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Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Biological Activity, and PK of ND-L02-s0201 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Protocol Reference Number: ND-L02-S0201-005

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Statistical Analysis Plan

Nitto Denko Corporation

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Glossary of Abbreviations

Abbreviation	Term
[redacted]	[redacted]
AE	Adverse event
AEOI	Adverse events of special interest
AIC	Akaike's information criterion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR(1)	First-order autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
bpm	beats per minute
CI	Confidence Interval
COVID-19	Coronavirus disease
CS	Compound symmetry
CTCAE	Common Terminology Criteria for Adverse Events
DLco	Diffusion capacity of the lung for carbon monoxide
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDISH	Evaluation of drug induced serious hepatotoxicity
EOT	End-of-Treatment
ET	Early Termination
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
[redacted]	[redacted]
HRCT	High-resolution computed tomography
ILA	Interstitial lung abnormalities
ILD	interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
[redacted]	[redacted]
KW	Kruskal-Wallis
KM	Kaplan-Meier
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
NCI	National Cancer Institute
PD	Pharmacodynamics
PFT	Pulmonary function testing
[redacted]	[redacted]
PK	pharmacokinetic(s)
PP	Per protocol
[redacted]	[redacted]
Q2W	Every 2 weeks
QLF	Quantitative lung fibrosis
QOL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SLB	Surgical lung biopsy
SOC	System Organ Class
SpO_2	Peripheral capillary oxygen saturation
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures and Listings
TOEP	Toeplitz
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
VA	Alveolar volume
WBC	White blood cell
WHO	World Health Organization
[redacted]	[redacted]

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol Amendment	17 June 2020	5.0
eCRF	19 February 2021	Prod 3.00

2. Protocol Details

2.1 Study Objectives

Primary:

- Evaluate the safety and tolerability of ND-L02-s0201, administered at 2 dose levels, once every 2 weeks (Q2W) over 24 weeks, versus placebo, in conjunction with standard of care

Secondary:

- Evaluate the biological activity of ND-L02-s0201 as measured by spirometry over 24 weeks
- Evaluate changes of interstitial lung abnormalities (ILA) as measured by high-resolution computed tomography (HRCT)
- [redacted]
- [redacted]

2.2 Overall Study Design

This is a Phase 2, double-blind, placebo-controlled, randomized, multicenter, international study of 2 doses of ND-L02-s0201 for Injection, consisting of 3 treatment arms: 2 dose levels of ND-L02-s0201, a low dose (45 mg) and a high dose (90 mg), will be evaluated in 2 arms; a third arm will be administered placebo. This study will evaluate safety, tolerability, biological activity, and PK in subjects with a diagnosis of idiopathic pulmonary fibrosis (IPF) with forced vital capacity (FVC) ≥45% of predicted and diffusion capacity of the lung for carbon monoxide (DL_{CO}) ≥30% of predicted.

Approximately 120 eligible subjects will be randomized 1:1:1 to 1 of following 3 treatment arms:

- ND-L02-s0201 for Injection high dose (90 mg)

- ND-L02-s0201 for Injection low dose (45 mg)
- Placebo.

The randomization via the interactive web response system (IWRS) will be stratified by the receipt of standard of care at the enrollment of the study, defined as administration of either nintedanib or pirfenidone, or no standard of care. As there is no minimum number of subjects for a given strata of standard of care, balance in strata across the 3 treatment arms is required.

Eligible subjects who meet the inclusion criteria and do not meet any of the exclusion criteria and have provided informed consent will be enrolled in the study. Subjects will participate in the study for approximately 40 weeks consisting of a Screening and Baseline period of up to 6 weeks, a treatment period of 24 weeks including a total of 12 doses and an End-of-Treatment visit 2 weeks after the final dose (Visit 14), and a follow-up visit 4 and 10 weeks after Visit 14, or until they withdraw from the study or the study is terminated by the Sponsor. During the treatment period ND-L02-s0201 for Injection will be administered by intravenous (IV) infusion Q2W (± 4 days for Visit 3 or ± 7 days for Visits 4 to 13, ensuring a minimum of 7 days between each dose) for a total of 12 doses. Subjects may be premedicated to mitigate the risk of infusion-related reactions at the discretion of the Investigator.

2.3 Sample Size and Power

Approximately 120 subjects will be enrolled into the study, with approximately 40 subjects in each of 3 arms. The study will include approximately 35-40 sites, and will enroll approximately 3 to 5 subjects per site.

[redacted]

3. Efficacy and Safety Variables

3.1 Primary Endpoints

Safety

- Incidence of TEAEs and treatment-emergent SAEs
- Proportion of subjects discontinuing study treatment due to TEAEs

3.2 Secondary Endpoints

Biological Activity

- Rate of decline in FVC from baseline to Visit 14 (Day 169) (measured in L and % of predicted over unit time)
- Absolute and relative change in FVC (L and % of predicted) at Visit 14 (Day 169) as compared with baseline
- Proportion of subjects with an FVC response (L and % of predicted) defined as either having improvement or a decline by 0% to ≤ 5%, > 5% to ≤ 10%, and by > 10% at Visit 14 (Day 169)
- Change in DL_{CO} (mL/min/mmHg) and DL_{CO} (mL/min/mmHg) corrected for hemoglobin at Visit 14 (Day 169)
- Changes of ILA as measured by HRCT (i.e., change in parenchymal feature [Baseline to Visit 14 (Day 169)]), as determined by qualitative assessment (central radiologist) and quantitative analysis (Quantitative Lung Fibrosis – QLF analysis)
- Time to first acute IPF exacerbation (i.e., an unexplained worsening of dyspnea, evidence of hypoxemia as defined by worsened or severely impaired gas exchange, new radiographic alveolar infiltrates, and an absence of an alternative explanation such as infection, pulmonary embolism, pneumothorax, or heart failure [Raghu et al, 2011]) or death
- Rate of hospitalization for respiratory ailments and time to first hospitalization for respiratory ailments or death
- Rate of mortality due to all causes and overall survival
- Rate of deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death and time to deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death

[redacted]

- [redacted]
- [redacted]
- [redacted]

3.4 Efficacy and Safety Variables

3.4.1 Spirometry

Spirometry variables include forced vital capacity (FVC) and percent predicted FVC (%FVC). FVC will be measured in units of liters (L) and rounded to 2 decimal places. %FVC will be measured in percent and rounded to 2 decimal places. The spirometry

variables will be provided by an external vendor in a data transfer and the results will not be entered into the EDC system.

[redacted] In the event that no baseline measurement is designated, then the baseline measurement will be the last non-missing value before the first infusion of study treatment. [redacted]

3.4.2 Diffusion Capacity of the Lung for Carbon Monoxide (DLco)

Diffusion capacity of the lung for carbon monoxide (DLco) in mL*(CO/min/mmHg) will be provided by an external vendor in a data transfer, and the results will not be entered in the EDC system. DLco will be provided with and without correction for hemoglobin and results will be rounded 2 decimal places.

[redacted] In the event that no baseline measurement is designated, then the baseline measurement will be the last non-missing value before the first infusion of study treatment. Values not designated as "Accepted" in the vendor data transfer will be excluded from statistical analyses. When more than two valid test values are obtained at a study visit in the event a PFT that has passed QC shows declines from baseline that need confirmatory testing, the average of both values will be included in the summary table.

3.4.3 High Resolution Computed Tomography (HRCT)

High resolution computed tomography (HRCT) data will be provided by a central reader and will include variables from qualitative and quantitative analyses of HRCT scans [redacted] Results of HRCT analyses will be provided by an external vendor in a data transfer and will not be entered in the EDC system [redacted]

3.4.3.1 Qualitative HRCT Variables

The qualitative HRCT variables will include central reader estimates of the extent of lung region abnormalities by lung (left and right) and region (upper, mid, and lower).

Possible values (as %) for each region will include "Absent", "1-25", "26-50", "51-75", and "76-100". Results for unreadable scans will be reported as "Unknown".

The central reader's assessment of overall change in interstitial lung disease (ILD) from baseline to Visit 14 (or ET) will have possible values of "Much Better", "Better", "Same", "Worse", "Much Worse", or "Unknown".

[redacted]

[redacted]

	[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.4.3.2 Quantitative HRCT Variables

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

3.4.5 Extent of Exposure

Extent of exposure to study treatment will be summarized descriptively as:

- Duration of exposure (days) is calculated as:
  - (date of last dose – date of first dose) + 1
- Number and percentage of subjects who received the premedication
- Number of doses, total dose (mg) administered, and total infusion volume (mL) administered
- Number and percentage of subjects with any infusion interruptions, number of infusion interruptions per subject, total duration of infusion interruptions per subject, and reason for the infusion interruptions.

Treatment compliance is calculated as:

- Treatment compliance = 100 * total actual cumulative dose of administrated (mg) / total cumulative dose of the planned (mg) during the study.

Where the cumulative dose of planned dose is defined as number of planned doses until last dose subject received multiplying by assigned dose (45 mg for low dose treatment arm and 90 mg for high dose treatment arm). The total planned dose is defined as the number of infusions planned until subject's last dose (i.e. if subject's last dose is at Week 22, then the subject's expected number of infusions would be 12).

If date of first dose date is missing, then the randomization visit will be used. The last dose is the date of the last dose administered as of the data cut-off date.

3.4.6 Adverse Events (AEs)

All AEs recorded on the eCRF will be coded using the latest version of MedDRA dictionary, per the Data Management Plan, throughout the study and classified as either pre-treatment AEs or TEAEs as follows:

- Pre-treatment AEs are events that started prior to the first dose of any study treatment, including pre-medication.
- TEAEs are events that occur on or after the first dose of any study treatment including pre-medication through two weeks after the last dose of study treatment or adverse events which start before the first dose of study treatment, but increase in severity after the first dose through two weeks after the last dose of study treatment.

Assessment of AE severity will be based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). The severity of all AEs is recorded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening consequences (Grade 4), or death (Grade 5), per CTCAE grading. If severity is missing for a TEAE, it will be considered severe only in the overall category in the summary tables.

The relationship between an AE and study treatment is assessed as definite, probable, possible, unlikely, or none. A drug-related AE is an AE considered by the investigator as definitely, probably, possibly, or unlikely related to study treatment. If the relationship is unknown or missing, it is also considered as related to study treatment.

AEs of special interest (AEOI) include [redacted] respiratory adverse events, and acute exacerbation of idiopathic pulmonary fibrosis.

3.4.7 Laboratory Evaluations

The following hematology, serum chemistry, and urinalysis analytes recorded in the eCRF will be analyzed in this study. Absolute values will be compared to the laboratory reference range and classified as

- lower than reference range, clinically significant;
- lower than reference range, not clinically significant;
- normal in reference range;
- higher than reference range, not clinically significant;
- higher than reference range, clinically significant.

All values classified as high or low will be flagged on the listings. The baseline value will be defined as last scheduled or unscheduled value prior to the first dose of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the drug administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

Hematology	Serum Chemistry	Urinalysis
[redacted]	[redacted]	[redacted]

3.4.8 Vital Signs and Pulse Oximetry

The following vital signs will be evaluated at the time points specified in study calendar.

- systolic and diastolic blood pressure (mmHg);
- heart rate (bpm);
- respiratory rate (breaths/min);
- oral temperature (°C).
- weight (kg) and height (cm). Height will be recorded only at first visit (visit 1a).
- SpO_2 (%).

The baseline value will be defined as last scheduled or unscheduled value collected prior to start of treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the drug administration, if

the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

3.4.9 Physical Examination

Complete and abbreviated physical examinations will be evaluated in this study. A complete physical examination includes general appearance, eyes/ears/nose/throat/head/neck, chest and lungs (including inspection of the thorax for scars consistent with surgical lung biopsy at Screening), cardiovascular, abdomen, musculoskeletal, lymphatic, dermatologic, neurologic, psychiatric, and extremities. An abbreviated physical exam includes general appearance, nose/throat, jugular venous distension (sitting; absent or present), auscultation of the lungs (anterior/posterior, 4 quadrants; wheezes, crackles, rhonchi [absent or present], other sounds [describe]), auscultation of the heart, lower extremity venous distention (absent or present), pitting edema (0, 1+, 2+, 3+, or 4+). Any clinically significant abnormal result after baseline should be recorded as an AE.

3.4.10 12-Lead Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- heart rate (bpm);
- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia's corrected QT (QTcF) interval (msec).

An overall investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant"). Clinically significant changes not already noted or significantly worsened than documented in Medical History will be recorded as AEs.

The baseline value will be defined as last scheduled or unscheduled value collected prior to start of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the drug administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables. When triplicate ECG tracings are obtained at a study visit or timepoint, the triplicate average (or if fewer, average of ECGs available) will be included in the analysis.

3.4.11 Other Safety Assessments

The following other safety assessments will be performed:

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

5. Analysis populations

5.1 Safety Population (SAF)

The safety population (SAF) will include all subjects who receive at least 1 dose of study treatment. Subjects will be analyzed according to the study treatment they actually received.

5.2 Intent-to-treat Population (ITT)

The ITT population will include any randomized subjects with treatment assignment according to the planned randomization.

5.3 Pharmacokinetic Population 1 (PK1)

PK population 1 will include subjects in the PK subset who receive at least 1 dose of study treatment and have a majority of scheduled PK samples drawn for serial PK measurements that allow for PK parameters to be generated. A majority of samples is defined by sampling to at least 4 hours after end of infusion. Subjects who do not complete the study treatment infusion (Visit 2) will be excluded from the PK analysis.

5.4 Pharmacokinetic Population 2 (PK2)

PK population 2 will include subjects who have at least 3 of the 7 planned trough samples collected for subjects in the PK subset and both 2 planned trough samples collected for non-PK subjects to allow for a comparison of trough levels across dosing weeks.

5.5 Per Protocol Population (PP)

The per protocol population (PP) will exclude non-evaluable subjects and subjects with important protocol deviations thought to impact the ability to assess the effect of study treatment.

Evaluable subjects are defined as subjects who received at least one dose of study treatment (not including pre-medication) and have baseline and at least one post baseline FVC or have baseline and at least one post baseline DLco.

Non-evaluable subjects are subjects who do not meet the evaluable criteria.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the correctness, accuracy, and/or completeness of the study data or that may significantly affect a subject's rights, safety, or well-being.

6. Data Handling

6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of treatment (visit 2). Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

All data will be analyzed using nominal study visits as defined in the Study Schedule of Assessment and eCRF. Data collected at unscheduled visits will be listed only, except for the following:

- Data from unscheduled visits will be included in the calculation of baseline laboratory values.
- Data from unscheduled visits will be included in the calculation of the worst CTCAE grade or abnormality used in the laboratory shift tables.
- For a nominal visit with a missing measurement, the measurements of the unscheduled visits occurring between this particular visit and the two adjacent visits will be used to assign the analysis value. The closest unscheduled visit value that is not assigned to previous visits will be assigned to this nominal visit.

6.2 Handling of Dropouts, Missing Data, and Outliers

Missing values on FVC, DL_{CO} and DL_{CO} corrected for hemoglobin, HRCT analysis variables, [redacted] at Visit 14 (Day 169) will not be imputed. In situations where the efficacy endpoints are missing, all available data will be analyzed with a mixed-effects model for repeated measures (MMRM). To evaluate robustness of results, sensitivity analyses will be performed by imputing missing data using statistical modelling of available data.

Incomplete dates (partial or missing dates) for start date of AEs will be imputed and used to determine treatment-emergent status as follows:

- If the start date of an AE is completely missing, the first dosing date (Day 1) and time will be used for the imputation and the AE will be considered treatment-emergent.
- If the start date of an AE is missing day and month:
  - If the year of the AE start date is the year of the first dosing date, the month and day will be imputed using the month and day of first dosing date;
  - Otherwise, the month and day will be imputed as January 1.
- If the start date of an AE is missing the day only:

  - If the year and month of the AE start date is the same as the year and month of the first dosing date, the day will be imputed using the day of first dosing date;
  - Otherwise, the day will be imputed as the first day of the month.
- If an imputed AE start date is later than the corresponding AE end date, the imputed AE start date will be replaced with the AE end date.

AEs with missing relationship (related or not related) to study treatment will be treated as related AEs in summaries of AEs by relationship to study treatment.

Partial dates with day or day and month missing for concomitant medications date will be imputed as follows:

- If the year and month are present and the day is missing, set the start date as the first day of the month, and set the end date as the last day of the month as applicable.
- If the year and day are present and the month is missing, set the month to January as the start date, and set month to December as the end month as applicable.
- If the year is present and the month and day are missing, set January 1 as the start date, and set December 31 as the end date as applicable.
- Completely missing dates will not be imputed.
- If the start date is completely missing and the end date is on or after the first dosing date, the medication will be classified as concomitant; if the end date is missing, the medication will be classified as ongoing. Medications for which both the start and end dates are missing will be classified as concomitant.

7. Statistical Methods

7.1 General Principles

[redacted]

Efficacy data will be summarized and analyzed on the ITT population and PP population. Safety and treatment compliance data will be summarized based on the SAF population. Demography and other baseline characteristics data will be summarized based on the SAF population.

Baseline is defined as the last scheduled or unscheduled value assessed on or before study day 1, prior to the first dose of study treatment, including pre-medication unless otherwise indicated. Assessments carried out on day of first dose administration are considered to have taken place before the dose administration, if

the corresponding times have not been recorded. Measurements that are obtained after the first date of study treatment will be considered post-baseline values. Change from baseline is defined as (post-baseline value – baseline value).

Time-to-event endpoints will be summarized using Kaplan-Meier (KM) method to estimate the median, and the 25th and 75th percentiles.

The following principles will be applied to all TFLs unless otherwise stated:

Principle	Value
Treatment arm labels and order presented	1. Placebo 2. ND-L02-s0201 45 mg 3. ND-L02-s0201 90 mg 4. Total (if applicable)
Tables	Data in summary tables for safety will be presented by treatment arm, and Total, and visit (where applicable). Data in summary tables for efficacy will be presented by treatment arm.
Listings	All data collected presented by treatment arm, subject, and visit date (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of subjects (n), mean, standard deviation, median, minimum, maximum
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator for percentages	By-visit summaries: number of subjects with non-missing data at the visit assessed in the analysis population of each treatment arm; Other summaries: Number of subjects in the analysis population of each treatment arm, unless specified otherwise.
Include "Missing" as category	Included for demographics and other baseline characteristics when the number of missing is greater than zero for at least one treatment arm. Missing post-baseline values will not be summarized, unless otherwise specified.
Display for percentage	One decimal place, except for 100%
Display for 0 percentages	blank
Display to one more decimal place than collected value	Mean, Median

Principle	Value
Display to two more decimal places than collected value	Standard Deviation Confidence interval
Display to p-value	P-values will be rounded to 3 decimal places. P-values less than 0.0005 (e.g. 0.0002) will not be rounded to 3 decimal places (e.g. 0.000) but instead be displayed as <0.001.
Date Format	DDMMMYYYY
Statistical Analysis	All statistical tests will be conducted at the 2-sided, 0.05 level of significance. There will be no adjustment for multiplicity.

7.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by treatment arm and overall for all randomized subjects and will include the number and percentage of subjects:

- randomized;
- randomized by randomization stratification factor (i.e., standard of care at enrollment);
- included in each analysis population (SAF, ITT, PK1, PK2, and PP).
- completed the study
- discontinued treatment
- primary reason for discontinuation of treatment
- terminated early from the study (terminated before Visit 8 or after visit 8) including early termination due to COVID-19 pandemic.
- primary reason for early termination.

7.3 Protocol Deviations

All protocol deviations will be listed. Important protocol deviations leading to exclusion from the PP population will be listed and summarized by treatment arm for the ITT population. Protocol deviations due to COVID-19 will be listed separately.

The deviations leading to exclusion from the PP population will be identified before data are unblinded.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment arm and overall for the SAF population. Standard descriptive statistics will be presented for the continuous variables of:

- age (years) [as reported in the eCRF];

- weight (kg);
- height (cm);
- body mass index (kg/m^2) [calculated as (weight/$height^2$) where weight is in kg and height is in m];
- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- body temperature (°C);
- pulse rate (beats/min);
- respiratory rate breaths (breaths/min);
- pulse oximetry (SPO_2) (%);
- forced vital capacity (FVC) in L;
- percent predicted FVC (%);
- forced expiratory volume in 1 second (FEV1) in L;
- percent predicted FEV1 (%);
- ratio of FEV1/FVC;
- diffusion capacity of the lung for carbon monoxide (DLco) ;
- percent predicted DLco (%);
- hemoglobin corrected DLco;
- hemoglobin corrected percent predicted DLco (%);
- [redacted]
- duration of IPF since diagnosis to start of study treatment (months)
    - calculated as (first dose date-initial IPF diagnosis date+1)/30.4375
- GAP IPF Risk of Mortality: The risk of mortality (1-, 2-, and 3-year risk) will be derived based on baseline data at the start of the treatment period using the Gender, Age, and Physiology (GAP) methodology described in Ley et al, 2012 (Appendix 1);

The total counts and percentages of subjects will be presented for the categorical variables of:

- gender;
- childbearing potential for females
- race;
- ethnicity;
- BMI group [Underweight (below 18.5); Normal (18.5 - 24.9); Overweight (25 - 29.9); Obese (30 and above)]
- smoking history(yes/no)
    - If smoking history is yes, active smoker(yes/no)
- background standard of care (nintedanib, pirfenidone, none);
- [redacted]
- [redacted]

- GAP IPF Stage: The IPF stage will be derived based on baseline data at the start of the treatment period using the Gender, Age, and Physiology (GAP) methodology described in Ley et al, 2012 (Appendix 1);

No formal tests of statistical significance will be performed on the demographic and baseline data.

7.4.1 Medical History

Medical history will be coded using the lasted version of Medical Dictionary for Regulatory Activities (MedDRA), per the Data Management Plan, throughout the study. All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for the SAF population by system organ class (SOC) and preferred term (PT) for each treatment arm and overall.

7.4.2 Previous and Concomitant Medications

Medications including COVID-19 vaccination received prior to or concomitantly with study treatment will be coded using the lasted version of WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) Classification codes, per the Data Management Plan, throughout the study. Only medications taken within 14 days before Visit 1a through end of study will be included in summary table and listing.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken and ended within the interval from 14 days before Visit 1a up to the earliest of 24 hours before Visit 1a or date of informed consent.
- Concomitant medications are those taken on or after the earliest of 24 hours before Visit 1a or date of informed consent. Medication taken prior to but ongoing after the earliest of 24 hours before Visit 1a or date of informed consent will be considered concomitant medication.

If a medication cannot be classified as "prior" or "concomitant" for missing/incomplete dates, it will be classified as both prior and concomitant.

Prior medications and concomitant medications will be listed together and summarized separately for SAF populations for each treatment arm and overall.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and preferred term. Tables will be sorted in descending overall frequency by ATC-Level 2, ATC-Level 4, and preferred term, and then alphabetically.

7.5 Efficacy

7.5.1 Primary Efficacy Analysis

No primary efficacy endpoint is identified in the study protocol. Analyses of secondary endpoints for biological activity are described in Section 7.5.2.

7.5.2 Secondary Efficacy Analysis

7.5.2.1 Analyses of FVC

Values of FVC variables described in Section 3.4.1 will be summarized with descriptive statistics by treatment arm and visit for the ITT Population. The summary will include FVC (or percent predicted FVC) values, the change and percentage change from baseline to each post-baseline visit for each parameter. Results from unscheduled visits will not be included in summary tables, but will be included in subject-level listings and statistical model.

A random coefficients model will be used to analyze the rate of decline in FVC (L) from baseline to Visit 14 (Day 169) as well as the absolute change from baseline in FVC at Visit 14 in the ITT Population. [redacted]

Reporting of model results will include the estimated mean change from baseline, adjusted for baseline FVC and standard of care, at each timepoint [redacted] with corresponding 95% CIs. In addition, mean slope (rates of change) of FVC from baseline to Visit 14 (Week 24) for each treatment arm will be estimated along with 95%CIs. Treatment differences between mean slopes and corresponding p-values will be presented. No adjustments for multiple comparisons will be made. Spaghetti plots of individual FVC (L) data over time will be produced for each treatment arm with estimated means from the random coefficient model and 95% CIs at each timepoint [redacted] superimposed.

Similar analysis will be repeated for FVC (L) relative change from baseline, absolute and relative change from baseline for percent predicted FVC (%FVC).

Study treatment response is defined as a decline in FVC (L and % of predicted) of no more than 10% in the relative change at Visit 14 that is calculated as:

$$Change\ in\ FVC\ L\ (\%) = \frac{(FVC\ L\ at\ Visit\ 14 - \ FVC\ L\ at\ Baseline)}{FVC\ L\ at\ Baseline} * 100\%$$

The change in FVC % of predicted (%) will be calculated as:

$$Change\ in\ FVC\ \%\ of\ predicted\ (\%) = \frac{(FVC\ \%\ of\ predicted\ at\ Visit\ 14 - \ FVC\ \%\ of\ predicted\ at\ Baseline)}{FVC\ \%\ of\ predicted\ at\ Baseline} * 100\%$$

A positive value indicates improvement. Number and percent of subjects responding to treatment will be summarized.

The number and percent of subjects within each treatment arm showing an improvement, and subjects showing a decline of 0% to ≤5%, >5% to ≤10%, and >10% at Visit 14 (day 169) will be summarized by treatment arm. Subjects with an FVC response is defined as improvement in FVC or a decline of ≤10% from baseline FVC value.

7.5.2.2 Analyses of DLco

Values of DLco variables described in Section 3.4.2 will be summarized with descriptive statistics by treatment arm and visit for the ITT Population. The summary will include the absolute and percent change from baseline to each post-baseline visit for each parameter. Results from unscheduled visits will not be included in summary tables or statistical models, but will be included in subject-level listings.

DLco corrected for hemoglobin and DLco not corrected for hemoglobin will be analyzed similarly as FVC as described in section 7.5.2.1.

7.5.2.3 Analyses of HRCT

Values of HRCT variables described in Section 3.4.3 will be summarized with descriptive statistics by treatment arm and visit for the ITT Population. The summary will include the change from baseline to Visit 14 (or ET) for each parameter. Results from unscheduled visits will not be included in summary tables or statistical models, but will be included in subject-level listings. In addition, subjects who have visit 14 assessment and subjects who withdraw from treatment before visit 14 and have only ET assessment will be summarized separately for each HRCT variable.

The qualitative overall change in ILD from baseline to Visit 14/ET will be analyzed using the Kruskal-Wallis (KW) test. The test statistic and p-value from the KW test will be reported along with the pairwise comparisons of each active treatment arm with placebo.

A random coefficients model will be used to analyze the rate of change in the quantitative QLF score from baseline to Visit 14 as well as the absolute change from baseline at Visit 14. The model will include QLF score as the dependent variable, background standard of care, treatment, time and the interaction of treatment*time and baseline QLF score as fixed effects, and subject and subject*time as random effects. Subjects with missing values at Visit 14 will not be imputed for the analysis. The unstructured covariance model (UN) will be used to estimate the variance and covariance of random slopes and intercepts. If the computational algorithm fails to converge, the variance components (VC) covariance structure will be used for the analysis.

Reporting of model results will include the estimated mean change from baseline, adjusted for baseline QLF and standard of care, at Visit 14 with corresponding 95% CIs for each treatment arm. In addition, mean slope (rate of change) of QLF from baseline to Visit 14 for each treatment arm will be estimated along with 95% CIs. Treatment differences between mean slope and corresponding p-values will be presented. No adjustments for multiple comparisons will be made. The analysis will be repeated for subjects who have visit 14 assessment and subjects who withdraw from treatment before visit 14 and have only ET assessment. Spaghetti plots of individual QLF data over time will be produced for each treatment arm with estimated means from the random coefficient model and 95% CIs at Visit 14 superimposed.

Similar analysis will be repeated for relative change of QLF from baseline (derived as 100*(QLF score at Visit 14/ET-Baseline QLF score)/Baseline QLF score).

Other quantitative HRCT variables including ground glass opacity, reticulation, honeycombing, normal lung, and emphysema will be analyzed similarly as QLF score.

7.5.2.4 Analysis of Time to First IPF Exacerbation or Death

Time to first IPF exacerbation or death is defined as the time from start of study treatment to first acute exacerbation of IPF which is determined by the investigator (Adverse event CRF, AE preferred term equal to Idiopathic pulmonary fibrosis) or death for each subject. Subjects who do not experience acute exacerbation of IPF will be censored to the last known alive date.

The analysis of time to first IPF exacerbation or death of each active treatment arm versus placebo will be performed using a log-rank test stratified with standard of care to generate p-value for each comparison. Median time to first IPF exacerbation and corresponding 95% CI as well as proportion of subjects without the event at 8-week interval will be summarized for each treatment arm using the Kaplan-Meier (KM) analysis. KM plot of time to first IPF exacerbation will also be presented by treatment. In addition, the hazard ratio and 95% CI will be calculated from a stratified Cox proportional hazards model that includes standard of care as the strata.

The rate of acute IPF exacerbation, which is defined as the number of patients with any acute IPF exacerbation divided by the total study duration (years) summed over patients in that treatment arm and then multiplied by 100 to present in terms of per 100 patient years, will be summarized by treatment arm. Tests of differences in rates between treatment arms will be assessed using chi-squared tests (χ^2) at the 2-sided, 0.05 level of significance. Corresponding exact 95% CIs of study treatment proportions and respective active ND-L02-s0201 differences from placebo will be estimated.

7.5.2.5 Other Secondary Analyses

The rates of hospitalization for respiratory ailments, which is defined as the number of patients with any hospitalization for respiratory ailments divided by the total study duration (years) summed over patients in that treatment arm and then multiplied by 100 to present in terms of per 100 patient years, will be tabulated by treatment arm. Tests of differences in event rate will be assessed using chi-squared tests (χ^2) at the 2-sided, 0.05 level of significance. Corresponding exact 95% CIs of study treatment proportions and respective active ND-L02-s0201 differences from placebo will be estimated. Time to hospitalization for respiratory ailments or death is defined as the time from start of study treatment to hospitalization for respiratory ailments or death for each subject. Subjects who do not experience hospitalization for respiratory ailments and have not died will be censored to last known alive date. The analysis of time to hospitalization for respiratory ailments or death of each active treatment arm versus placebo will be performed using a log-rank test stratified with standard of care to generate p-value for each comparison. Median time to hospitalization for respiratory ailments or death and corresponding 95% CI as well as proportion of subjects without the event at the 8- week interval will be summarized for each treatment arm using the Kaplan-Meier (KM) analysis. KM plot of time to hospitalization for respiratory ailments or death will also be presented by treatment. The hazard ratio and 95% CI will be calculated from a stratified Cox proportional hazards model that including standard of care as the strata.

Rate of mortality due to any cause, which is defined as the number of patients who died due to any cause, divided by the total study duration (years) summed over patients in that treatment arm and then multiplied by 100 to present in terms of per 100 patient years, will be analyzed similarly as the rate of hospitalization for respiratory ailments. In addition, overall survival which is defined as the time from start of study treatment to death due to any cause will be analyzed similarly as time to hospitalization for respiratory ailments. Any patient not known to have died at the time of analysis will be censored to the last known alive date.

Rate of deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death, which is defined as the number of patients with

any deterioration of IPF resulting in lung transplantation divided by the total study duration (years) summed over patients in that treatment arm and then multiplied by 100 to present in terms of per 100 patient years, will be analyzed similarly as the rate of hospitalization for respiratory ailments. In addition, time to deterioration of IPF resulting in lung transplantation or death defined as the time from start of study treatment to deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death will be analyzed similarly as time to hospitalization for respiratory ailments. Any patient not known to have IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death at the time of analysis will be censored to 12 weeks after the end of study treatment or the last known alive date, whichever is earlier.

7.5.3 Sensitivity Analysis

- **Multiple imputation assuming missing not at random (MNAR)**

Sensitivity analysis will be performed for secondary efficacy endpoints including change and percent change from baseline in FVC (L) and percent predicted FVC (%), change from baseline in DLco corrected for hemoglobin and DLco not corrected for hemoglobin, and change and percent change from baseline in quantitative HRCT variables using multiple imputations with missing data imputed prior to fitting the linear regression. An assumption of MNAR will be made based upon an approach using regression based multiple imputations with missing data for all subjects imputed from a regression model estimated from patients in the placebo arm who stay on until visit 14. SAS PROC MI and MIANALYZE will be used to generate 100 complete datasets and combine the results from each complete dataset analyzed using ANCOVA model with baseline value, treatment arm, and standard of care as covariates.

- **Excluding subjects with deviations**

All the secondary efficacy analysis described in section 7.5.2 will be repeated using the PP population.

7.5.4 Subgroup Analysis

Subgroup analysis will be conducted comparing both active treatment arms with placebo arm to assess consistency of treatment effects across potential prognostic factors.

The following subgroups of ITT population will be analyzed for the secondary efficacy endpoints:

- Standard of care (none vs. nintedanib vs. pirfenidone)
- Anti-fibrosis (none vs. nintedanib or pirfenidone)

- BMI (<30 vs. ≥30)
- GAP IPF Stage (I vs. II vs. III)
- Duration of IPF since diagnosis to start of study treatment (≤1 vs. 1<-2 vs. 2<-3 vs. 3<-4 vs. ≥4 year)
- Subjects who adhere to the protocol schedule vs. subjects who missed at least one treatment but continued treatment after the interruption vs. early terminated subjects (subjects did not miss any treatment before early termination)
- COVID-19 vaccination (not vaccinated vs. vaccinated prior to treatment start vs. vaccinated while on treatment)

More subgroup analysis may be done ad-hoc given feasible data support.

No adjustment to the significance level for testing will be made. For each subgroup level, the analysis will be as described in 7.5.2 except for subgroup analysis of standard of care, the standard of care covariate will be removed from the analysis model.

If there are less than 10 subjects across both treatment arms in comparison in a subcategory then only descriptive summaries will be provided.

Forest plots will be provided for the secondary efficacy analysis. For rate of decline in FVC (L) or FVC (%FVC) from baseline to Visit 14, the estimated mean slope difference and 95% CI will be summarized and presented on the forest plot for each subgroup category as well as the overall ITT population. For change from baseline in FVC (L), percent predicted FVC (%FVC), DLco corrected for hemoglobin, DLco not corrected for hemoglobin, and quantitative HRCT variables (as described in 3.4.3), estimated means difference and 95% CI will be summarized and presented on the forest plot for each subgroup category as well as the overall ITT population. If the model does not converge then only descriptive summaries will be presented.

For time to event analysis described in section 7.5.2.4 and 7.5.2.5, for each subgroup level of a factor, the hazard ratio (HR) and 95% CI will be calculated from a Cox proportional hazards model that includes treatment and presented on a forest plot. If there are too few events available for a meaningful analysis of a particular subgroup (less than 10 events across both treatment arms in comparison in a subcategory), the HR and 95% CI will not be created for the subgroup and only descriptive summaries (number of event and proportion of subjects with events) will be provided.

[redacted]

[redacted]

[redacted]

7.5.5.2 Other analyses

Analyses to compare treatment effect between the two active treatment arms may be conducted ad hoc if both low dose and high dose treatment arm shows significant results versus the placebo arm.

7.6 Safety

7.6.1 Extent of Exposure

Duration of exposure will be summarized descriptively as a continuous variable in days, and also in the following categories:

- 0 - <2 weeks (14 days);
- 2 - <4 weeks (28 days);
- 4 - <6 weeks (42 days);
- …;
- 20 - ≤23 weeks (161 days)

The number and percent of subjects who received the premedication will be summarized by visit and overall and treatment arm. The volume and dosage for study treatment infusion will be summarized descriptively by visit or overall and treatment arm.

The number and percent of subjects who have at least 1 infusion interruption, and number and percent of subject who have at least 1 infusion interruption not resumed at any visit as documented in the eCRF will be summarized by visit or overall and treatment arm.

The number of infusion interruptions per subject will be summarized both as a continuous variable using descriptive statistics, and as a categorical variable (categories: 0, 1, and ≥2) by visit or overall and treatment arm. Reasons for the infusion interruptions will also be presented. A reason that was recorded multiple times at different visits for one subject will be counted once for this subject for overall summary. In addition, the number of subjects who have at least 1 infusion interruption resumed at any visit, and the duration of such interruptions will be summarized. A listing will be provided for subjects with any infusion interruptions.

Treatment compliance will be summarized descriptively by treatment arm for the SAF population. The following percentage compliance categories will also be summarized:

- <60%
- 60 – 79%
- 80 – 100%
- >100%

Subjects who missed 1 or 2 doses of study treatment due to COVID-19 pandemic as permitted by protocol will be summarized separately for exposure duration, total number of doses, and treatment compliance. A swimmer plot will be created for all scheduled study treatment administration from Day 1 to end of study. Events of IP administration, skipping study treatment due to COVID-19 pandemic, or treatment termination will be included.

7.6.2 Adverse Events

All AE data will be listed. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of serious AEs (SAEs), AEs resulting in death, TEAEs leading to discontinuation of study treatment, and TEAEs of special interests will be produced.

An overview table will summarize the number of all TEAEs, the number and percentage of subjects with at least one of the following TEAEs, by standard of care (none, nintedanib, pirfenidone), treatment arm and overall, where subjects with more than one TEAE in a particular category are counted only once in that category:

- any TEAE;
- any TEAE by relationship (definite, probable, possible, unlikely, none);
- drug-related TEAE;
- any TEAE by severity (mild, moderate, severe, life-threatening consequences, death);
- TEAE leading to study treatment interrupted;
- TEAE leading to study treatment withdrawn;
- TEAE leading to discontinuation from the study;
- Treatment-emergent SAEs;
- drug-related SAE;
- AEOIs
- Each AEOIs
  - [redacted]
  - [redacted]
    - Respiratory adverse events
    - Acute exacerbation of idiopathic pulmonary fibrosis
- TEAE leading to death;

This summary table will be repeated for each of the following COVID-19 vaccination status:

- Subjects vaccinated prior to start of study treatment
- Subjects vaccinated while on treatment
- Subjects not vaccinated

The number and percentage of subjects reporting each TEAE will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment arm and overall for the SAF population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- TEAEs, by SOC and PT;
- TEAEs by PT; this table will also be repeated for each COVID-19 vaccination status as described above;
- TEAEs with frequency >10% in one or more treatment arms by PT;
- TEAEs related to the study treatment, by SOC and PT;
- TEAEs related to the study treatment, by PT;
- TEAEs by relationship to the study treatment, by SOC and PT;
- TEAEs related to pre-medication, by SOC and PT;
- TEAEs by maximum severity and PT;
- TEAEs related to the study treatment by maximum severity and PT;
- TEAEs leading to the study treatment interruption, by SOC and PT;
- TEAEs leading to the study treatment withdrawn, by SOC and PT;
- TEAEs related to the study treatment leading to the study treatment withdrawn, by SOC and PT;
- Serious TEAEs, by SOC and PT;
- Serious TEAEs related to the study treatment, by SOC and PT;
- Serious TEAEs with frequency >5% in one or more treatment arm by PT;

In the above summaries, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. AEs with missing severity will be included as severe in the overall count of subjects with AEs, but will not be included in the counts of subjects with AEs within a SOC or PT.

The number and percentage of subjects with at least 1 treatment-emergent AEOI, and each type of treatment-emergent AEOI will be summarized. The number and percentage of subjects reporting at least 1 treatment-emergent AEOI will be summarized by SOC and PT for the following in the SAF population:

- treatment-emergent AEOI by SOC and PT;
- serious treatment-emergent AEOI by SOC and PT;
- treatment-emergent AEOI leading to study treatment interruption by SOC and PT;
- treatment-emergent AEOI leading to study treatment withdrawn by SOC and PT.

[redacted]

No statistical comparisons of AEs between treatment arms will be performed.

7.6.3 Laboratory Evaluations

All laboratory data will be reported in conventional units. Reference range will be presented in the listing. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

Laboratory data will be summarized by treatment arm, overall, and visit using standard descriptive statistics for the SAF population. Changes from baseline will also be summarized.

For hematology and serum chemistry, shift tables presenting movement in and out of reference range from baseline to each scheduled post-baseline visit will be provided for each treatment arm.

[redacted]

For subjects with abnormal baseline values, the following summary will also be created:

- ALT or AST >2x Baseline or total bilirubin >1.5x Baseline
- ALT or AST >2x Baseline and a concomitant total bilirubin >2x Baseline
- If baseline measurements were <2.5x ULN: ALT or AST >5x baseline

For all subjects, number of subjects with elevated ALT or AST and Total Bilirubin following the Hy's Law (ALT or AST >3X ULN and Total Bilirubin >2X ULN) will be summarized. The onset date of ALT or AST elevation should be prior to or on the date of Total Bilirubin elevation. Additionally, Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plots will be generated for peak total bilirubin vs peak ALT and peak AST.

Box-plots of the absolute value of lab tests at each scheduled visit will be provided. All lab tests results will also be listed.

7.6.4 Vital Signs and Pulse Oximetry

Vital signs and SpO_2 data and changes from baseline in vital signs and SpO_2 will be summarized by visit using standard descriptive statistics for the SAF population. For visits that have vital sign data collected before, during, and after study treatment infusion, the pre-infusion vital sign will be included in the summary table. A table for change from pre-infusion will also be provided for the visits with multiple vital sign measurements before, during, and after study treatment infusion. Vital sign findings per subject will be detailed in a listing.

7.6.5 Electrocardiograms

The ECG measurements and changes from baseline in ECG will be listed and summarized by treatment arm and visit using standard descriptive statistics for the SAF population. For visits (visit 4 and visit 8) where both pre-infusion and post-infusion ECG are measured, the pre-infusion ECG will be included in the summary table of change from baseline. In addition, difference of ECG measurements between pre-infusion and post-infusion of study treatment for visit 4 and visit 8 will be listed and summarized.

The number and percent of subjects with the averaged QT interval (msec) and Fridericia's corrected QT (QTcF) interval (msec) meeting below criteria will be summarized by treatment arm for baseline and post-baseline visits:

- QT interval >450 msec;
- QT interval >480 msec;
- QT interval >500 msec;
- QTcF interval >450 msec;
- QTcF interval >480 msec;
- QTcF interval >500 msec.

In addition, the number and percentage of subjects with average QT or QTcF interval meeting the following criteria will be summarized by treatment arm for each post-baseline visit:

- change from baseline in QT interval >30 msec;
- change from baseline in QT interval >60 msec;
- change from baseline in QTcF interval >30 msec;
- change from baseline in QTcF interval >60 msec.

ECG overall interpretation (normal, abnormal not clinically significant and abnormal clinically significant) will be presented as a categorical summary by treatment arm and scheduled visit. The ECG measurements and changes from baseline in ECG Shifts from baseline (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) at each post-baseline visit will be presented.

7.6.6 Physical Examination

Physical examination results (normal/abnormal) will be summarized for each visit by treatment arm. Details of abnormalities will be listed for each subject.

7.6.7 Other Safety Analyses

[redacted]

Serology tests of HIV, HIV-1 RNA, hepatitis B, and hepatitis C as well as SARS-COV-2 will be listed.

[redacted]

7.6.9 Impact of COVID-19 Pandemic

The impact of COVID-19 pandemic on subject participation in the study will be summarized by treatment arm (including a total column) and visit with the number and percentage of subjects whose planned study visit was not performed, partially performed, performed by telephone visit, or performed outside of the protocol-specified window. In addition, a summary of subjects who early terminated study treatment or the study due to COVID-19 also will be provided. The subject-level listing will be provided and it will include any alternative procedures used to collect data per the eCRF.

Listing of protocol deviations due to COVID-19 will also be provided.

7.7 Interim Analysis

No formal interim analyses are planned for this study.

8. Changes in Planned Analysis

The following changes from protocol specified statistical analyses are made in this SAP.

Section 3.2 and 7.5.2.4 The efficacy endpoint Time to first acute IPF exacerbation has been updated to Time to first acute IPF exacerbation and death to avoid dependent censoring.

Section 7.5.2.1, 7.5.2.2, 7.5.2.3, and 7.5.5 Analysis of change from baseline in FVC, DLco, HRCT QLF, [redacted] will be using random coefficient model instead of ANCOVA. The random coefficient model will handle missing data by making use of all available data include subjects with missing data and no missing value will be imputed.

Section 7.5.3 Sensitivity analysis of FVC will use multiple imputation instead of ANCOVA without missing value imputation.

[redacted]

[redacted]

Appendices

Appendix 1: GAP Algorithm for IPF Stage and Predicted Mortality

GAP IPF stage for each subject will be derived by summing the points in each of the following categories for each randomized subject:

Gender	**Points**
Male	0
Female	1
Age	
≤60	0
61-65	1
>65	2
Baseline FVC, % Predicted	
>75	0
50-75	1
<50	2
Baseline DLco*, % Predicted	
>55	0
36-55	1
≤35	2
Not Performed	3

*Corrected for hemoglobin

IPF stage for each subject will be assigned based on the total points as follows:

Sum of Points	**IPF Stage**
0-3	I
4-5	II
6-8	II

Risk of mortality will be derived using the following algorithm:

Step 1: Calculate S

S = [0.337 (GENDER) – 0.015 (FVC – 68.464) + 0.092 (AGE1 – 67.676) – 0.052 (AGE2) + 2.237 (DLco1) + 0.024 (DLco2)] x 0.909

Where:

1) GENDER =

a. 0.293 if the patient is male

b. –0.707 if the patient is female

2) FVC = FVC, % predicted at baseline

3) AGE1 = patient's age (years)

4) AGE2 = refer to the table below. Enter the value of AGE2 that corresponds to the patient's age.

AGE	AGE2	AGE	AGE2	AGE	AGE2	AGE	AGE2
≤50	0	60	0.236	70	6.345	80	22.043
51	0	61	0.408	71	7.625	81	23.739
52	0	62	0.648	72	9.009	82	25.435
53	0	63	0.968	73	10.481	83	27.130
54	0	64	1.378	74	12.027	84	28.826
55	0	65	1.890	75	13.632	85	30.522
56	0.002	66	2.516	76	15.280	86	32.217
57	0.015	67	3.266	77	16.959	87	33.913
58	0.051	68	4.153	78	18.652	88	35.609
59	0.121	69	5.183	79	20.348	89	37.304

5) DLco1 =

a. 0.921 if the subject could not do the DLco test

b. –0.079 if the subject could do the DLco test

6) DLco2 =

a. –50.549 if the subject could not do the DLco test

b. (49.451 – the subject's baseline DLco, % predicted) if the subject could do the test

Step 2: Calculate risk using S:

1-year risk = 100 x [1 – exp(–exp (S) x 0.225)]

2-year risk = 100 x [1 – exp(–exp (S) x 0.486)]

3-year risk = 100 x [1 – exp(–exp (S) x 0.768)]

Appendix 2: Schedule of visits

	Screening[a]		Treatment Period						EOT	Follow-Up	
Visit	**1a**	**1b**	**2**		**3**	**4**	**5, 7, 9, 11, 13 (Simple tests)**	**6, 8, 10, 12 (Detailed tests)**	**14 (or ET)**	**15**	**16**
Week	**-6 to -1**		**0**		**2**	**4**	**6, 10, 14, 18, 22**	**8, 12, 16, 20**	**24 (2 wk postdose)**	**28 (4 wk post V14/ET)**	**34 (10 wk post V14/ET)**
Study Day	**-42 to -7**		**1**	**2**	**15**	**29**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**169**	**197**	**239**
Allowable Window (days)[b]					**± 4**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Study Procedure											
Informed Consent	X[c]										
Eligibility	X	X	X								
Demographics and baseline characteristics	X										
Medical history	X										
Adverse events	X[d]	X	X	X[e]	X	X	X	X	X	X	X
IPF history and previous treatments	X										
Prior medications	X										
Concomitant medications	X[d]	X	X	X[e]	X	X	X	X	X	X	X
Physical examination (complete)	X								X		
Physical examination (abbreviated)[f]		X	X								
Height	X										
Weight	X								X		
12-lead ECG	X	X				X[g]			X		
Vital signs[h]	X	X	X		X	X	X	X	X	X	X
[redacted]											
Chemistry	X		X		X	X		X	X		X
Hematology	X	X[n]	X			X		X	X	X[n]	X
Urinalysis	X								X		X
Pregnancy test (urine) for WCBP[o]	X		X			X		X	X	X	X
[redacted]											
Serology (HCV Ab, HBsAg, HIV 1/2)	X										
SARS-CoV-2 test[r]	X										
Randomization			X								

	Screening[a]		Treatment Period					EOT	Follow-Up	
Visit	**1a**	**1b**	**2**	**3**	**4**	**5, 7, 9, 11, 13 (Simple tests)**	**6, 8, 10, 12 (Detailed tests)**	**14 (or ET)**	**15**	**16**
Week	**-6 to -1**		**0**	**2**	**4**	**6, 10, 14, 18, 22**	**8, 12, 16, 20**	**24 (2 wk postdose)**	**28 (4 wk post V14/ET)**	**34 (10 wk post V14/ET)**
Study Day	**-42 to -7**		**1 2**	**15**	**29**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**169**	**197**	**239**
Allowable Window (days)[b]				**± 4**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
[redacted]										
Premedication (optional)[w]			X	X	X	X	X			
Study treatment			X	X	X	X	X			

Abbreviations: [redacted] COVID-19 = coronavirus disease; [redacted] ECG = electrocardiogram; EOT = end-of-treatment; ET = Early Termination; [redacted] HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV 1/2 = human immunodeficiency virus type 1 or 2; [redacted] ICF = informed consent form; IPF = idiopathic pulmonary fibrosis; [redacted] QC = quality control; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted]; SOC = standard of care; [redacted]; V = Visit; WCBP = women of childbearing potential; [redacted]

Note: Refer to Section 18.6 of the protocol for guidance on clinical trial conduct relating to COVID-19.

[a] Screening begins with the first Visit 1a procedure (excluding signing the ICF) and may be shorter than 42 days. If possible, plan Visit 1b and schedule the [redacted] at the time of Visit 1a. To assure that an ineligible subject does not undergo an unnecessary [redacted] ALL Visit 1a procedures MUST be completed before any Visit 1b procedures may be started. [redacted]

[b] Subjects should be dosed on the study day listed in the Study Schedule (± 4 days for Visit 3 or ± 7 days for Visits 4 to 13), ensuring a minimum of 7 days between each dose. Assessments not associated with study treatment infusion may be performed on days other than the dosing day for scheduling purposes, as long as they are performed before the infusion.

[c] The ICF should be signed before Visit 1a to allow the site to instruct the subject to withhold bronchodilator use as required for the Visit 1a PFT (see Section 11.2.2 of the protocol) [redacted]

[d] Adverse event and concomitant medication collection will begin 24 hours before Visit 1a.

[e] On Day 2, study personnel will call subjects not returning to the site to collect any AEs and concomitant medications that may have occurred after leaving the site on Day 1.

[f] Other abbreviated physical examinations may be performed at the discretion of the Investigator on the basis of signs or symptoms. See Section 11.1.3 for more information.

[g] During Visit 4 (Day 29), ECGs will be performed once, within 30 minutes after the end of the study treatment infusion.

[h] Vital signs and SpO_2 will be measured at every study visit, except at Visit 2 (Days 2 and 3; subjects participating in the PK substudy will only have vital signs measured). On dosing days vital signs and SpO_2 will be measured thrice: once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication), midinfusion ± 5 minutes [redacted] and within 15 minutes after the end of the study treatment infusion. The frequency of monitoring vital signs may be increased as warranted by clinical management. See Section 11.1.4 and Section 11.2.1 of the protocol for more information.

[redacted]

[o] A positive urine pregnancy test will be followed up with a serum pregnancy test.

[redacted]

[r] Every effort should be made to test for SARS-CoV-2 virus or viral antigen at Visit 1a if testing is available. The test used should have regulatory approval for marketing and sample collection should be performed per the assay's specifications. Depending on the site and its location, options for subject testing may vary. Refer to Section 8.3.3 of the protocol for guidance on SARS-CoV-2 testing.

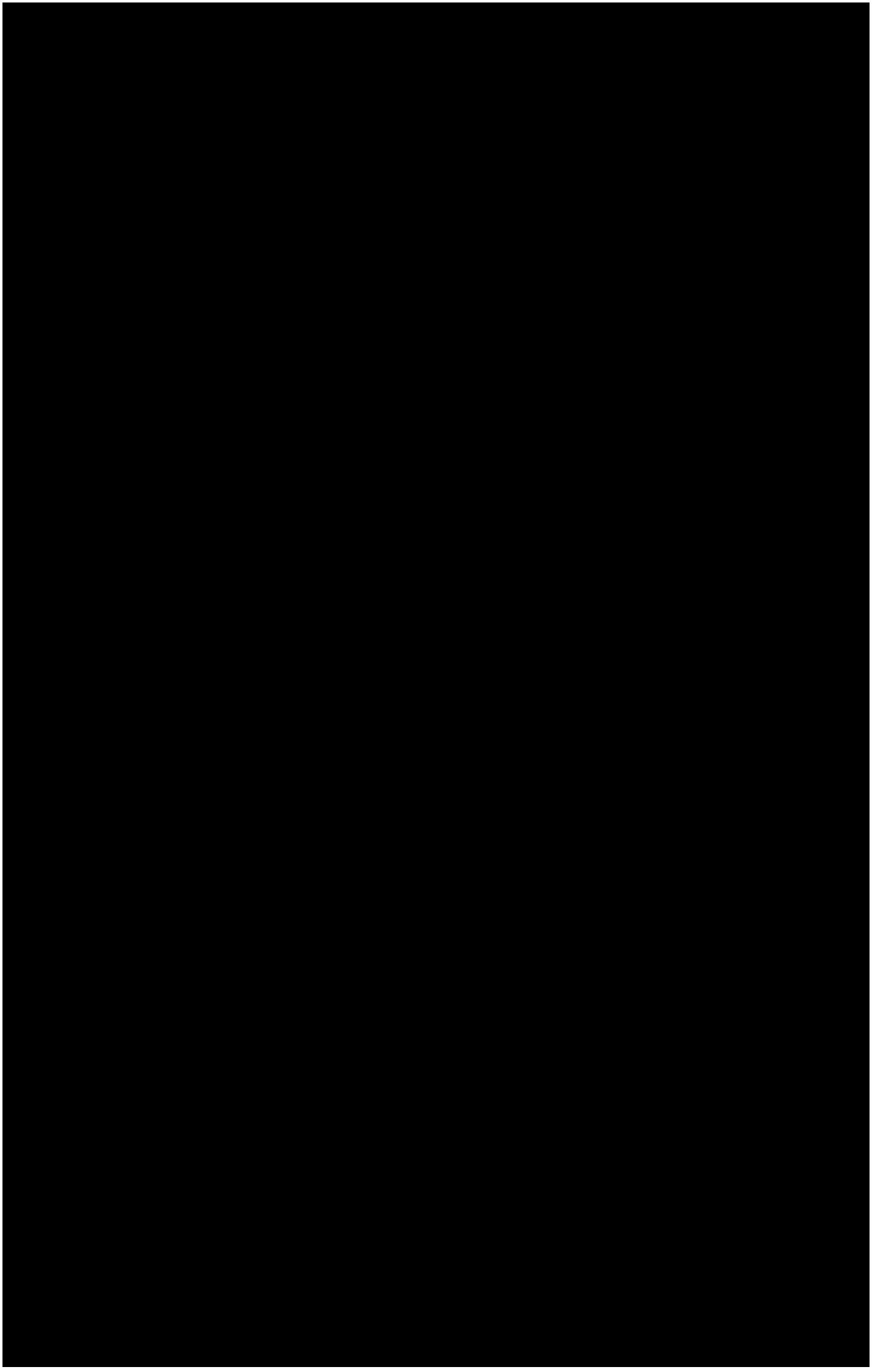
[redacted]

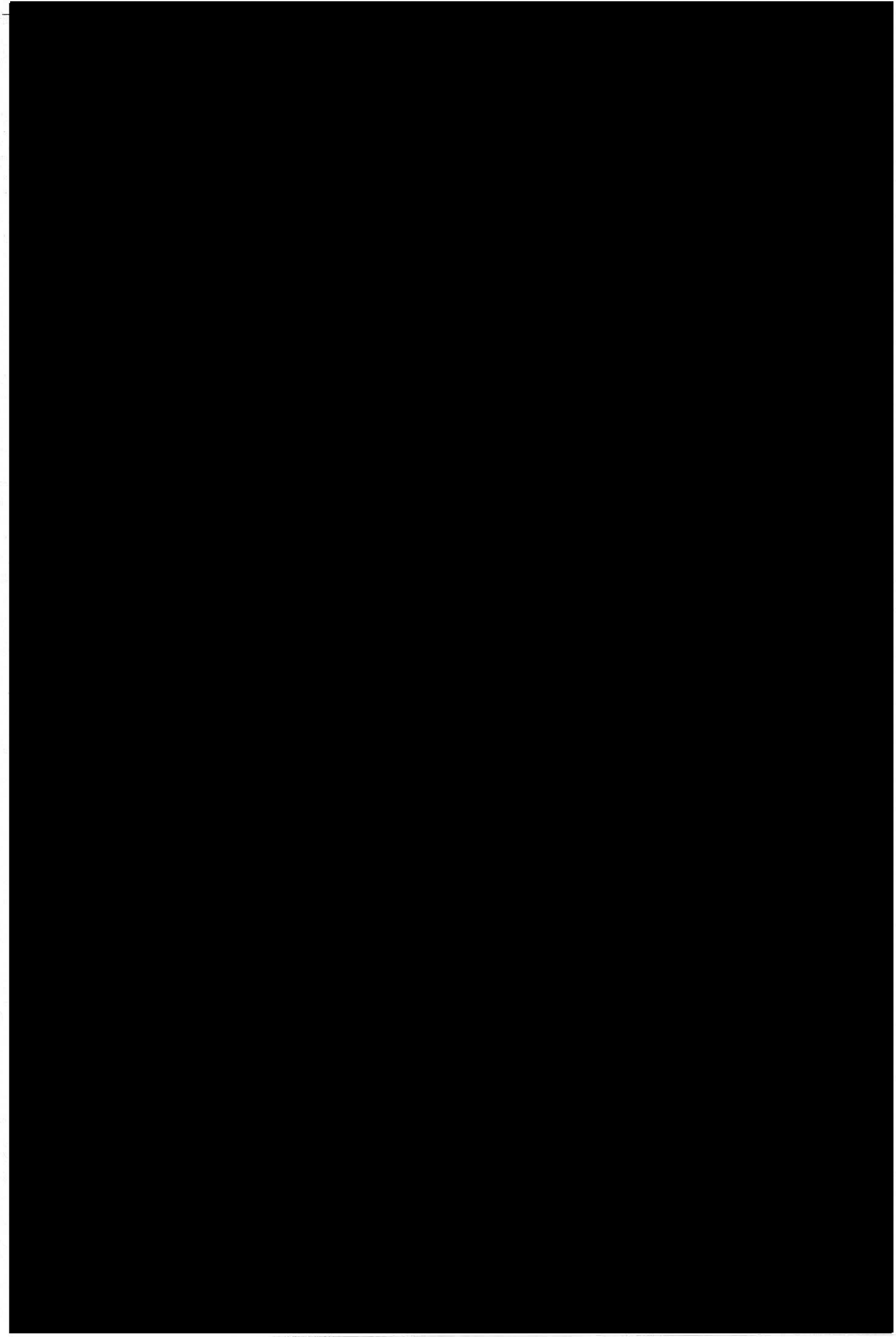
[w] Subjects may be premedicated to mitigate the risk of infusion-related reactions at the discretion of the Investigator (see Section 18.5 of the protocol).

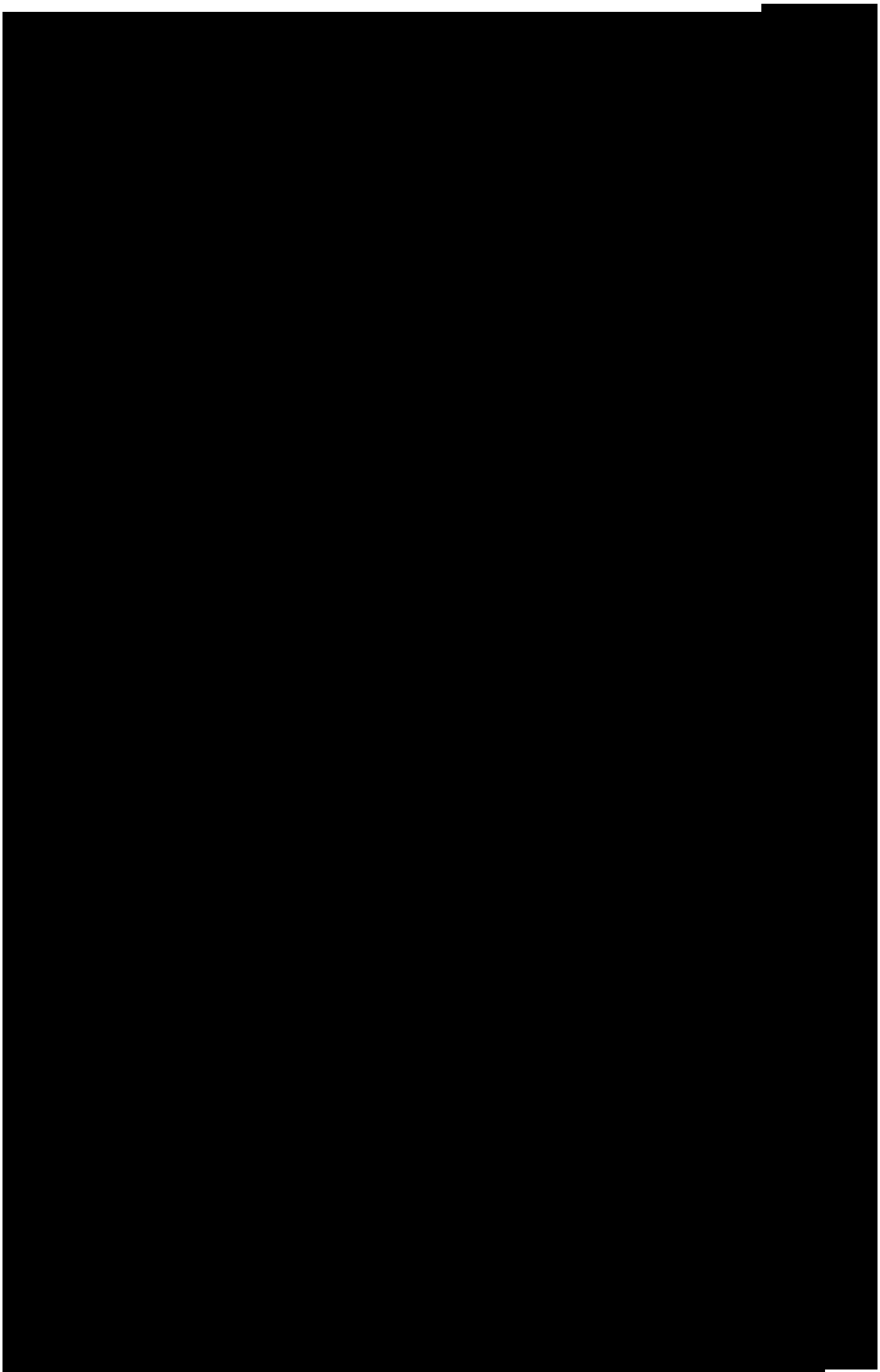
Appendix 3: FVC and %FVC Baseline Determination

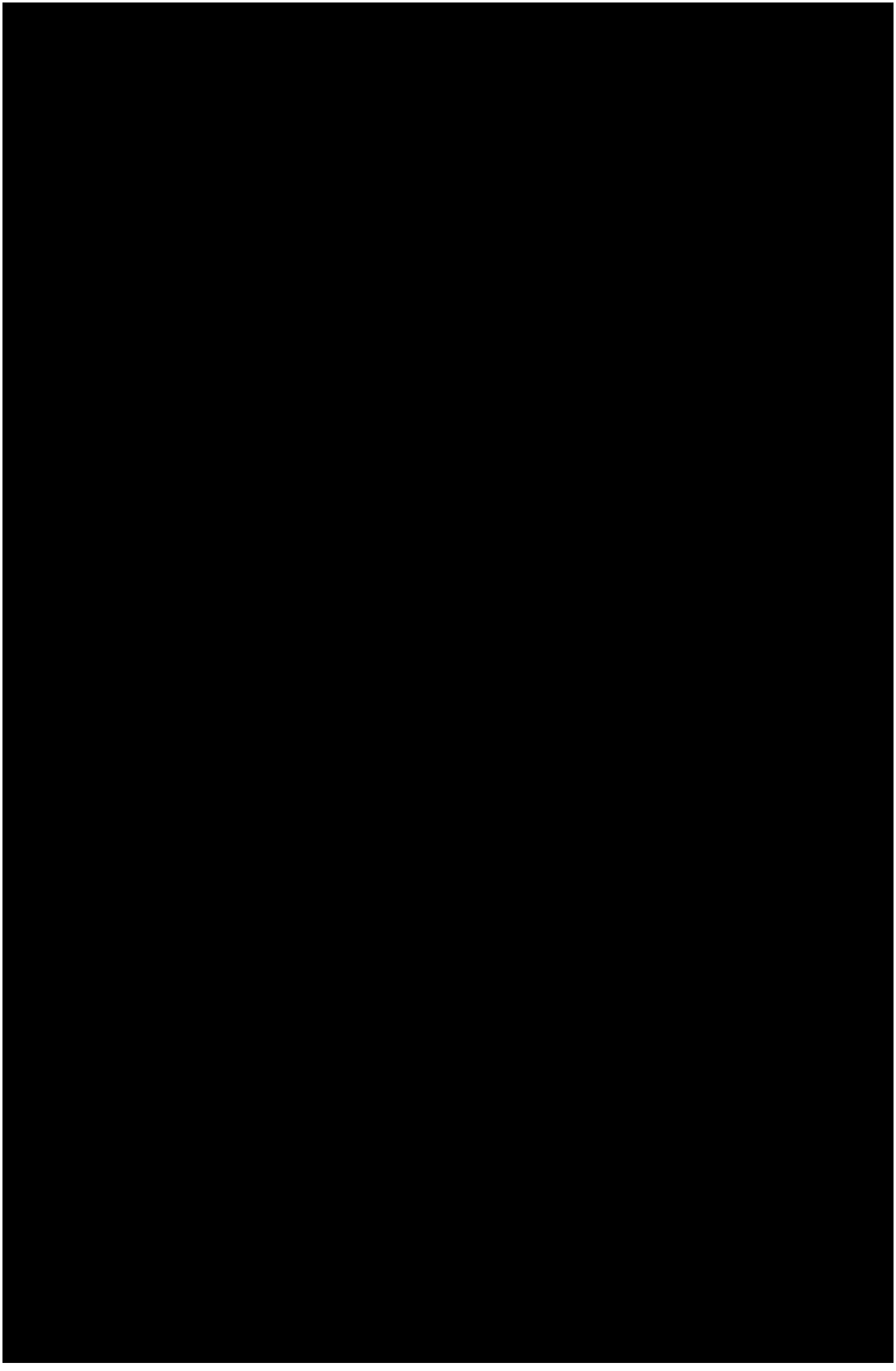
The baseline for FVC and %FVC will be determined as per the [redacted] Specification.

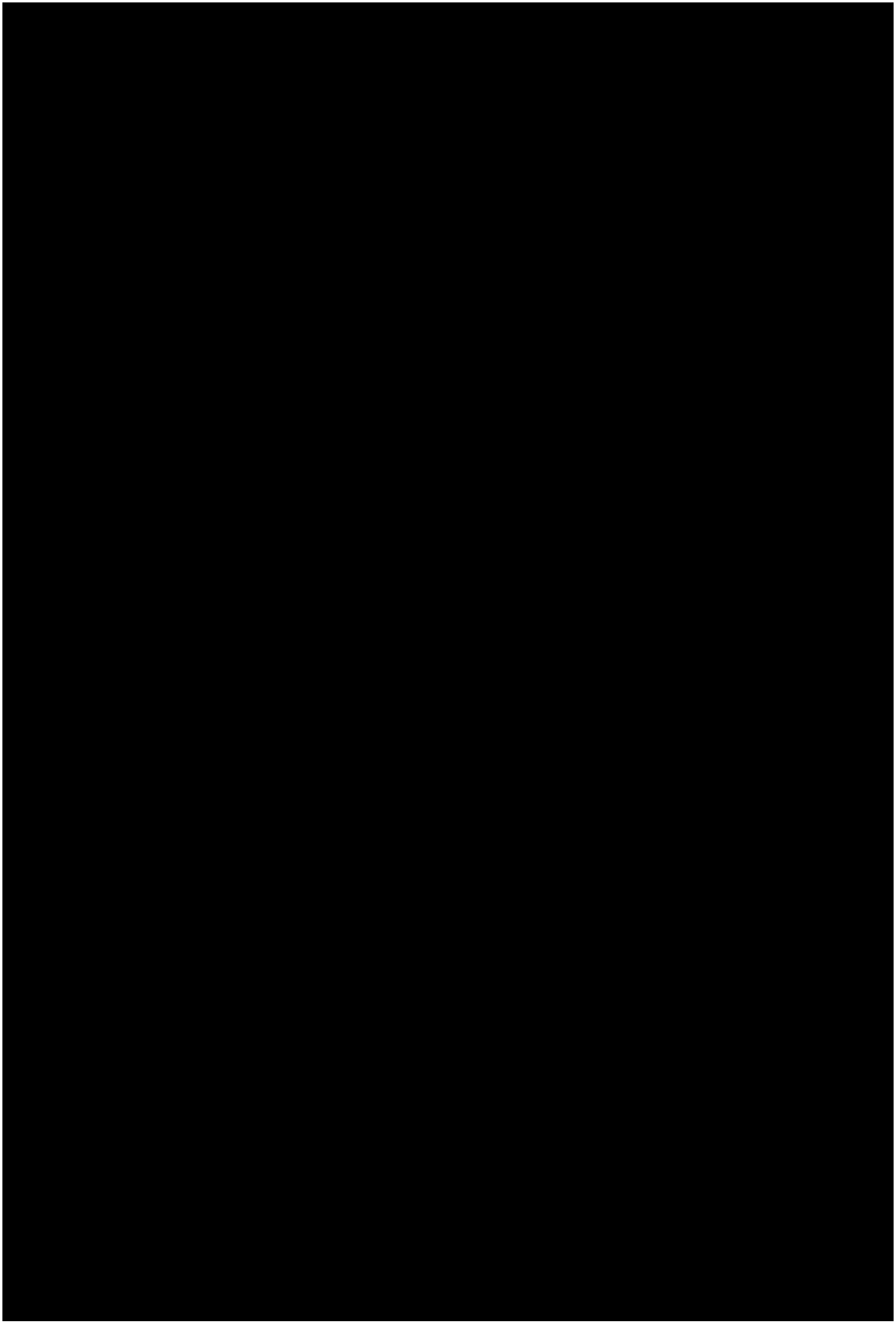
[redacted]

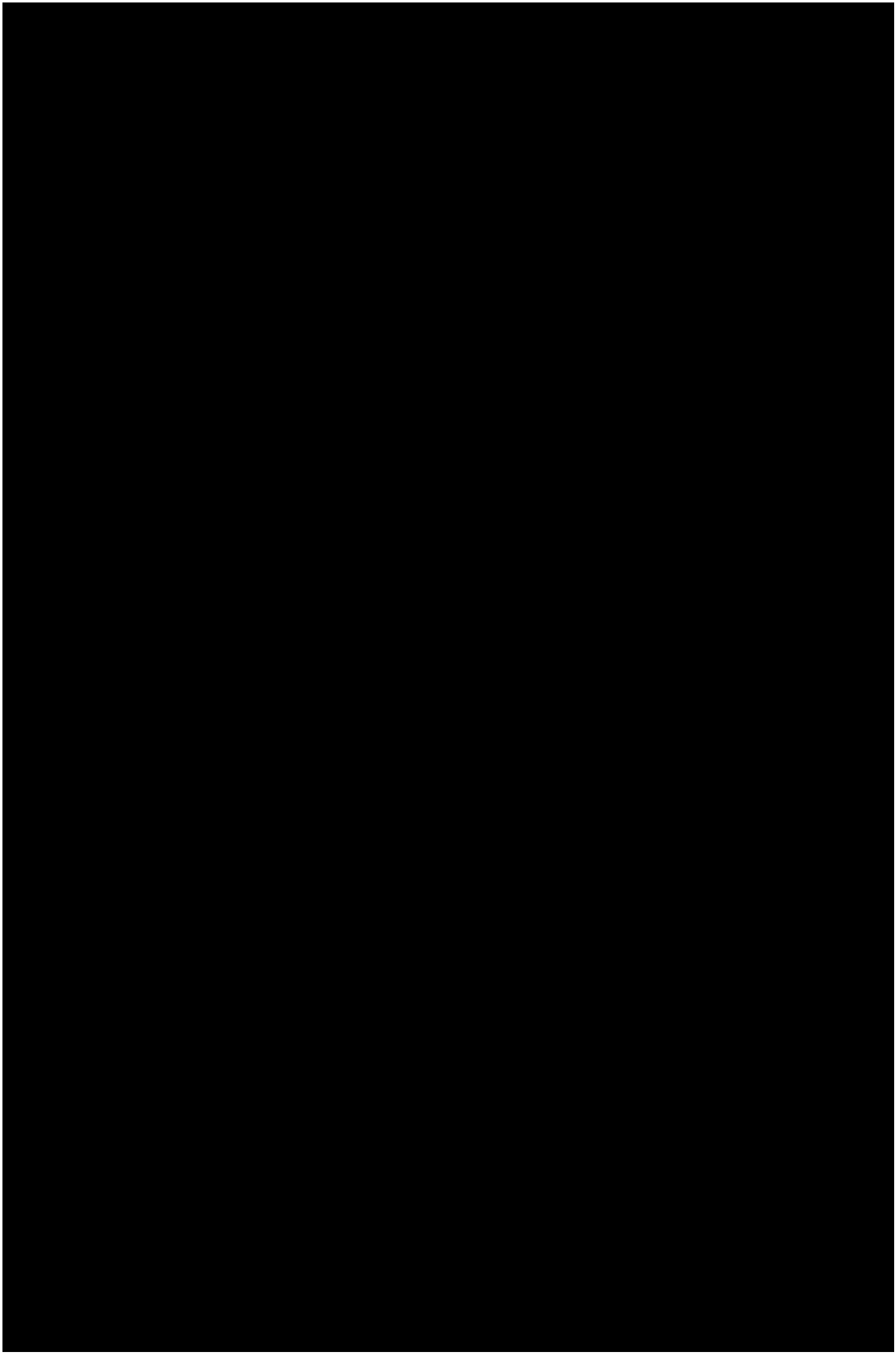


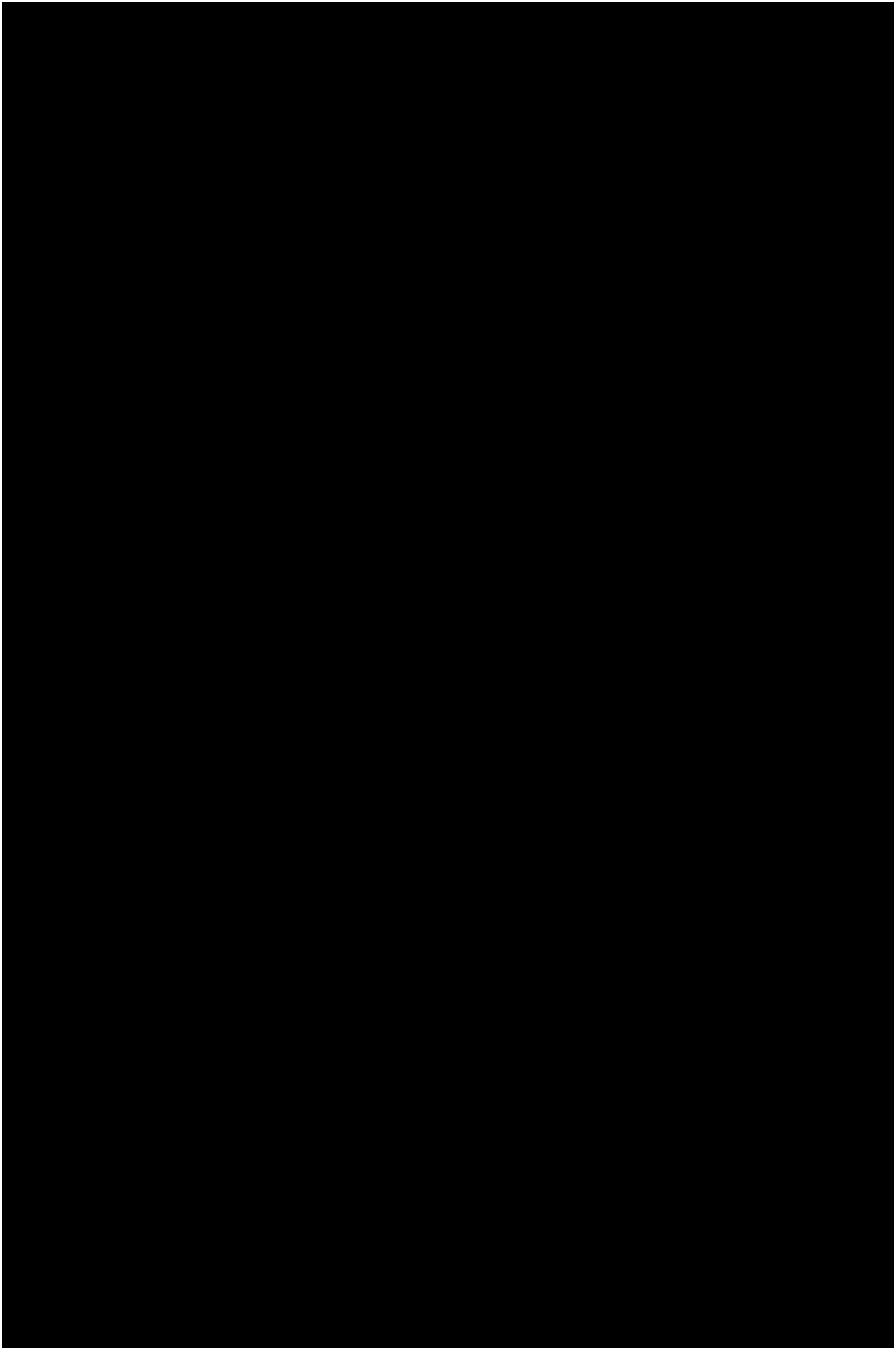


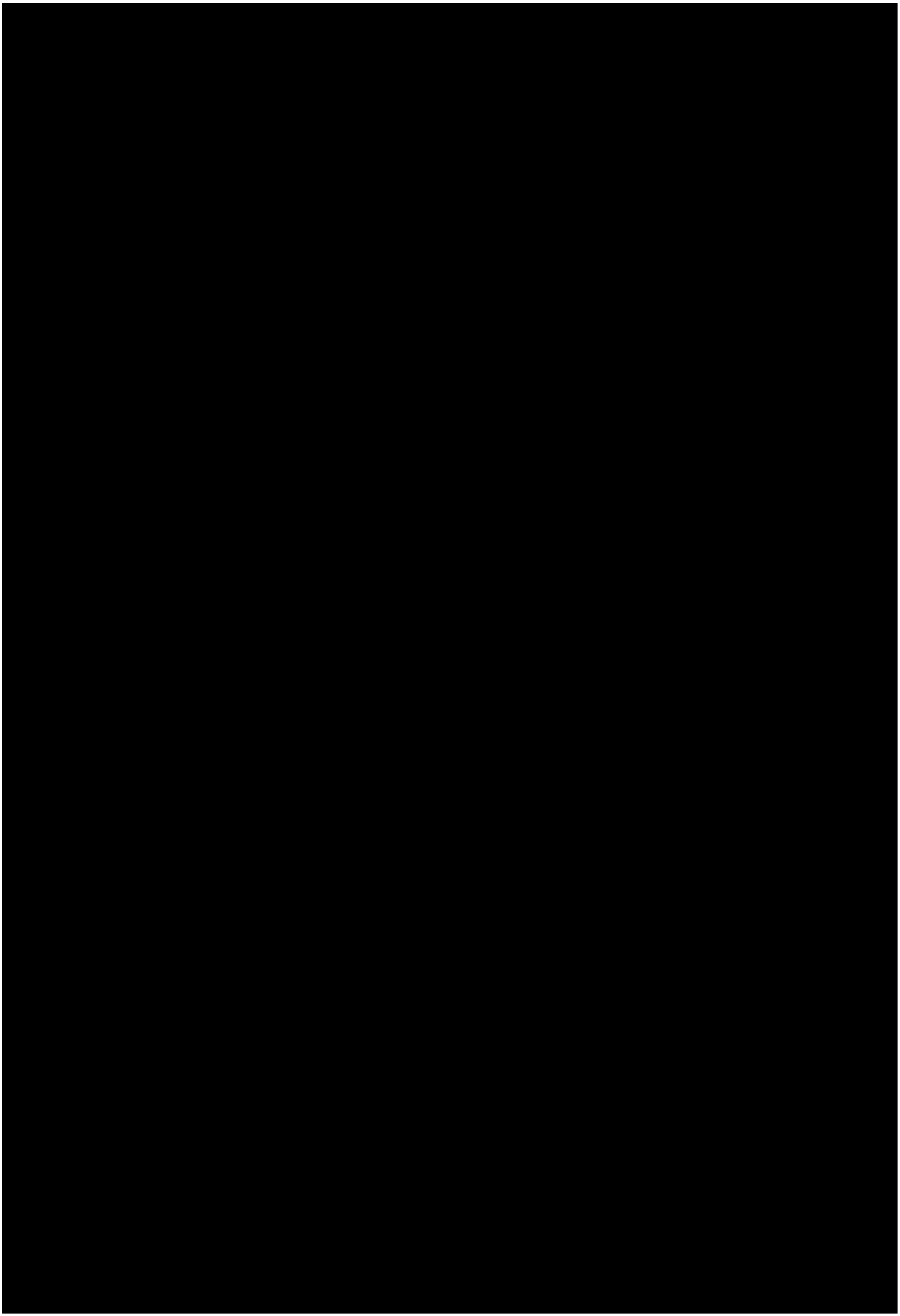












Appendix 4: HRCT Assessment

The qualitative and quantitative HRCT assessments are included in the [redacted] Independent Review Charter V 3.0.

[redacted]