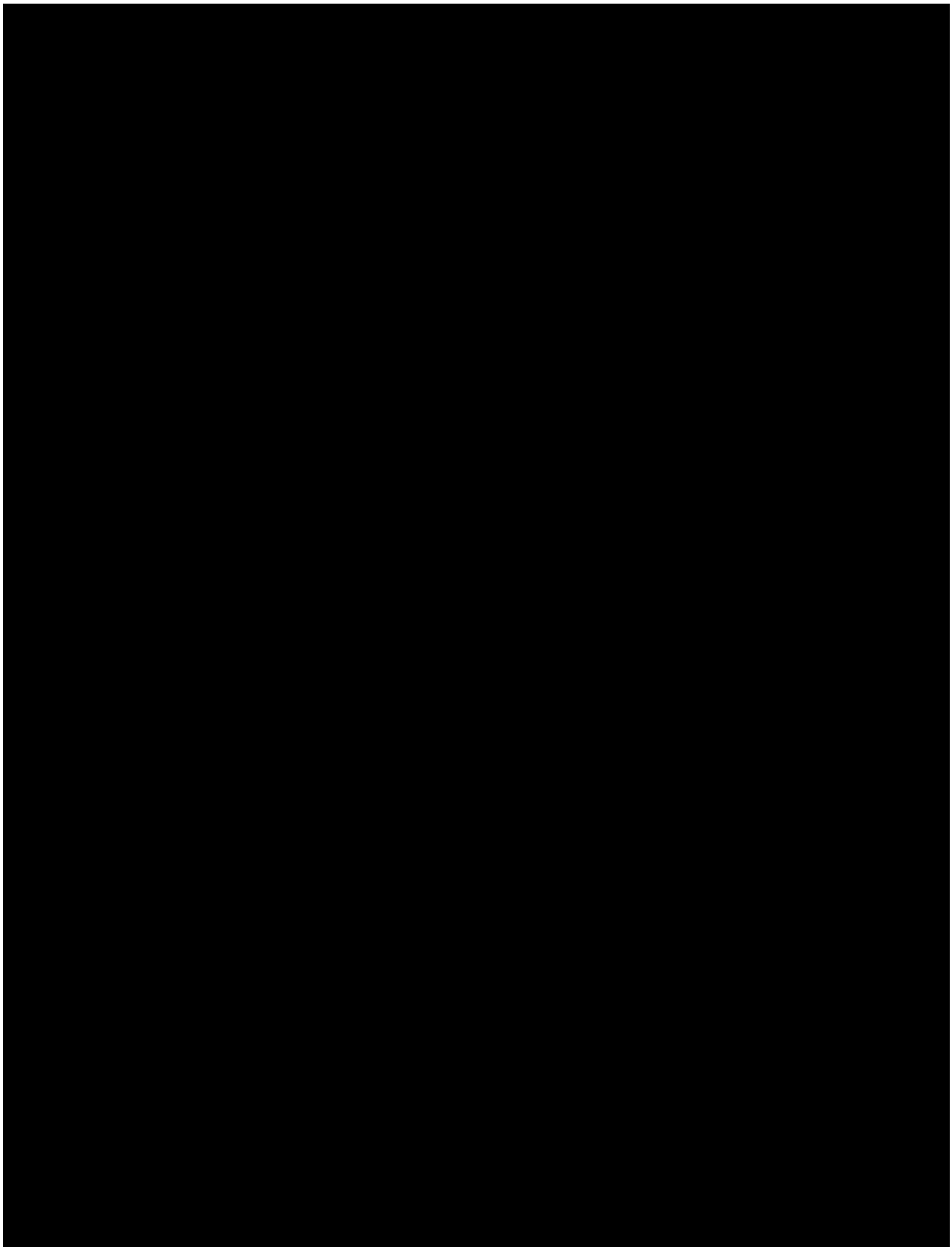
No adjustment for multiplicity is planned beyond primary and key secondary objective analyses.

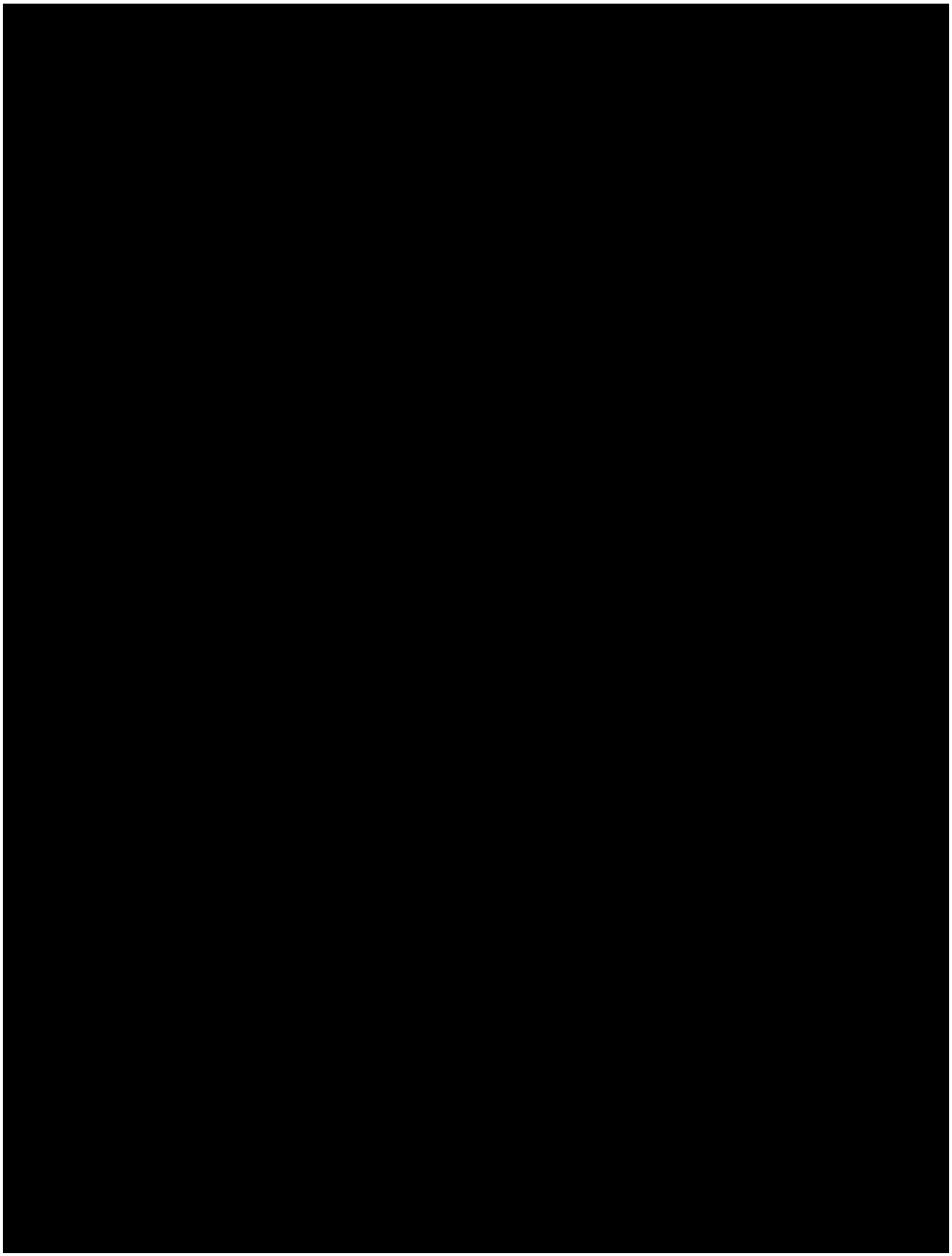
[redacted]

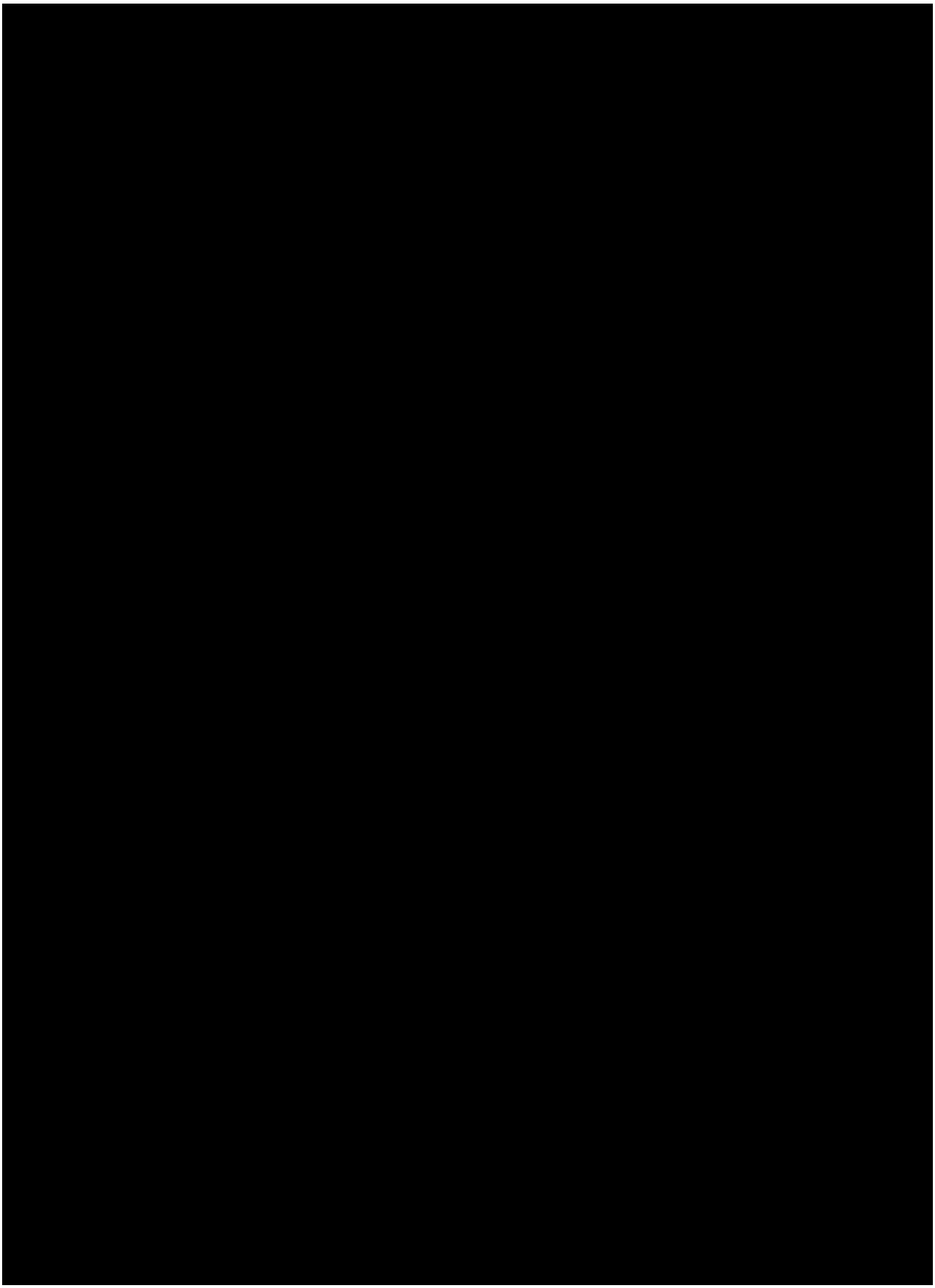


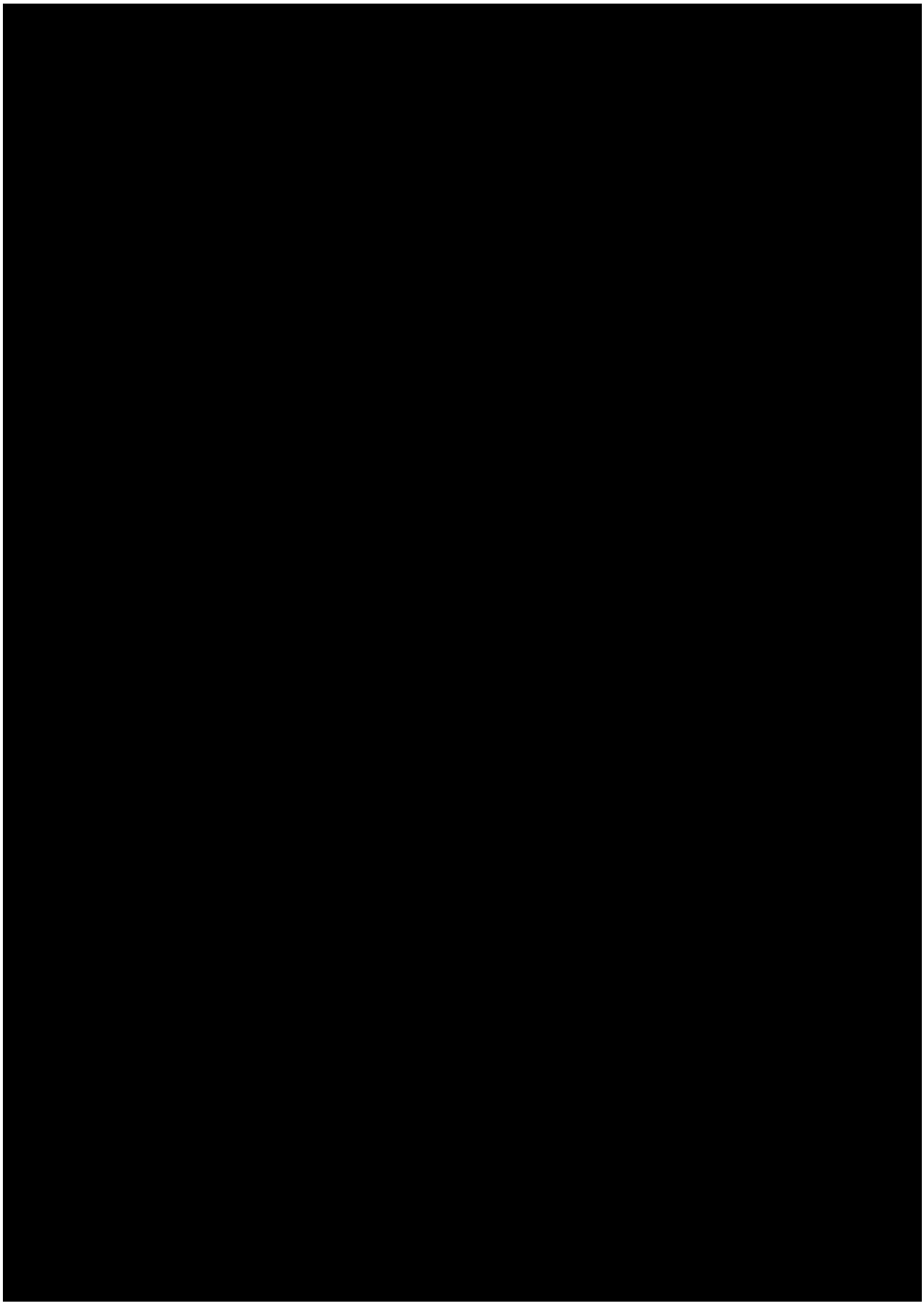


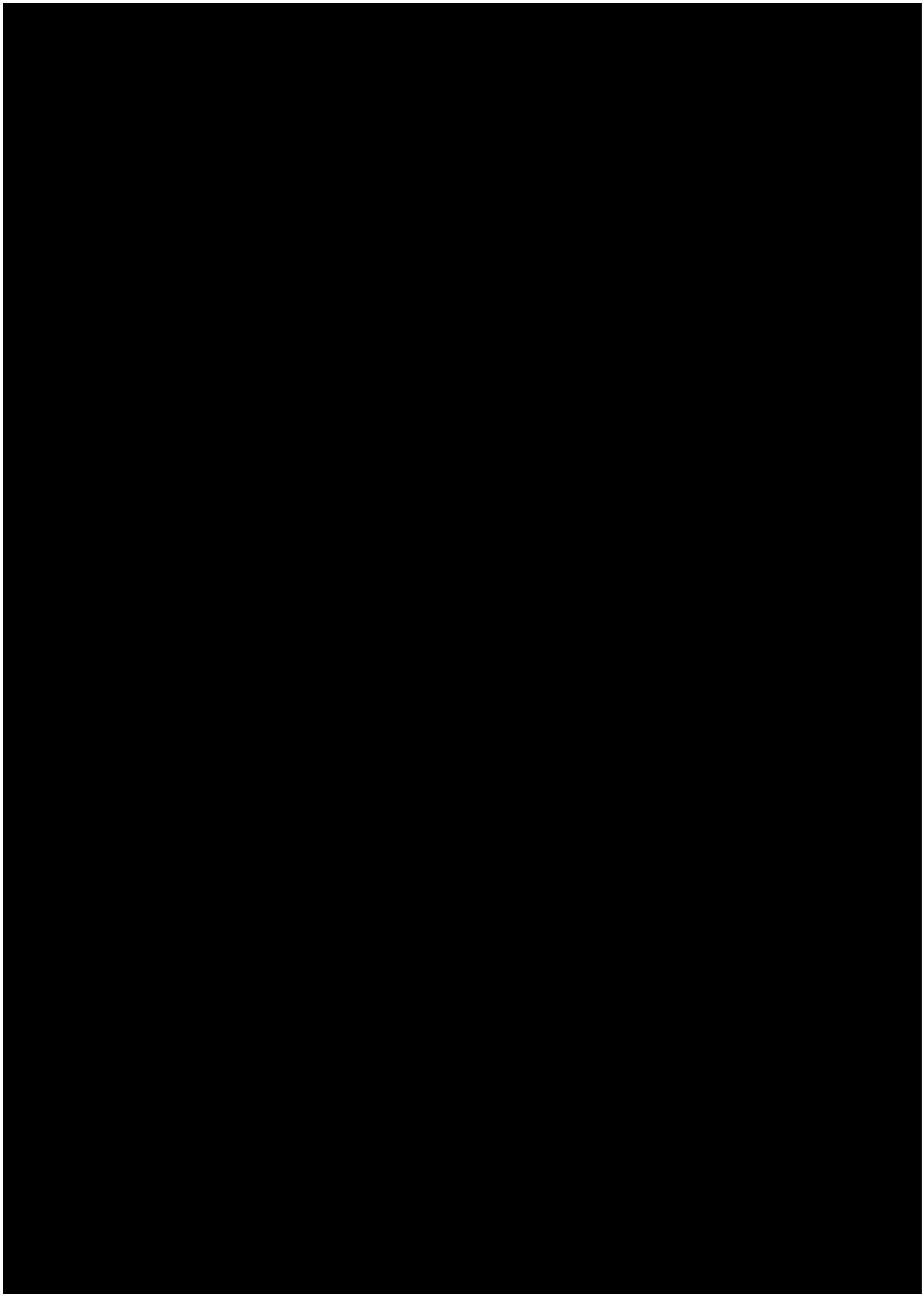












7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

7.5.1.1 Primary analysis of the key secondary endpoint(s)

The key secondary endpoint of time to first acute ILD exacerbation, first hospitalization for respiratory cause or death over the whole trial will be analysed with a Cox proportional hazards model using data over the whole trial, i.e., including data beyond 52 weeks. The model will include the treatment effect, baseline intake of AF treatment, age (continuous), FVC % predicted, DLCO % predicted (corrected for haemoglobin), HRCT pattern at baseline as covariates. Breslow's method for handling ties will be used.

Same as for the primary endpoint, the primary analysis will be performed on the FAS using a treatment policy estimand for ICEs other than death or lung transplant.

The number of patients with any event in the composite and the number of patient with event for each component as the first event during the trial will be shown. The two-sided p-value testing for equality of the hazard rates by the Wald test for the treatment effect will be displayed.

Kaplan-Meier plots by treatment group will be presented. In addition, percentage of patients with event over the whole trial will be presented by Kaplan-Meier estimates. Event rate comparison at Week 52 based on Kaplan-Meier estimates will be performed. The Kaplan-Meier survival probabilities at Week 52 will be calculated for each treatment, with the variances calculated using Greenwood's formula. The difference in probabilities comparing

each dose versus placebo will be calculated as the weighted average of the difference in Kaplan-Meier probabilities within each stratum. The weights are proportional to the inverse of the variance of the within-stratum difference in the Kaplan-Meier probabilities, normalised so that the sum is equal to 1. Based on independence among treatment groups and across stratum, the variance can be calculated accordingly.

In general, for all time-to-event endpoint, the time to the event of interest will be computed as (event date – first drug intake date) +1. All events observed after first drug intake date until trial termination will be included in the analysis except for events occurring after a lung transplant, in which case patients will be censored at the time of lung transplantation.

For patients who have more than one event during the trial, the time to the first event will be considered for the analysis. Event count for the first event will be summarized by treatment. In case of tie, i.e., multiple events occur on the same day, the time order of acute exacerbation, then respiratory hospitalization, then death will be assumed.

Patients who do not have an event during the trial period will be censored at the last day that the patient was known to be free of the event (See Section 5.2.1). The time to censoring will be computed as (individual day of trial completion or the last day known to be free of the event or the day of lung transplant – first drug intake date) + 1.

7.5.2 Other Secondary endpoint(s)

Any p-values presented for the other secondary endpoints will be considered nominal in nature and no adjustment for multiplicity will be made.

7.5.2.1 Living with Pulmonary Fibrosis (L-PF) Symptoms scores at Week 52

The absolute change from baseline in L-PF Symptoms Dyspnea, Cough and Fatigue domain scores at Week 52 will be analysed respectively with a similar MMRM approach for the primary endpoint as detailed in Section 7.4.1. The analysis will include the fixed, categorical effects of treatment at each visit, baseline intake of AF treatment at each visit, baseline HRCT pattern at each visit, and the fixed continuous effects of baseline L-PF score at each visit.

Each endpoint will be presented graphically as well as numerically to illustrate the impact of the underlying condition on the patient's health status.

The descriptive analyses of the absolute change from baseline over time in the various L-PF total and domain scores will also be shown.

7.5.2.2 Time to event endpoints over the whole trial

Similar analysis models as described in Section 7.5.1.1 for key secondary endpoint will be implemented for time-to-event endpoints analysis in this section. The number of patients with any event in the composite and the number of patients with event for each component as the first event during the trial will be shown. The two-sided p-value testing for equality of the hazard rates by the Wald test for the treatment effect will be displayed. Kaplan-Meier plots by treatment group will be presented. Event rate comparison at Week 52 based on Kaplan-Meier estimates will be performed.

If the number of events in the respective endpoint is less than 20, only Kaplan-Meier curve and frequencies of events by treatment group will be provided for that endpoint.

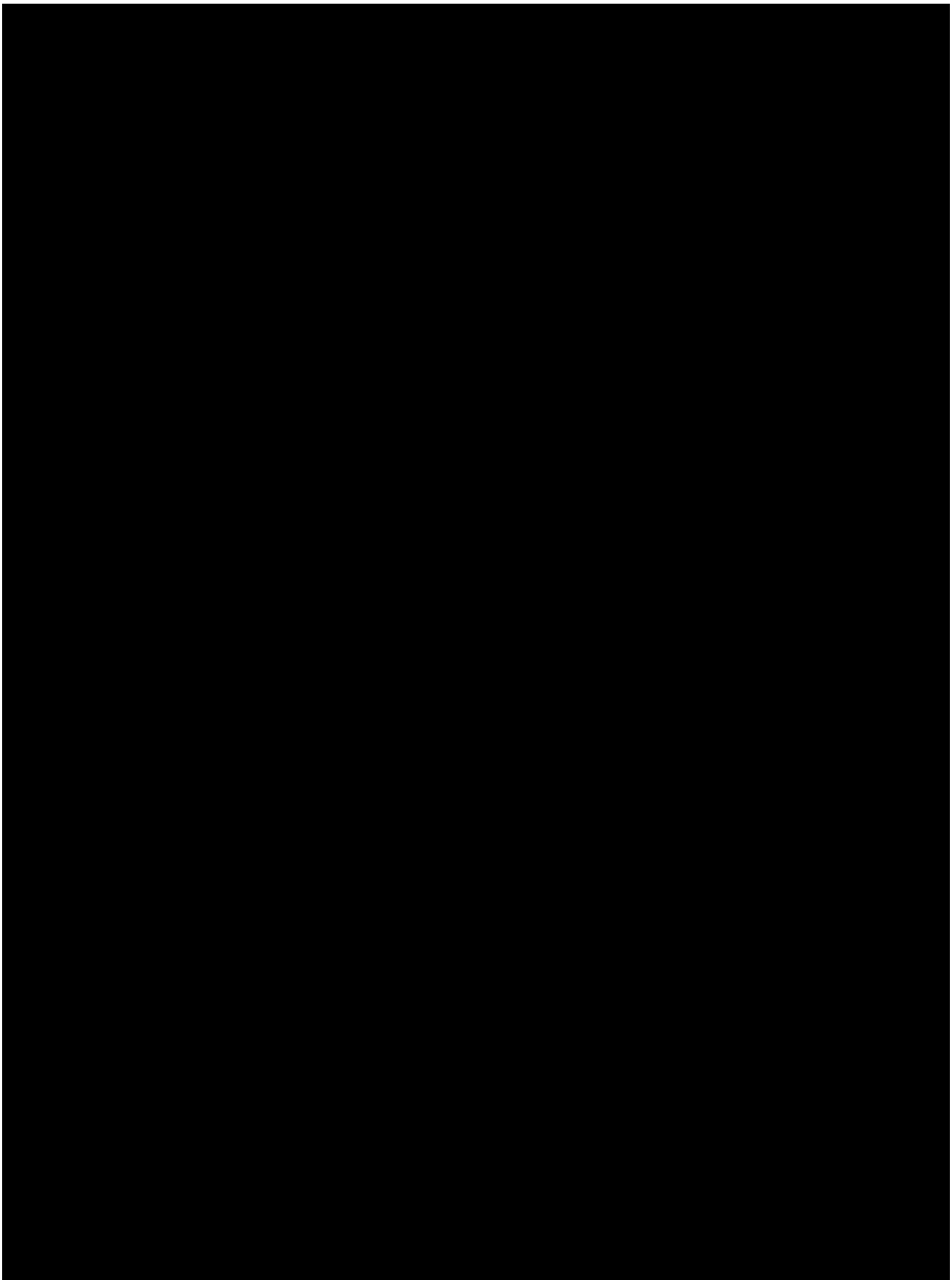
Rules for deriving event time and censoring time are specified in Section 5.2.1.1.

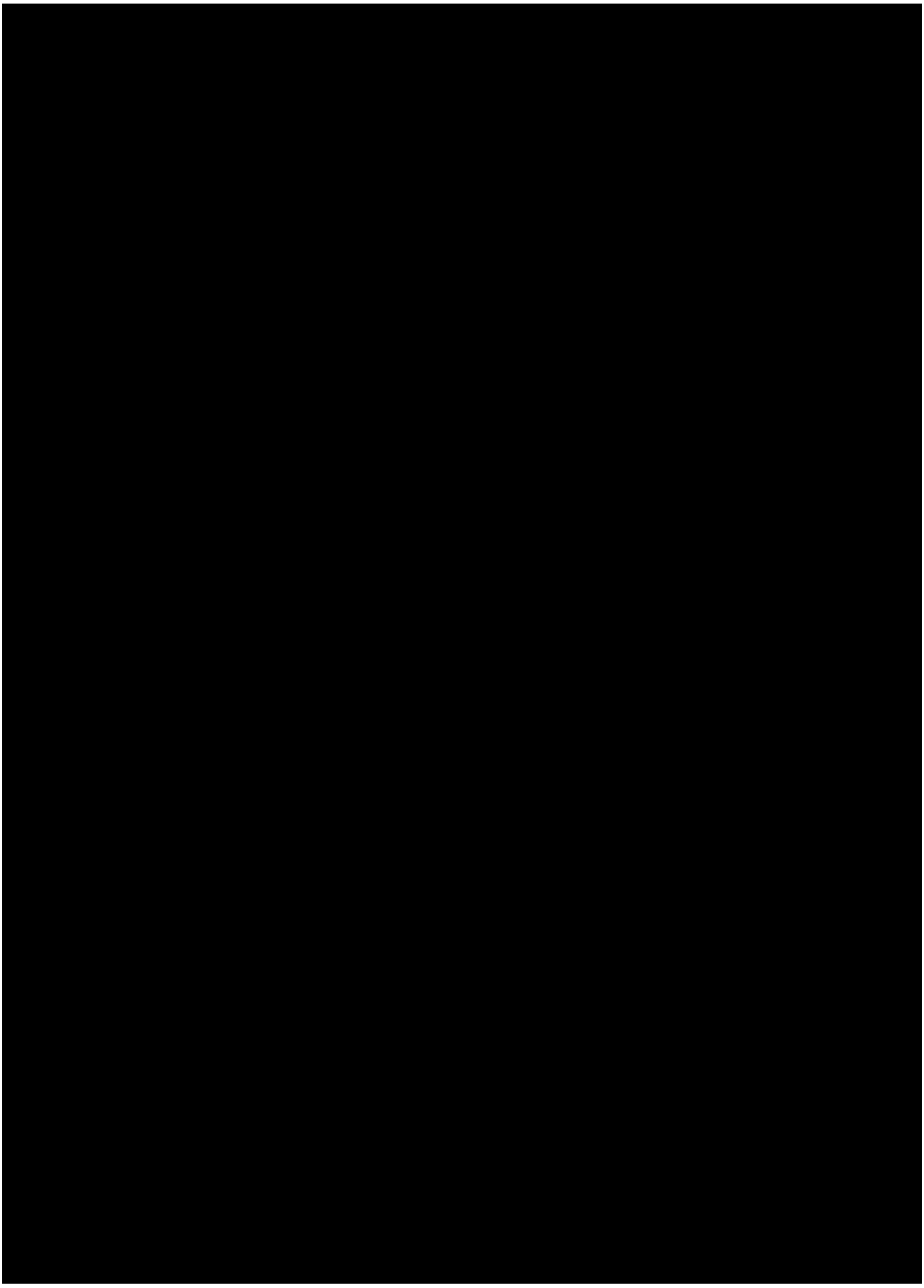
7.5.2.3 Absolute change from baseline in FVC % predicted at Week 52

A similar analysis based on MMRM as for the primary endpoint will be performed for the absolute change in FVC % predicted at Week 52. Please refer to Section 7.4.1.

7.5.2.4 Absolute change from baseline in DLCO % predicted at Week 52

A similar analysis based on MMRM as for the primary endpoint will be performed for the absolute change in DLCO % predicted at Week 52. Please refer to Section 7.4.1.





7.7 EXTENT OF EXPOSURE

Exposure to study medication will be summarized based on three methods:

1. Summary of exposure time, including off-treatment periods (treatment interruption)
2. Summary of exposure time, excluding off-treatment periods (treatment interruption)
3. Summary of treatment interruption and premature discontinuation

The exposure time is the duration from first drug intake until last drug intake date. The end of exposure time is defined as:

- Last drug intake date for patients who discontinued from trial medication or completed the planned treatment period
- The snapshot date, for treatment ongoing patients

Summary of extent of observational time including before and after study medication discontinuation will be provided.

The observational time is the duration from the first drug intake date until end of observation date. The end of observation date is defined as:

- Earliest date of end of study date, last contact date or death date, for patient completed the study (including completed as planned and early terminated from the study)
- The snapshot date, for ongoing patients

For variables on time of exposure defined in Section 5.4.3, relevant descriptive statistics (summary statistics for continuous variables; tabulations of frequencies and percentages for categorical variables) by treatment arm will be shown.

Number of patients with at least one dose interruption, number of dose interruption in categories (0, 1, 2, >2), and reasons for dose interruption (AE related, AE unrelated, Other) will be summarized with counts and percentages by treatment group.

Number of patents with premature treatment discontinuation will be summarized with counts and percentages by treatment group.

Kaplan-Meier curves will be generated for time to first permanent treatment discontinuation defined in Section 5.4.3. Relevant descriptive statistics (tabulations of frequencies and percentages for categorical variables) will be generated for the categorical variables, by treatment arm.

In addition, first dose and last dose administration, dose interruptions as well as the reason for a dose interruption will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS. Treatment will be evaluated as treated.

Safety analysis will be planned for both over 52 weeks as well as over the whole trial beyond 52 weeks. See Section 6.1 of this document for further details of the treatment period specifications and refer to Table 6.1: 1 for the start and end dates for these analyses.

7.8.1 Adverse Events

In general, all analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs. For further details on handling and analysis of AE data, please refer to (4)

7.8.1.1 Assignment of AEs to treatment

In general, AE analysis tables will present only treatment emerging AEs (applying the rule of 7 days for assignment as on-treatment) for the treatment groups.

For listings, all AEs occurring before first drug intake will be assigned to ‘screening’ and all AEs occurring after last drug intake + 7 days will be assigned to ‘post-treatment’ or ‘follow-up’. All adverse events occurring between the start of an interruption of trial medication and the end of interruption of trial medication will be assigned to ‘off-treatment’ period. For details on the treatment definition, see Section 6.1.

7.8.1.2 General AE summaries

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class and PT (mention MedDRA levels to be displayed in the tables). In general, both frequency and incidence rates as defined in Section 7.8.1.8 will be included for over the whole trial analysis as well as for the over 52 weeks analysis.

The SOCs and grouped PTs or PTs will be sorted in descending order by overall prevalence.

Frequency and incidence rate tables of patients with AEs with an onset during the on-treatment period over the whole trial and over 52 weeks will be produced for:

- Patients with AEs
- Patients with SAEs

- Patients with severe AEs
- Patients with investigator reported drug-related AEs
- Patients with AEs of Special Interest as documented by the investigator
- Patients with AEs leading to death
- Patients with AEs leading to permanent discontinuation of trial medication
- Patients with AEs leading to trial medication interruption
- Patients with AEs occurring with an incidence in preferred term greater than 2% (at least one treatment arm)
- Patients with AEs occurring with an incidence in preferred term greater than 5% (at least one treatment arm)
- Patients with SAEs occurring with an incidence in preferred term greater than 1% (at least one treatment arm)
- Patients with AEs by user-defined safety topics (See Section 7.8.1.5)
- Patients with serious user-defined safety topics
- Patients with user-defined safety topics leading to permanent discontinuation of trial medication

7.8.1.3 Subgroup analyses of adverse events

Frequency and incidence rate tables of patients with AEs with an onset during the on-treatment period over the whole trial and over 52 weeks by the subgroup categories of the subgroups for safety analyses defined in Section 6.5 will be produced for:

- Overall AE summaries
- Patients with AEs
- Patients with SAEs
- Patients with AEs leading to permanent discontinuation of trial medication
- Patients with AEs of Special Interest
- Patients with user-defined safety topics

Time-to-event analyses for selected AEs as specified in Section 7.8.1.9 will be repeated in subgroups unless numbers of events are too small to allow for a meaningful analysis (refer to criteria defined in Section 6.5).

7.8.1.4 Protocol-specified and investigator-defined adverse events of special interest (AESI)

Frequency and incidence rate table will be reported for pre-specified AESI in the CTP Section 5.2.6.1.4. These are investigator reported on the eCRF and will be identified using this information for this analysis.

CTP defined AESI:

- Potential severe DILI
- Vasculitis
- Severe infections (CTCAE >2), serious, opportunistic, or mycobacterium tuberculosis infections
- New onset of severe depression, defined as HADS subscore >14
- New onset of severe anxiety, defined as HADS subscore >14

Table 7.8.1.4: 1 AESI dictionary

AESI	Definition (MedDRA search per safety topic) Update
Potential severe DILI	Sub SMQ Cholestasis and jaundice of hepatic origin [narrow] OR Sub SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions [narrow] OR Sub SMQ Liver related investigations, signs and symptoms [narrow] OR Sub SMQ Hepatitis, non-infectious [narrow]
Vasculitis	SMQ Vasculitis [broad]
Severe infections (CTCAE >2), serious, opportunistic, or mycobacterium tuberculosis infections	(SOC Infections and infestations (primary SOC allocation only) AND (any seriousness criterion OR CTCAE >2)) OR SMQ opportunistic infections [narrow]
Severe depression	SubSMQ Depression (excluding suicide and self injury) [narrow]
Severe anxiety	HLGT Anxiety disorders and symptoms (primary SOC allocation only)
Other	Any AESI that do not fall into any of the categories above

7.8.1.5 User-defined AE categories (UDAEC) based on MedDRA search (safety topics)

Further adverse event groupings by system have been defined outside the trial protocol as medically relevant to the clinical development program and are specified in Table 7.8.1.4: 1 based on selection of coded terms based on MedDRA.

The frequency and incidence rate tables of patients with AEs, SAEs and AEs leading to discontinuation within these groupings will be summarized by treatment, safety topic and preferred term. Also, an AE summary will be provided for each of these safety topics.

Table 7.8.1.5: 1 Additional safety topics based on UDAEC

#	Safety Topic	Definition (MedDRA search per safety topic) Update
1	Vasculitis	SMQ Vasculitis [narrow]
2	Suicidal ideation and behaviour	SMQ Suicide/self-injury [narrow]
3	Depression	SubSMQ Depression (excl suicide and self injury) [narrow]
4	Nervousness and anxiety	HLGT Anxiety disorders and symptoms (primary SOC allocation only)
5	Insomnia	HLT Disturbances in initiating and maintaining sleep (Primary SOC allocation only)
6	Weight decrease	BIcMQ Weight loss [narrow]
7	Gastrointestinal symptoms	PT Diarrhoea, PT Nausea, PT Vomiting, HLT 'Gastrointestinal and abdominal pains (excl oral and throat)' (Primary and secondary path)
7a	Abdominal pain	HLT 'Gastrointestinal and abdominal pains (excl oral and throat)' (Primary and secondary path)
8	Malignancies	Sub SMQ malignant tumours [narrow]
9	Severe, serious and opportunistic infections including mycobacterium tuberculosis infections	(SOC Infections and infestations (primary SOC allocation only) AND (any seriousness criterion OR CTCAE >2)) OR SMQ opportunistic infections [narrow]
9a	Severe (CTCAE of at least 3) or serious infections	SOC Infections and infestations (primary SOC allocation only) AND (any seriousness criterion OR CTCAE >2)
9b	Opportunistic infections	SMQ opportunistic infections [narrow]
10	MACE	BIcMQ 3-point MACE for analysis [narrow]
11	Tachyarrhythmia	SMQ Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) [narrow]
12	QT prolongation	SMQ Torsade de pointes/QT prolongation [narrow]

#	Safety Topic	Definition (MedDRA search per safety topic) Update
13	Foetal loss	SMQ Termination of pregnancy and risk of abortion [narrow]
14	Potential DILI	Sub SMQ Cholestasis and jaundice of hepatic origin [narrow] OR Sub SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions [narrow] OR Sub SMQ Liver related investigations, signs and symptoms [narrow] OR Sub SMQ Hepatitis, non-infectious [narrow]

These definitions are based on MedDRA Version 27.0. Note that changes to these definitions due to MedDRA updates will not trigger a TSAP update. As the terms may be continuously updated at project level, the latest approved version of the project level safety topic definitions archived prior to database lock will be used in the corresponding CTR.

A listing of all Preferred Terms associated to each safety topic as per definition – irrespective of reported terms in AE eCRF page – will be prepared.

7.8.1.6 Adverse events with additional information collection

Diarrhoea, ILD acute exacerbation and vasculitis are AEs with additional AE-specific information collected on the eCRF. These are investigator reported on the eCRF and will be identified using this information for this analysis. That is if the diarrhoea information has been completed for an adverse event then the adverse event will be considered as diarrhoea for this analysis regardless of subsequent MedDRA coding of the verbatim term. Likewise, if the ILD acute exacerbation or vasculitis information has been completed for an adverse event then the adverse event will be considered as ILD acute exacerbation or vasculitis for this analysis regardless of subsequent MedDRA coding of the verbatim term.

The frequency of patients with AEs with additional information collection will be summarized by treatment, primary SOC and PT separately for diarrhoea, ILD acute exacerbation. The additional information collected will also be summarized at the AE level rather than at the patient levels.

For each event of diarrhoea, ILD acute exacerbation, a summary table will be produced containing information which would include, but not be limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.

Listing for diarrhoea and ILD acute exacerbation events will be provided.

7.8.1.7 Adjudicated adverse events

An independent adjudication committee will review all fatal cases and adjudicate cause of death to cardiovascular death, respiratory related death, non-cardiovascular/non-respiratory death, or undetermined cause of death on a per patient basis, e.g., one cause per patient. The adjudication committee will also review all AEs categorised as MACE or vasculitis according to the definition in the adjudication charter.

In addition to standard safety analyses, the frequency and incidence rate of patients with AEs leading to death will be summarized by treatment, adjudicated cause of death (Cardiovascular, Respiratory, Non-cardiovascular/non-respiratory or Undetermined), and specific cause of death.

The frequency and incidence rate of patients with AEs categorised as MACE (that is all AEs with trigger terms for MACE and therefore sent for adjudication) will be summarized by treatment and outcome of adjudication (adjudicated as MACE or as not MACE or as not assessable, including subcategories myocardial infarction and stroke as well as kind of stroke (ischemic, hemorrhagic, undetermined). The frequency of patients with AEs adjudicated as MACE will also be summarized by treatment and PT.

The frequency and incidence rate of patients with AEs categorised as vasculitis (that is all AEs with trigger terms for vasculitis and therefore sent for adjudication) will be summarized by treatment and outcome of adjudication (adjudicated as vasculitis or as not vasculitis or as unable to assess). The frequency of patients with AEs adjudicated as vasculitis will also be summarized by treatment and PT.

7.8.1.8 Exposure adjusted analysis of adverse events

Time at risk analyses of AEs will be presented and incidence rates per 100 patient years will be calculated based on the first onset of an AE.

For a specific AE, the total AE time at risk [years] is defined as the sum of time at risk [days] across all contributing patients / 365.25, with for each patient the time at risk [days] defined as follows:

- Date of first start of AE – date of first study medication administration +1 day for patients with the specific AE
- End of time at risk – date of first study medication administration + 1 day for patients without the specific AE

For the AE analyses over 52 weeks, the end of time at risk is the minimum of either end of the REP if day of last drug intake < 372 days after first drug intake, or day 373 if day of last drug intake ≥ 373, the date of the corresponding database lock snapshot, date of death and date of trial completion.

For the AE analyses over the whole trial, the end of time at risk is the minimum of either "+7 days after termination of trial mediation", the date of the corresponding database lock snapshot, date of death and date of trial completion.

The AE incidence rate [1/100 Patient years (pt-yrs)] = 100 * number of patients with specific AE / total specific AE time at risk [years].

For this trial, tables on selected AEs based on SOC and PT, but also on safety topic level, will be created for the week 52 analyses as well as for the analyses over the whole trial, showing the incidence rate, incidence rate ratio and incidence rate difference (each with 95% confidence interval) per the specifications given in Section 7.8.1.9.

7.8.1.9 Time-to-event analysis of selected adverse events

Time-to-event analysis will be performed for selected AEs and will only be provided over the whole trial. Kaplan-Meier plots by treatment will be created. The same type of Cox models specified in Section 7.5.1. The model will include the treatment effect, baseline intake of AF treatment and baseline HRCT pattern as covariates. If the number of events in the respective endpoint is less than 20, only Kaplan-Meier curve and frequencies of events by treatment group will be provided. For patients with at least one event, the event time is the AE start date of the earliest event. Patients without an event will be considered censored at the earliest dates of last drug intake + 7, date of death, date of trial completion and database lock snapshot date.

No formal hypothesis testing or adjustment for multiple testing will be performed for these endpoints, hazard ratio with confidence interval estimate will be presented.

Selected AEs:

- Diarrhoea
- Weight decrease
- Nausea
- Abdominal pain
- Depression
- Severe infection
- AEs leading to permanent treatment discontinuation
- SAEs

For diarrhea, nausea, weight decrease and depression, frequencies and incidence rates after 1 month, 2 months, 3 months, 6 months and 12 months will be provided.

7.8.1.10 Risk comparison measures

For rate ratios, the estimates and 95% confidence intervals will be based on the Poisson method.

For rate differences, the estimates and 95% confidence intervals will be based on the test-based method (13).

The risk ratio is the ratio of the incidence risks of nerandomilast over placebo. The risk ratio and its Wald type 95% CI will be calculated.

The risk difference is the difference of (incidence risk of subjects exposed to nerandomilast - incidence risk of subjects exposed to placebo). The risk difference and corresponding 95% CI will be calculated. Newcombe hybrid (Wilson based) method (18) CI will be used for calculation.

7.8.2 Laboratory data

7.8.2.1 Standard analysis of laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on SI units according to BI standards (12). Note that data from the central laboratory will be used for all displays described below, unless otherwise specified. All analyses will be performed for over the whole trial, and over 52 weeks as well.

Standard descriptive summaries will be provided by treatment group for baseline, last value on-treatment and changes from baseline to last value on treatment. These summaries will be based on converted values.

Graphs over time will be prepared for:

- aPTT (activated Partial Thrombopl. Time)
- PT (Prothrombin time)
- INR
- Creatinine
- eGFR
- Sodium
- Potassium
- Chloride
- CK (Creatine Kinase)
- CRP
- Haemoglobin
- Haematocrit
- Amylase
- Bilirubin
- Urea nitrogen
- Urate
- ALT
- AST

Laboratory values will be compared to their reference ranges (where available) via frequency tables showing the number of patients within and outside the reference range at baseline and for the last value on treatment. Frequency tables will also summarise the number of patients with potentially clinically significant abnormalities, as defined using standard BI criteria.

Liver enzyme and bilirubin elevations will be reported using the following definitions:

- ALT and/or AST ≥ 3 fold ULN)
    - AND bilirubin ≥ 2 fold ULN
    - AND bilirubin ≥ 2 fold ULN And ALKP >= 2xULN
    - AND bilirubin ≥ 2 fold ULN And ALKP < 2xULN
    - AND bilirubin ≥ 1.5 fold ULN

This analysis will be based on standardized laboratory values. These elevations are defined within a time window of 30 days i.e. the elevation of bilirubin should appear within 30 days after the elevation of AST and/or ALT. For alkaline phosphatase the elevations should have occurred in the same blood sample. The proportion of patients presenting signs of hepatic injury will be summarized, based on the following definition for signs of hepatic injury:

- ALT and/or AST ≥ 3 fold ULN and appearance of fatigue, nausea, vomiting, abdominal pain or anorexia within +/- 7 days of the abnormal ALT and/or AST laboratory test result (PT Fatigue, PT Nausea, PT Vomiting, HLT Gastrointestinal and abdominal pains (excl oral and throat), PT anorexia and PT decreased appetite)

In addition, maximum individual elevations based on worst value on treatment will be defined as:

- ≥3 fold ULN; ≥5 fold ULN; ≥10 fold ULN; ≥20 fold ULN for AST and/or ALT
- ≥1.5 fold ULN; ≥2 fold ULN for bilirubin
- ≥1.5 fold ULN; ≥2 fold ULN for ALKP
- ≥ 3 fold ULN for GGT

All frequency tables will be repeated for over the whole trial and over the 52 weeks during the on-treatment period. Displays by visit will only be prepared over the whole trial since week 52 results are available within these.

A graphical analysis of the maximum ALT and total bilirubin (maximum within 30 days after maximum ALT elevation), the so called eDISH plot, over the whole trial and over the 52 weeks during the on-treatment period will also be performed.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, and body weight) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline will be provided. Time profiles of mean and SD will be provided and displayed graphically by study treatment.

Special emphasis is given to body weight once at each study visit. Statistical analysis will be in line with the analysis applied for vital signs: Descriptive statistics including change from baseline and percent change from baseline will be calculated by study treatment and by

planned time point. Tables and figures will be provided based on the TS. Listings of patients with weight loss categories > 10% will be provided.

All frequency tables will be repeated for over the whole trial and over the 52 weeks during the on-treatment period. Displays by visit will only be prepared over the whole trial since week 52 results are available within these.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator and will be analysed as such.

7.8.4 ECG

Not applicable as ECG findings will be reported as adverse events.

7.8.5 Others

C-SSRS category types

All C-SSRS reports of suicidal ideation type 1, 2, 3, 4 and 5, and group type 1-3 and 4-5, will be summarized at each study visit. Suicidal behavior type 6, 7, 8, 9 and 10 and group type 6-9 and 10 will be summarized at each study visit. Shift tables of type 1-3 to 4-5 per visit will be provided for over the whole trial and over 52 weeks during the on-treatment period.

HADS depression and anxiety scores

Anxiety and depression subscore change over time will be summarized descriptively (graphically and numerically).

Time to HADS subscore > 14 defined as AESI (investigator reported) will be summarized in the time-to-event analysis in Section 7.8.1.8.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Handling of individual patient treatment information

This is a double-blinded trial. Blinding at individual patient level will be applied for patients, investigators, and personnel at the sites involved in trial conduct. The access to the (planned) randomization code list will be kept restricted until it is released for analysis. The treatment information for an individual patient will be available in the trial database after database lock .

Handling of aggregated treatment information

While the trial is in progress and prior to submission of the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form for primary analysis (i.e., prior to the data being declared ready for unblinded aggregate analysis by the trial team), access to tabular results of trial outcomes by treatment will not be made available to patients, investigators, personnel at the sites involved in trial conduct, the trial statistician, clinical team, or members of the steering committee (unless the DMC advises otherwise). Any tabular displays of trial outcomes generated by the trial team prior to submission of the RUN form will be produced using mock (dummy) treatment codes.

The DMC (which includes the DMC statistician) and the independent statistician (iSTAT) will be unblinded.

Release of treatment information

Once the last patient has completed their Week 52 visit (Visit 10) and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form (DBL1).

The data collection after DBL1 will continue into the unblinded trial database. Once trial data collection has been completed and all data has been entered and cleaned as documented on the RUN form, a final database lock will be performed (DBL2).

After the release of treatment information, it is expected that only trial data occurred after DBL1 will be entered and changed. Therefore, after the timepoint of release of treatment information, all changes affecting trial data up to DBL1 will be documented and summarized in the CTR.

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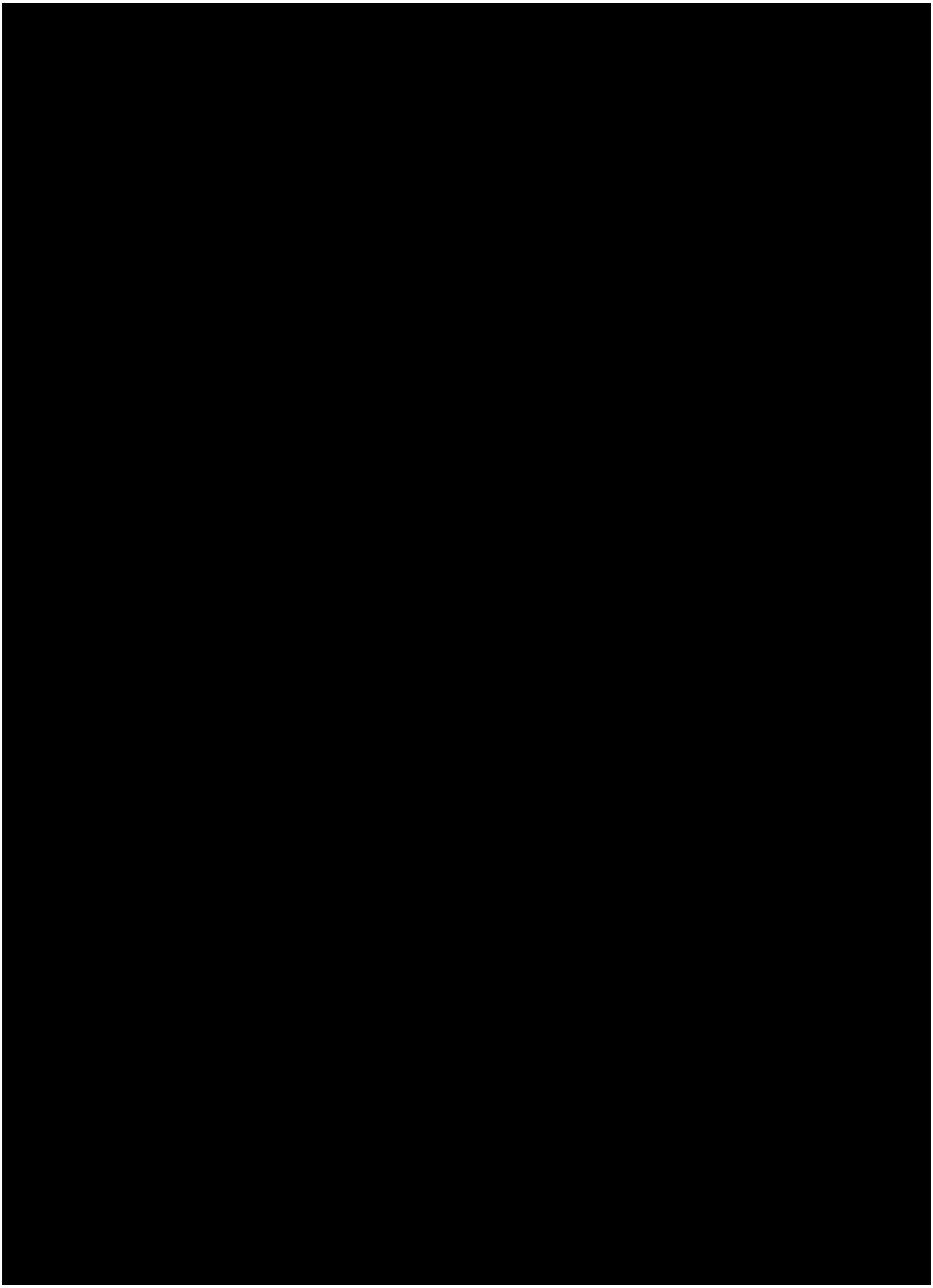

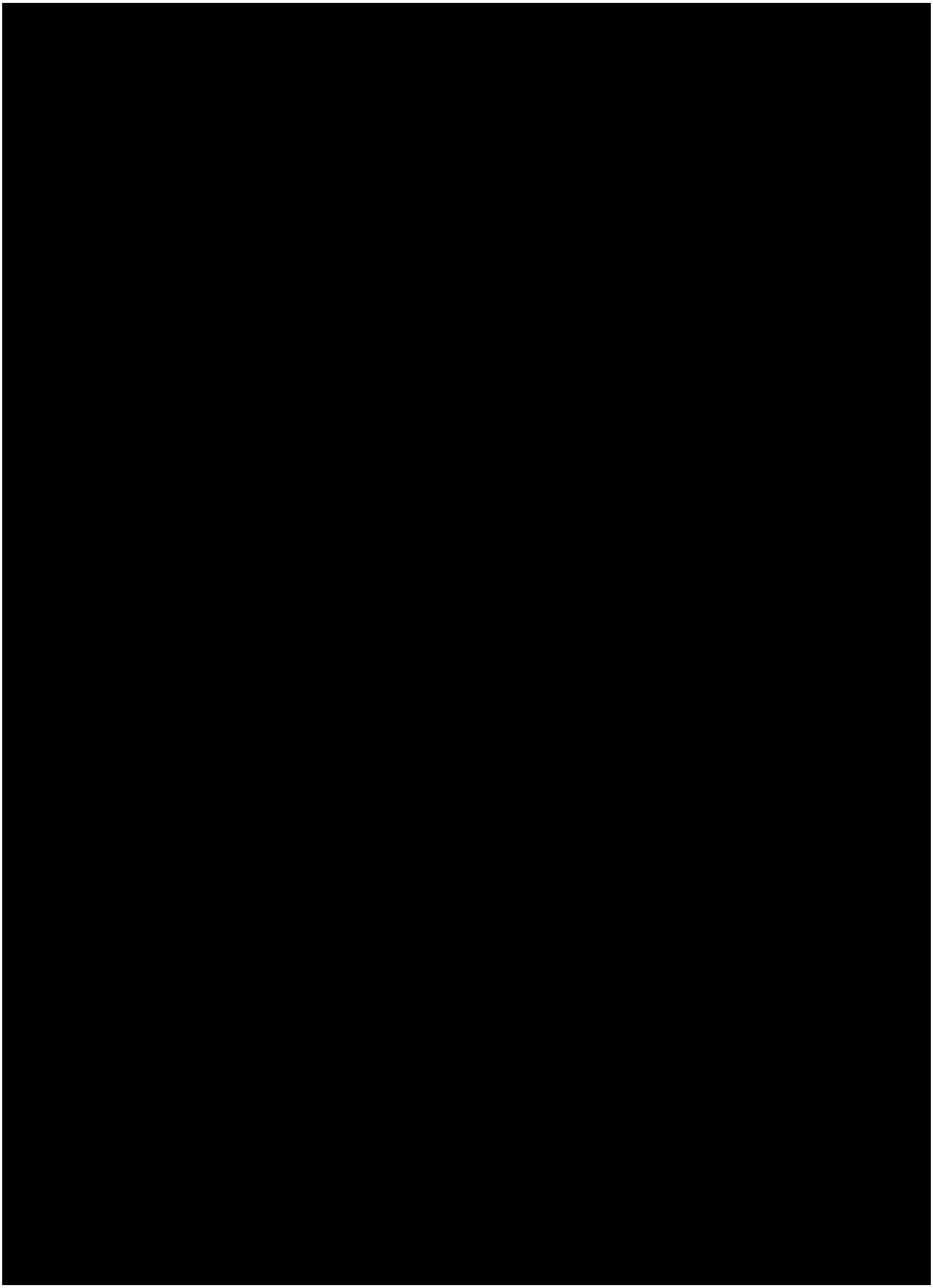

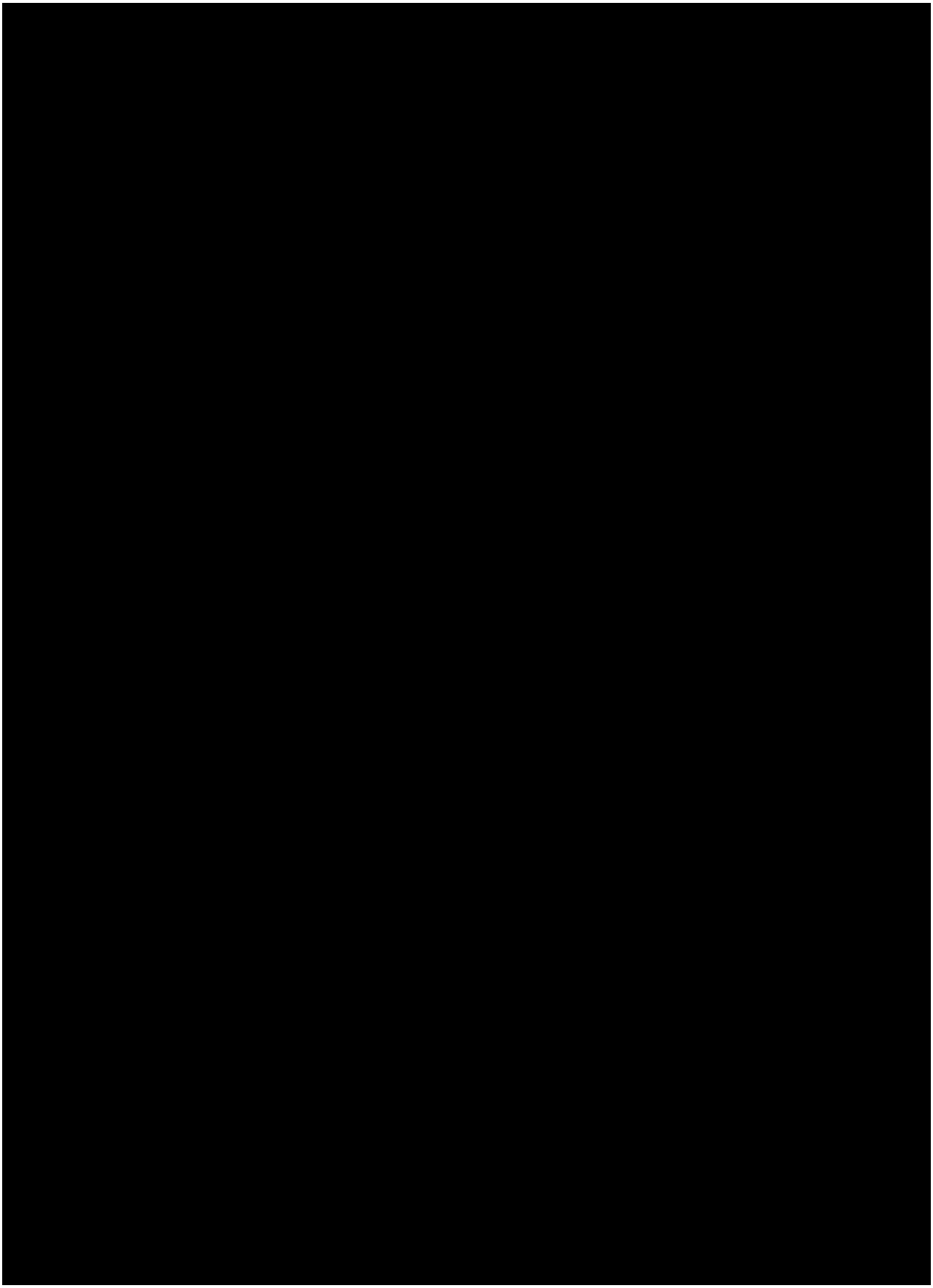

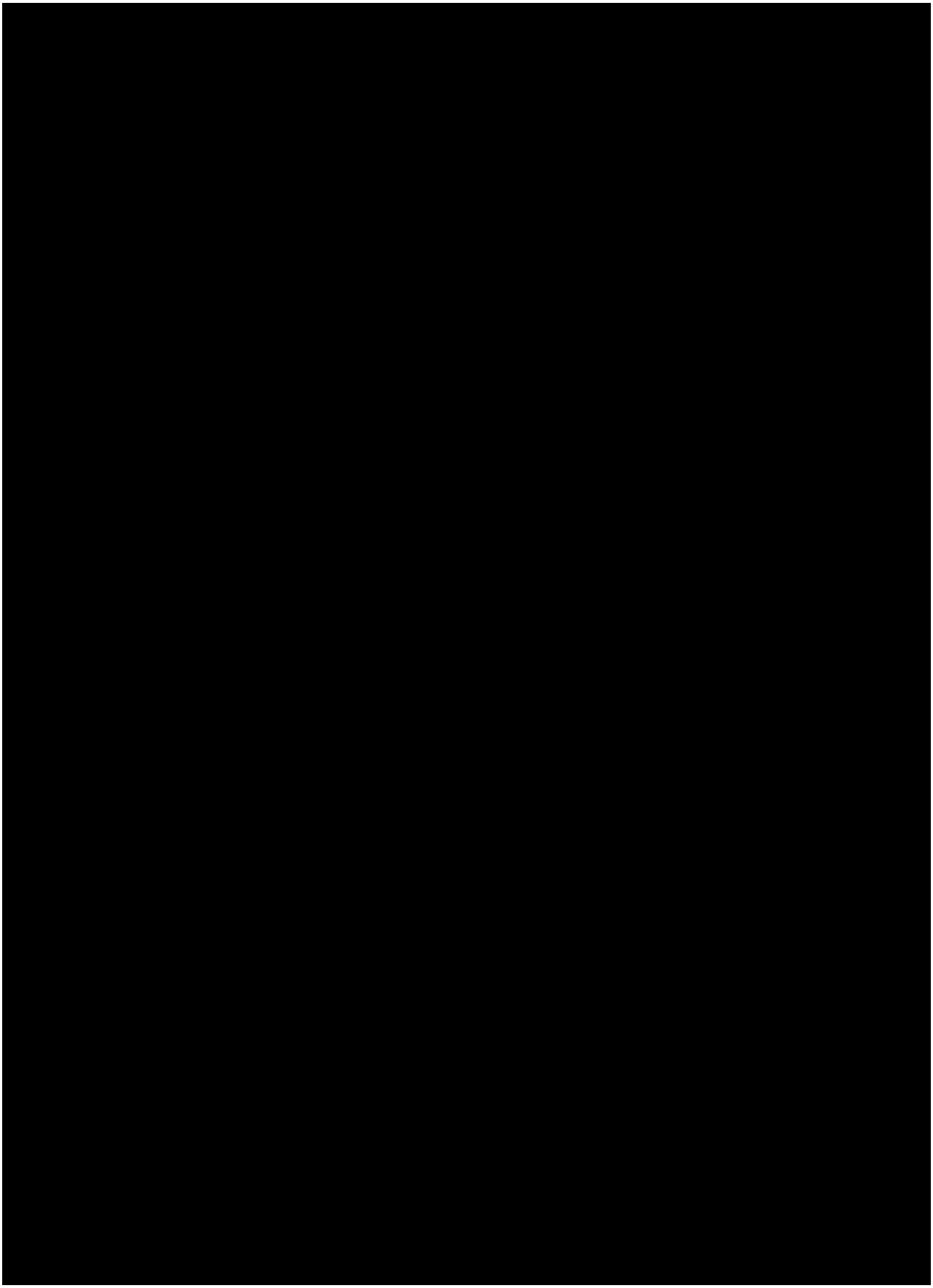

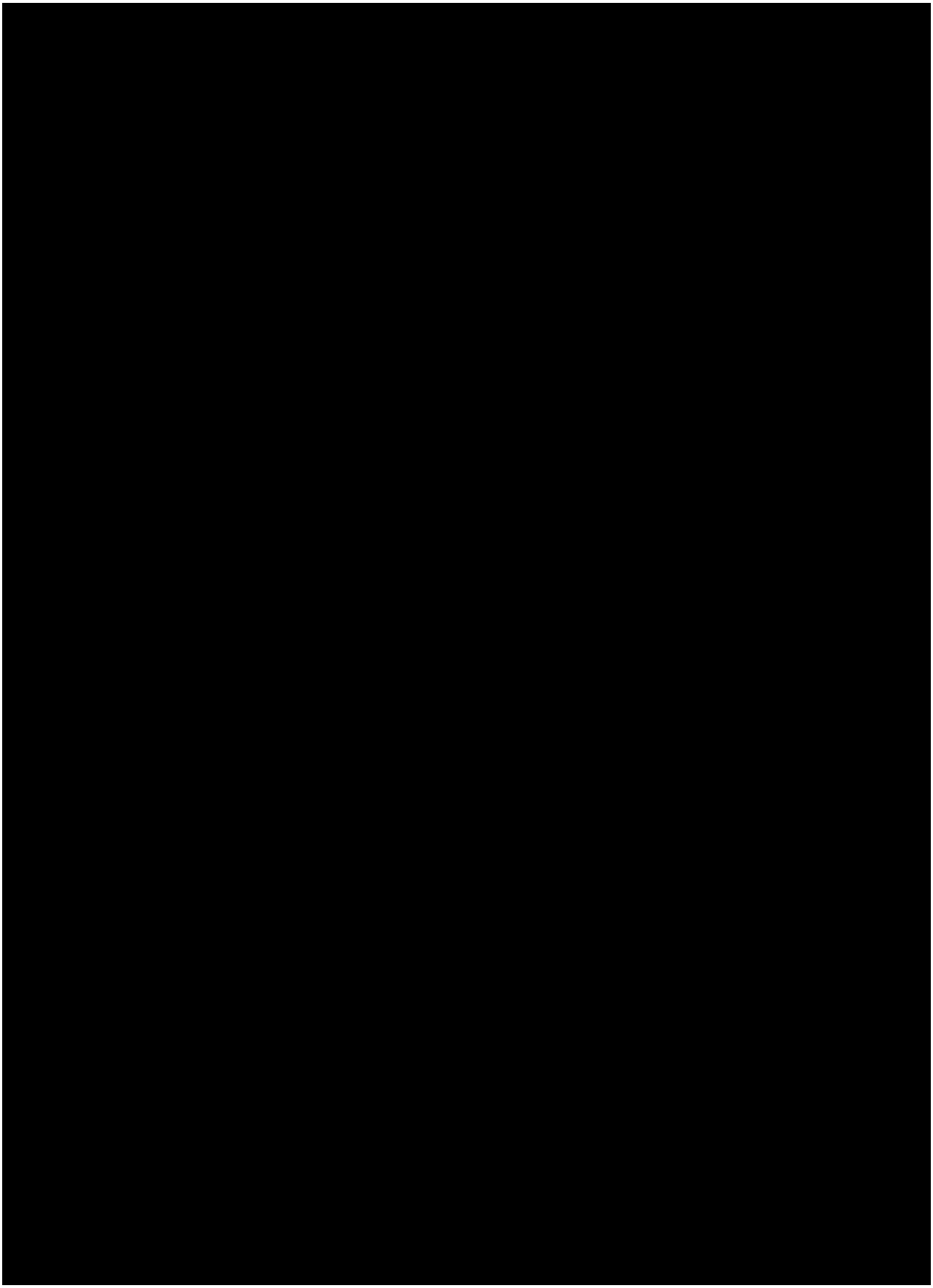

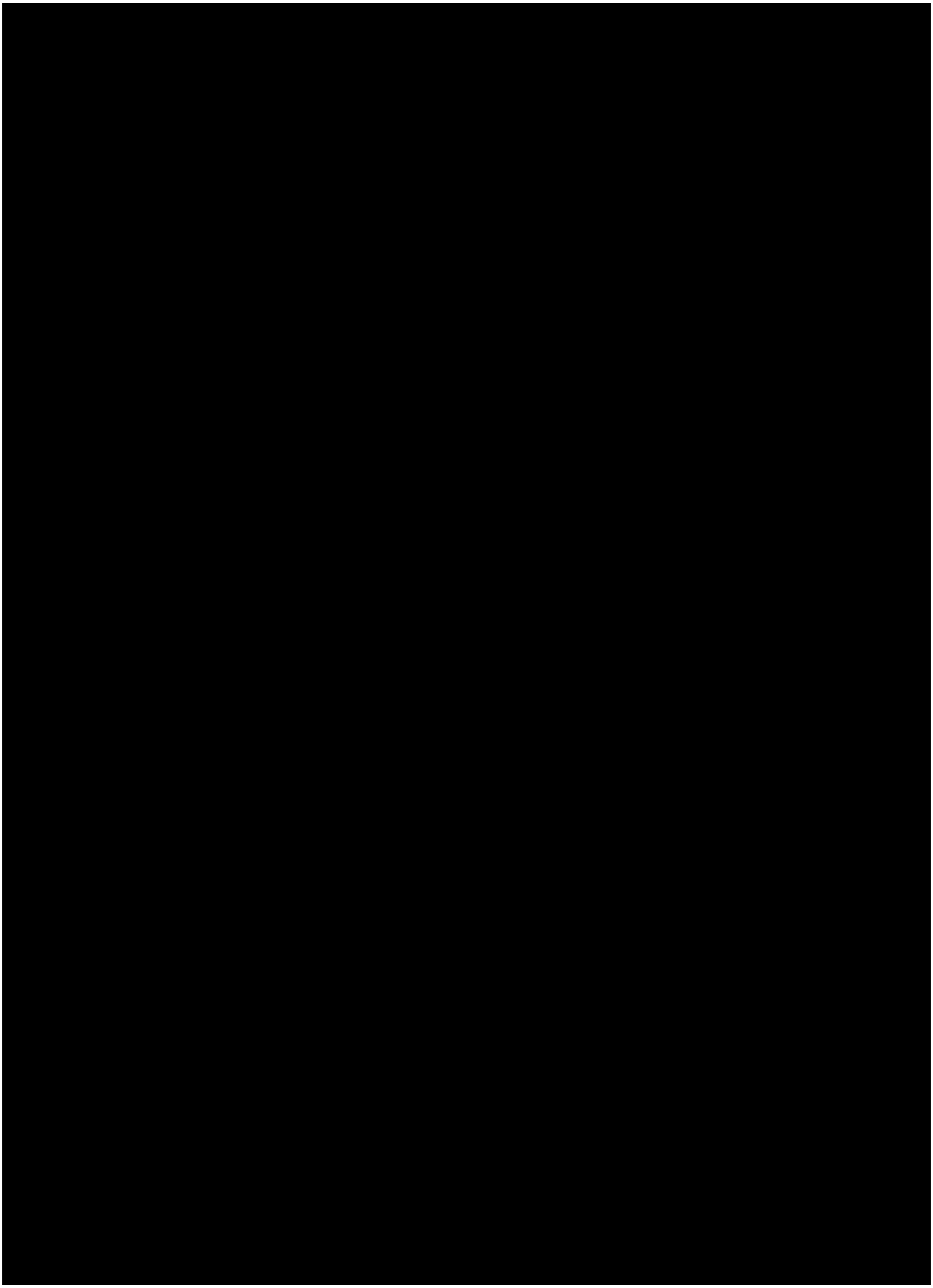

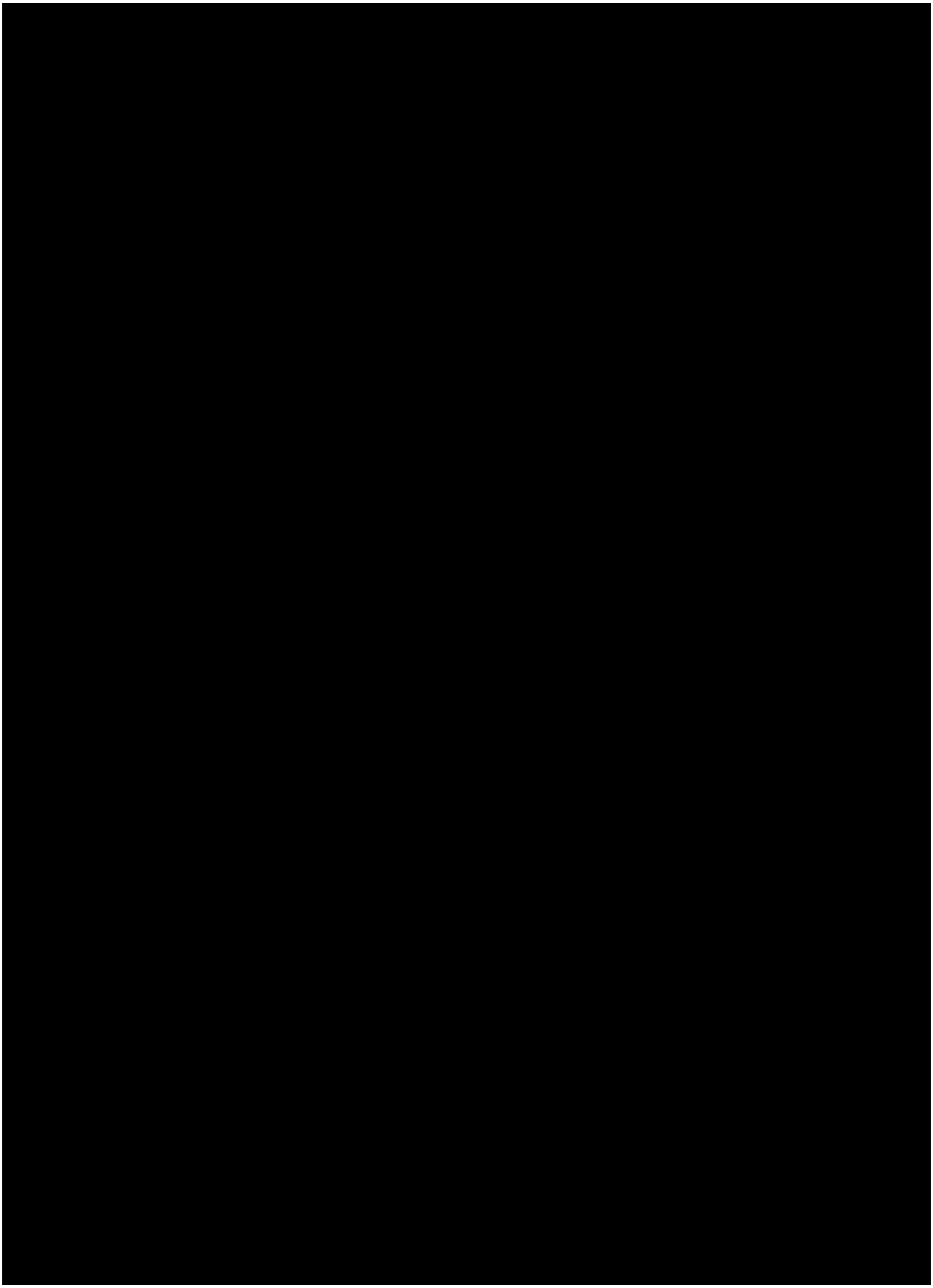

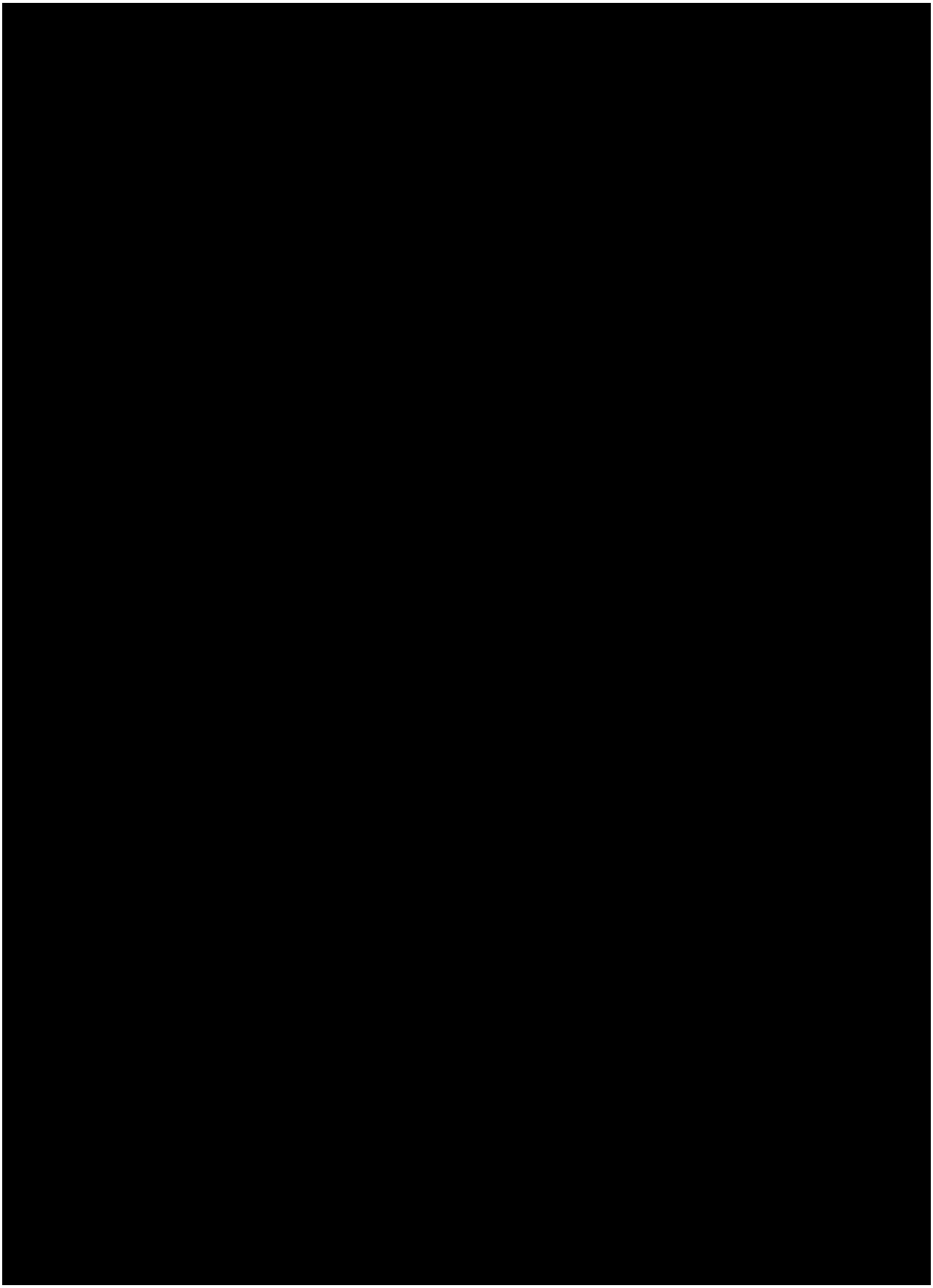

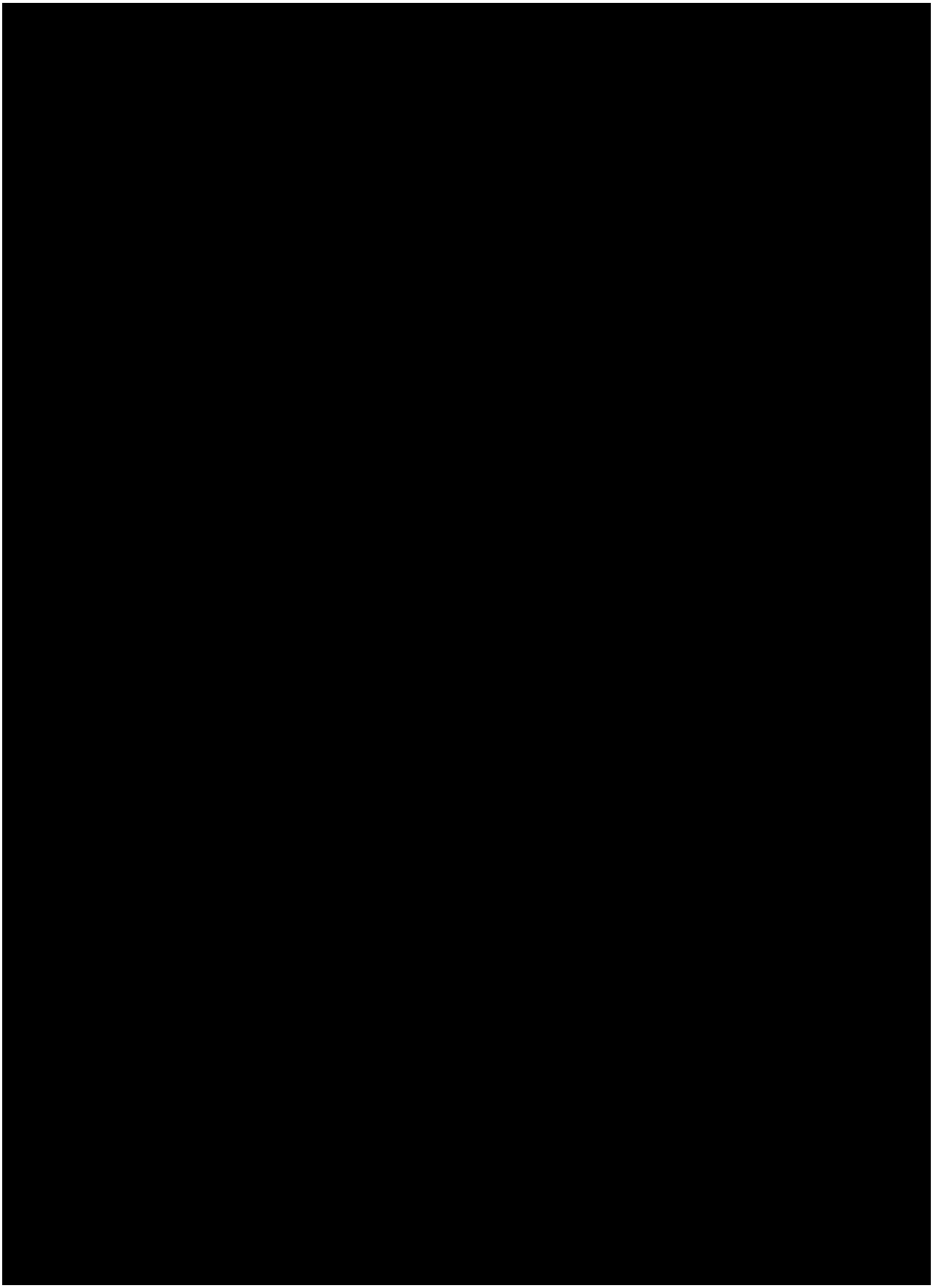

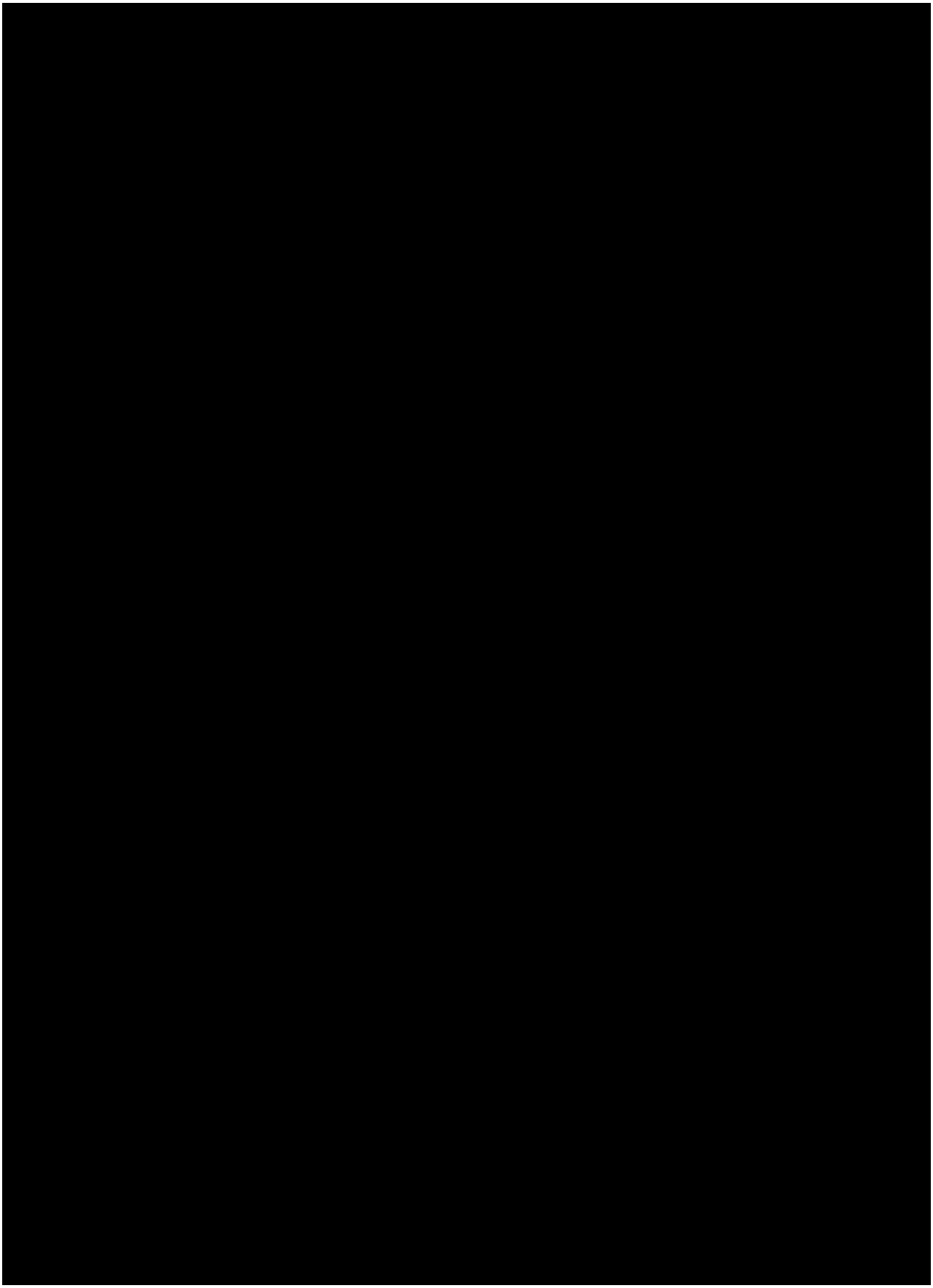

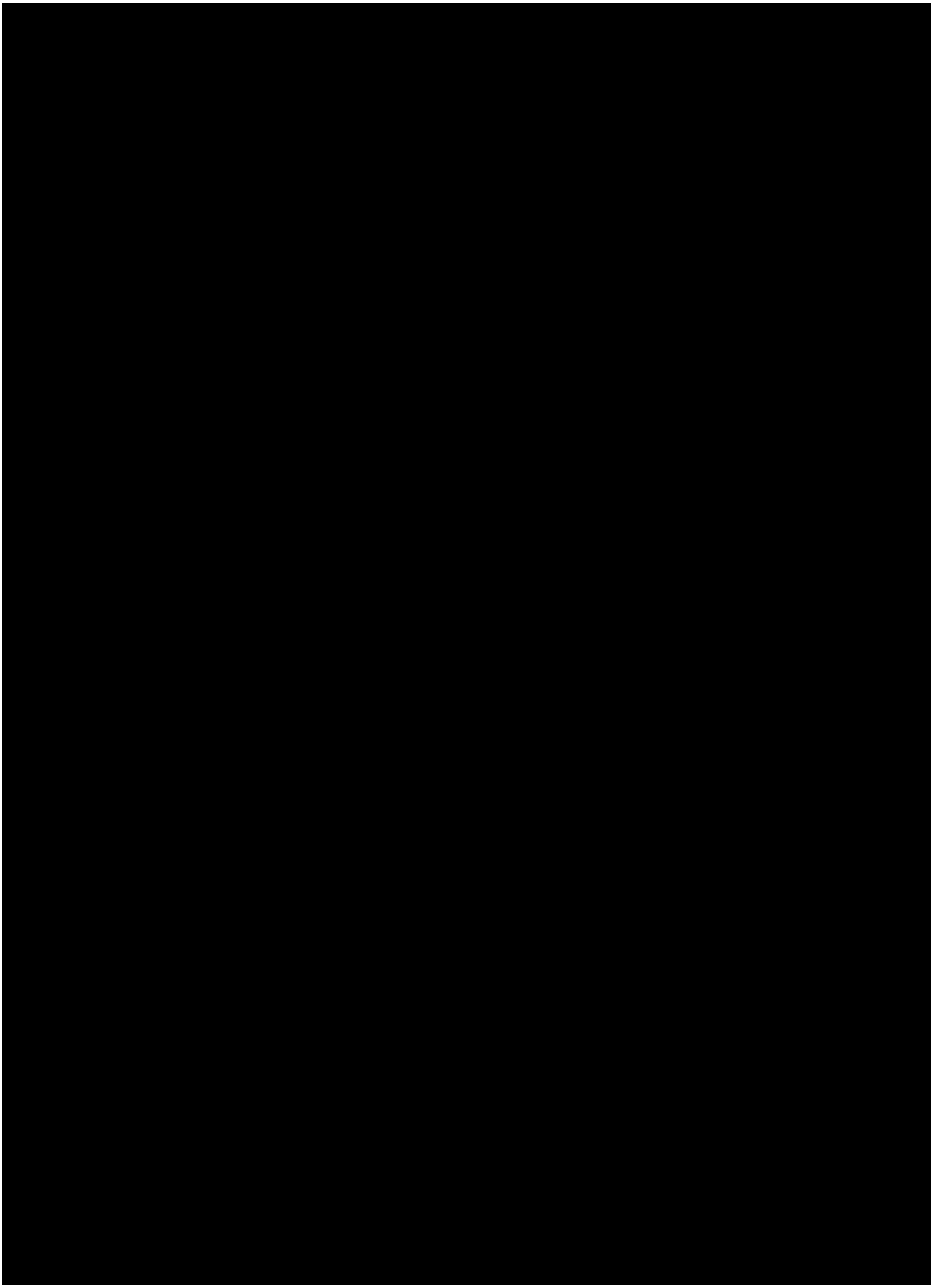

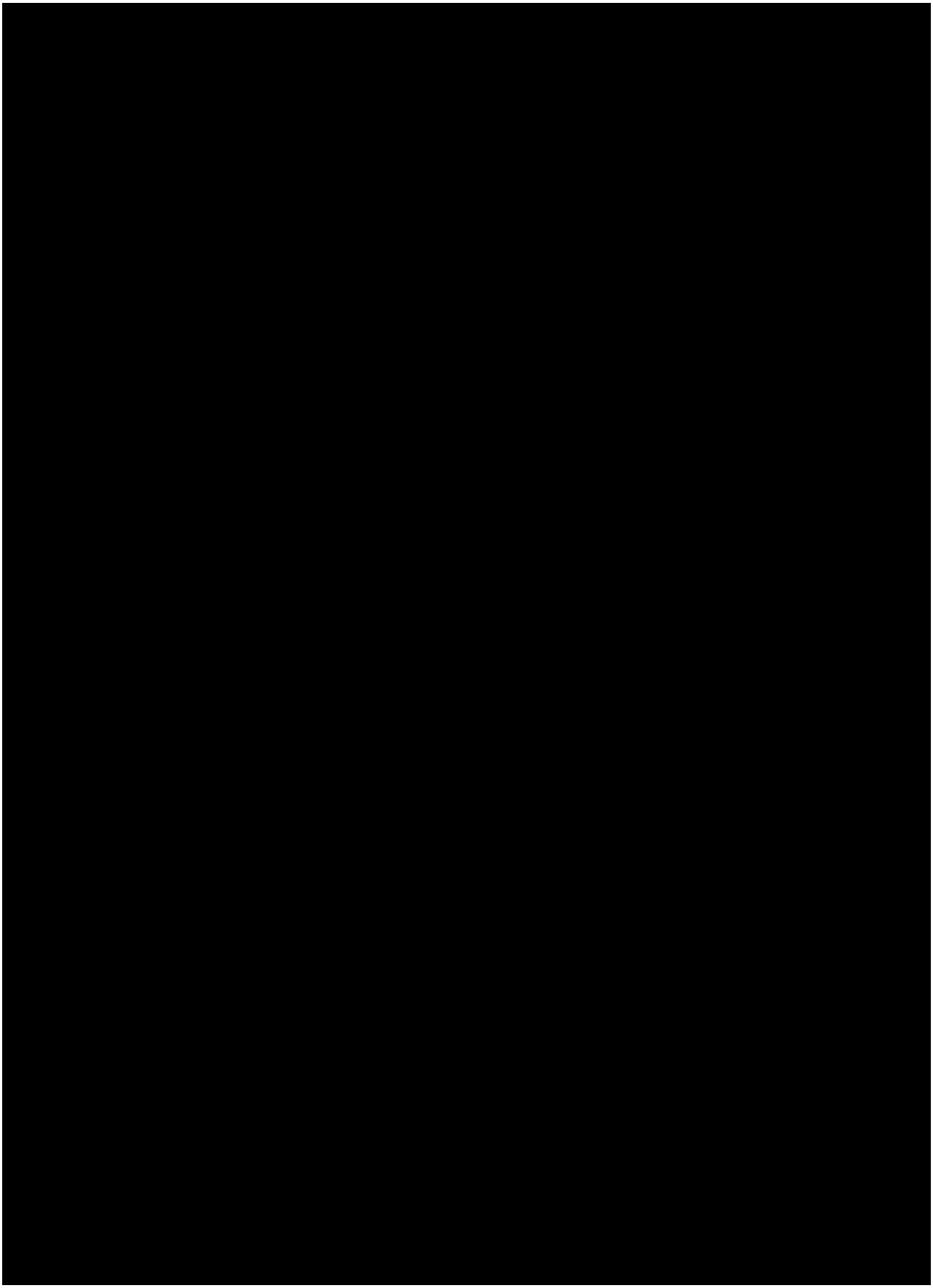

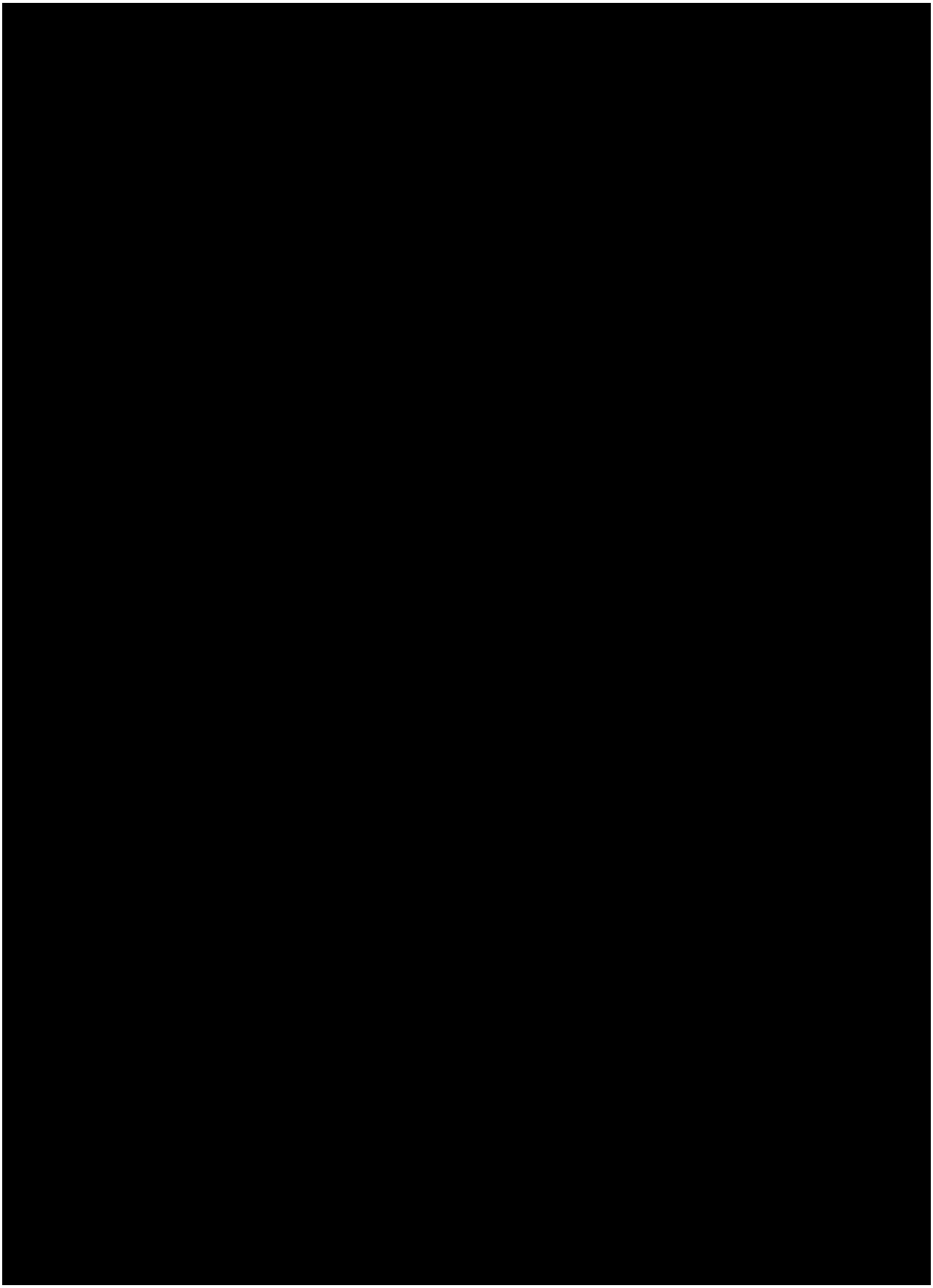

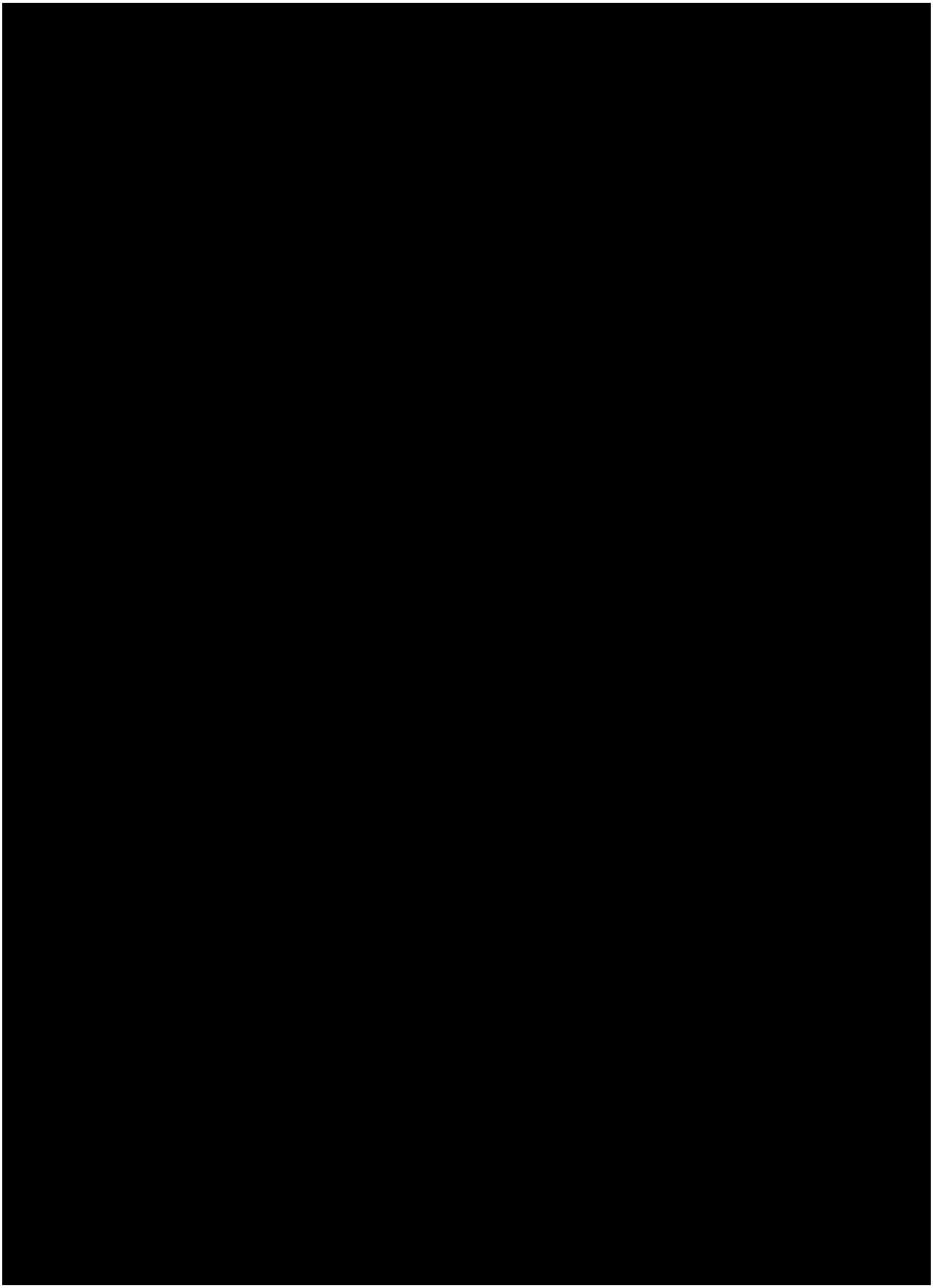

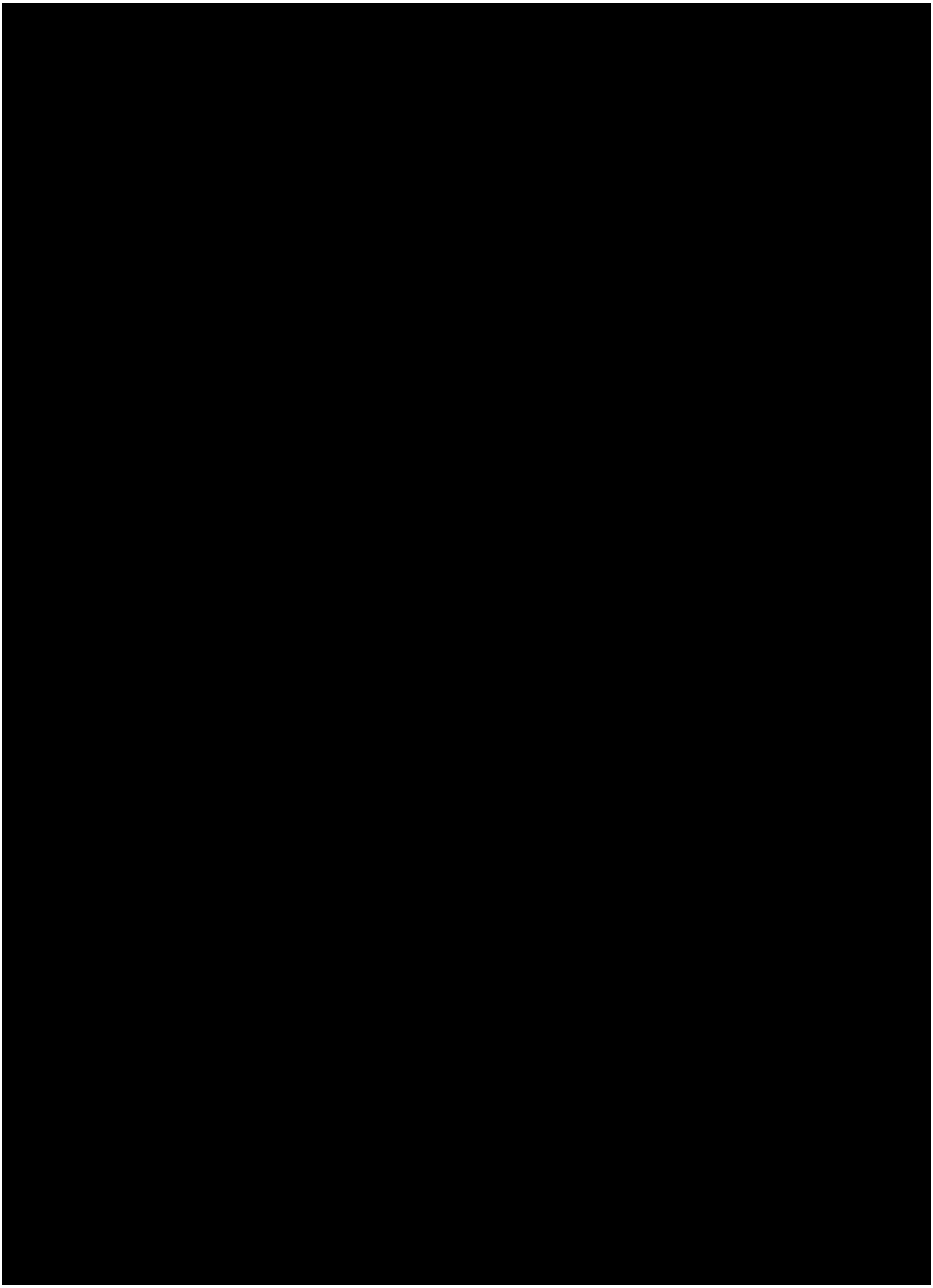

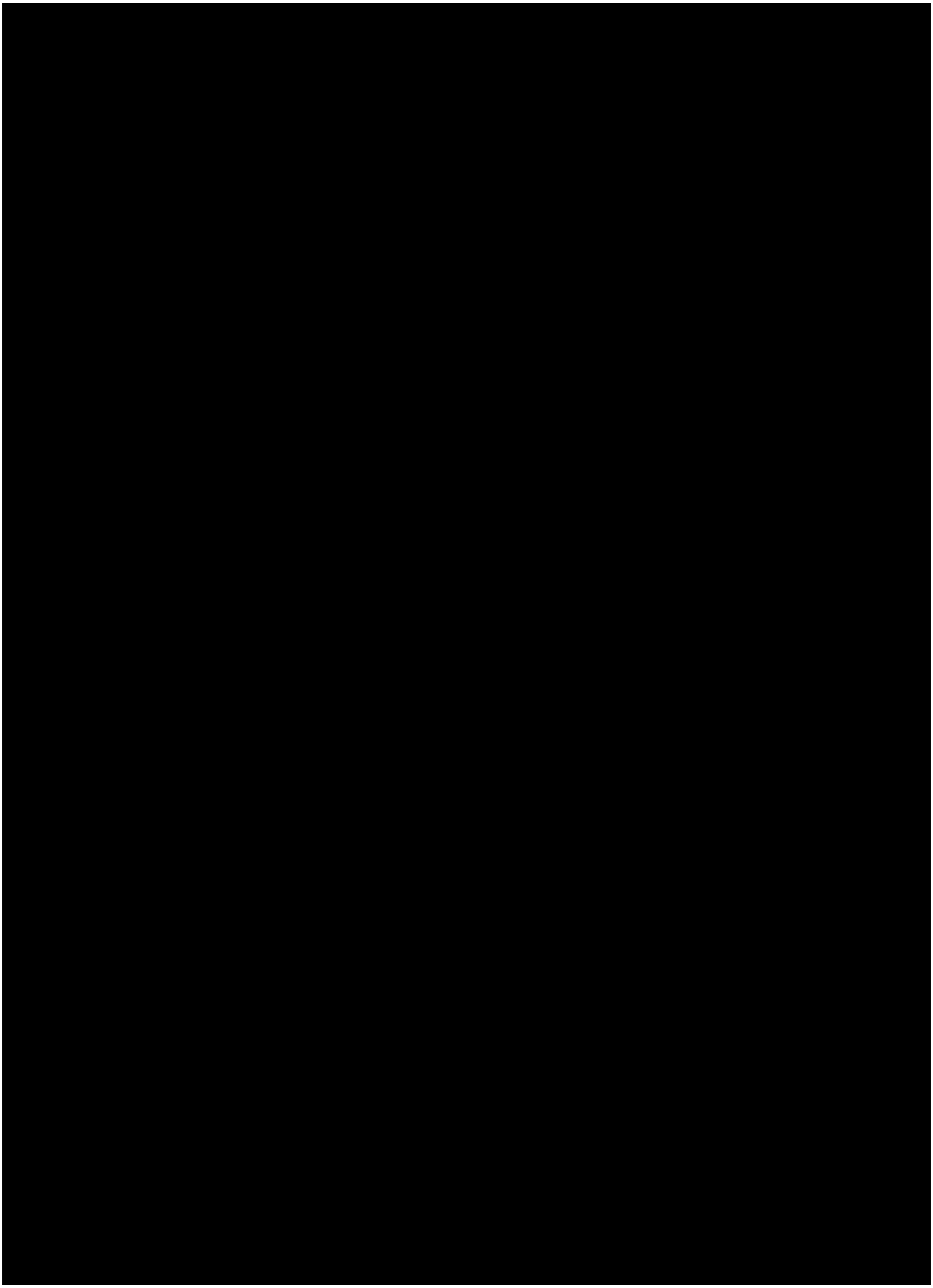

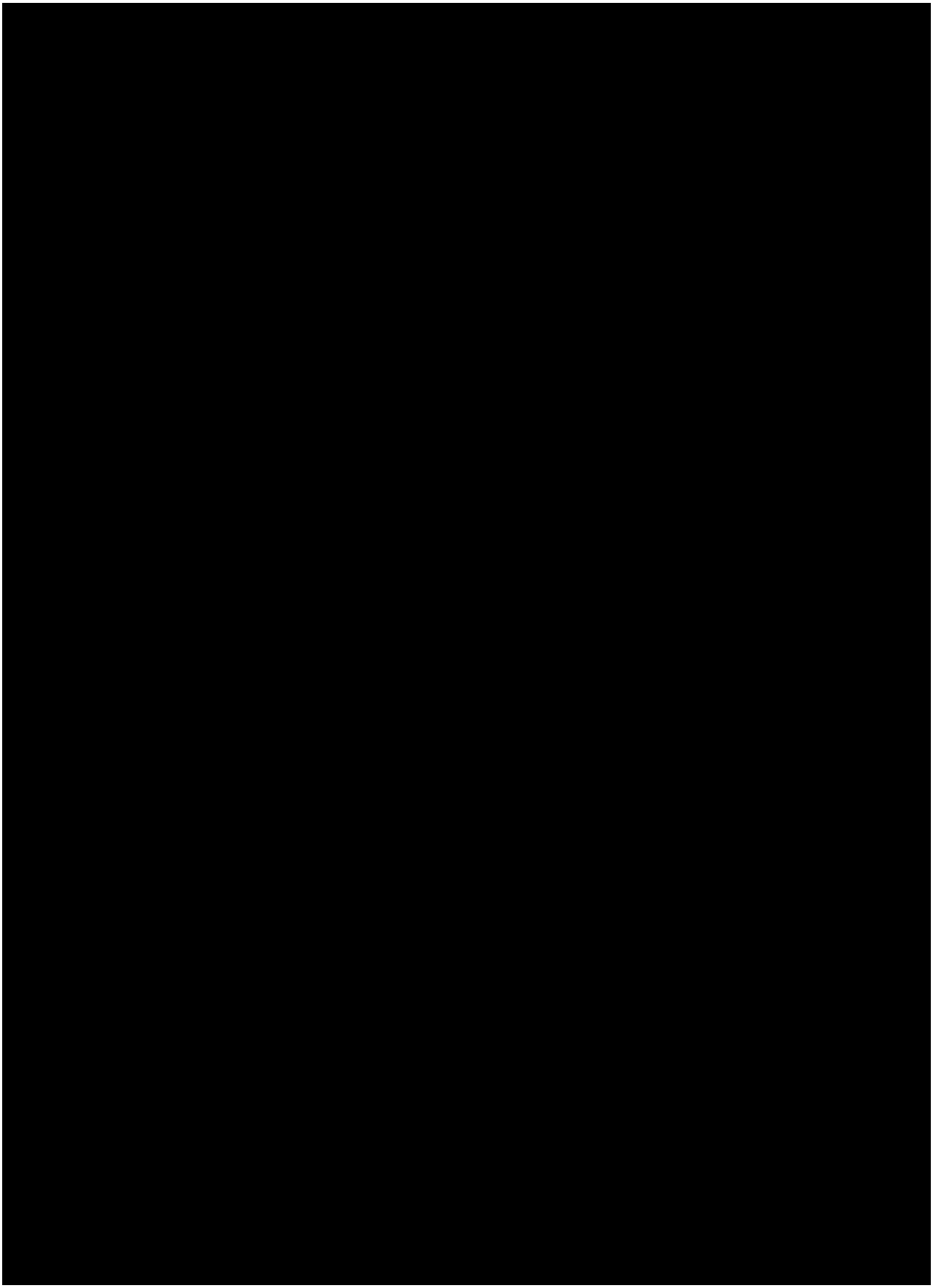

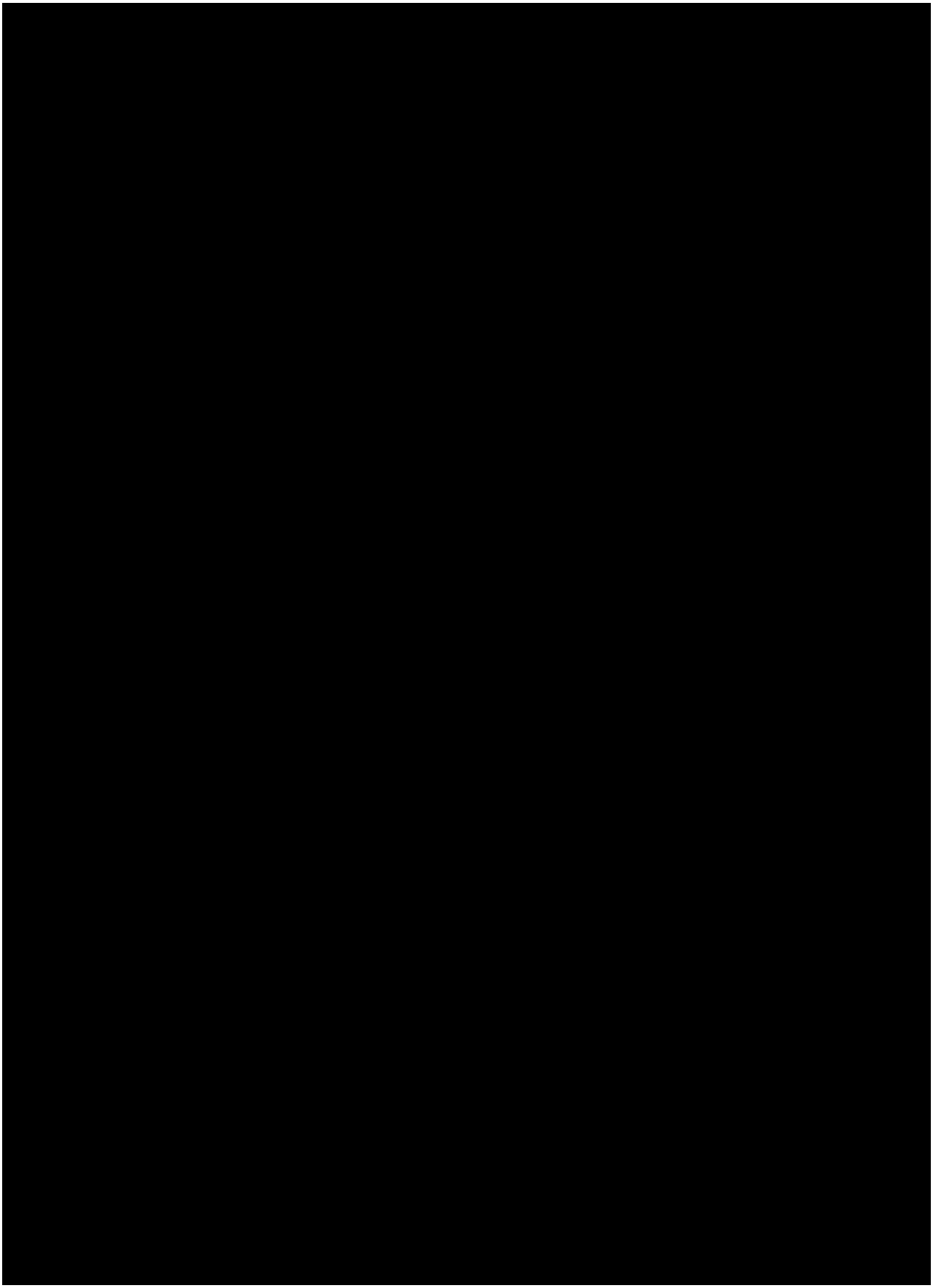

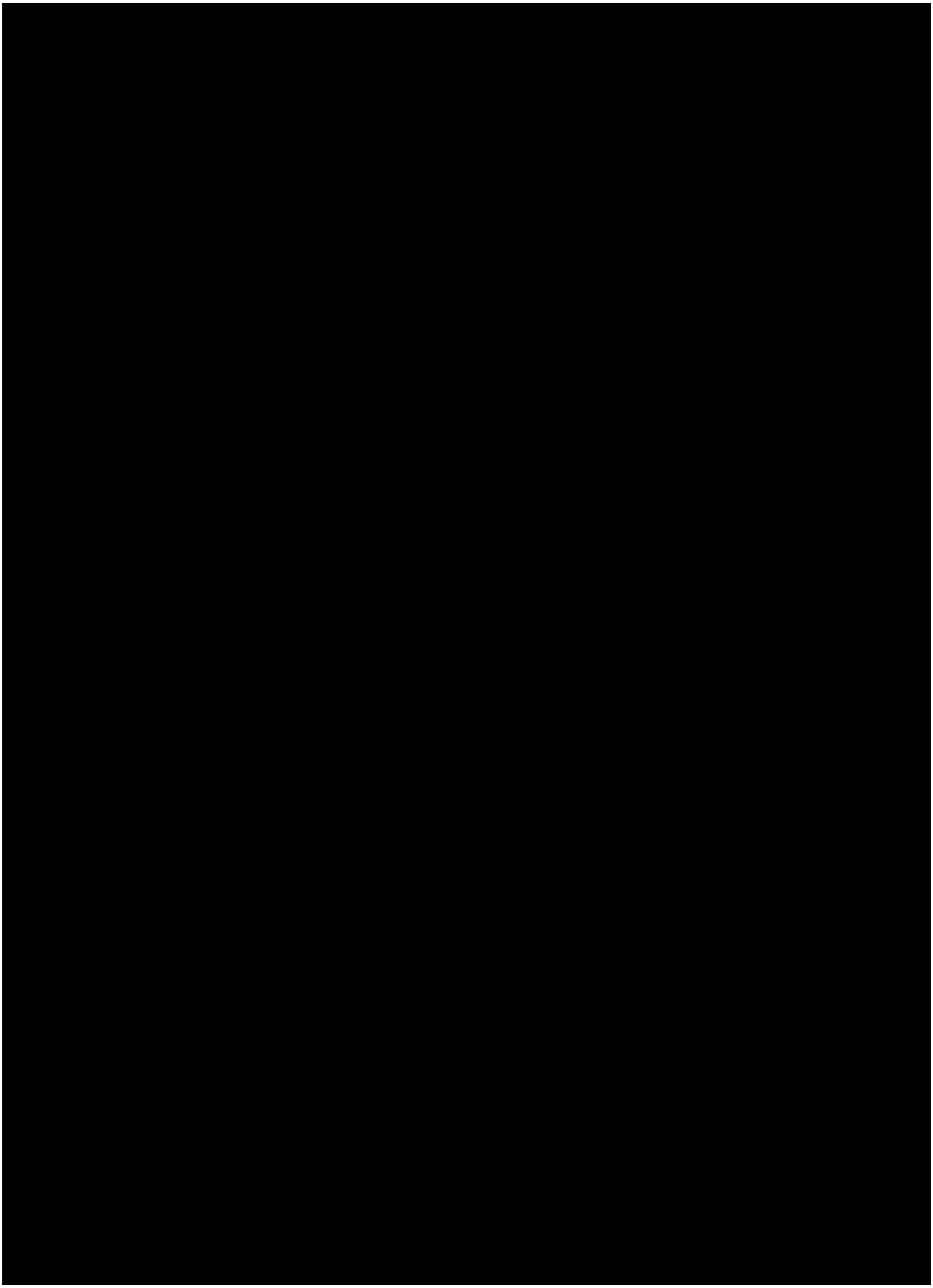

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**28-JULY-2023**	[redacted]	NA	TSAP version 1.0 before interim futility analysis
2.0	**23-AUGUST-2024**		All	This is the TSAP before the DBL1 of trial 1305-0014
3.0	**30-DEC-2024**		All	Add some further endpoints and the relevant analyses per team discussion results, and some other minor changes.