TRIAL STATISTICAL ANALYSIS PLAN

c41233121-01

BI Trial No.:	1490-0005
Title:	A multi-center, longitudinal 12-week pilot study to evaluate cough severity and its impact, utilizing a next generation cough monitor, in participants with idiopathic pulmonary fibrosis (IPF) or Non IPF Pulmonary Fibrosis
Investigational Product(s):	[redacted]
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	09 APRIL 2024 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ANOVA	Analysis of variance
BMI	Body Mass Index
CC	Couth Count
CfB	Change from baseline
CTP	Clinical Trial Protocol
CV	Coefficient of Variation
ES	Enrolled Set
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
LOCF	Last Observation Carried Forward
OC	Observed Case
OR	Original Results
[redacted]	[redacted]
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
[redacted]	[redacted]

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.”

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

For the endpoint "Cough frequency and number of cough bouts at each of the activity levels (exertion): stationary/low, medium/high", activity levels will be categorized as:

- Low activity
- Medium activity
- High activity

"Stationary" activity represents non-wear time.

Only inspiratory crackles will be summarized for the endpoint "Lung sound events (potentially including, but not limited to, inspiratory crackles)

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoints as stated in the CTP are: Cough count per hour (CC/hr) measured over a 24-hour period at baseline visit, Week 4(V4), Week 8(V5), Week 12 (V6).

Note that these endpoints are the average CC/hour at each of the 4 visits.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable, there are no defined key secondary endpoints

5.2.2 Secondary endpoint(s)

Cough related endpoints:

- Change from baseline in CC/hr at Week 4, Week 8, Week 12.

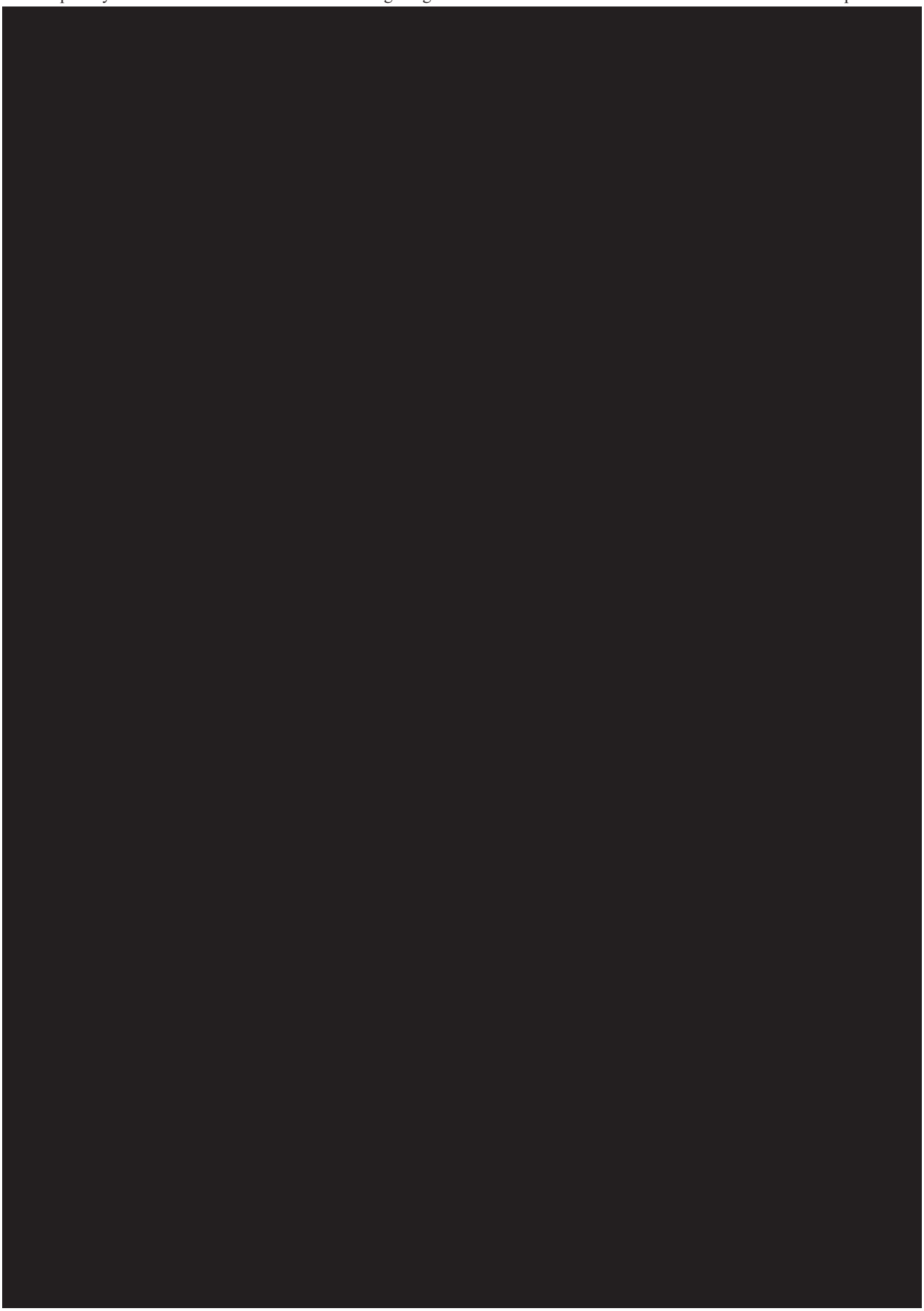
Spirometry related endpoints:

- FVC (mL) at baseline
- FVC (mL) at Week 12
- Change from baseline in FVC (mL) at Week 12

Study feasibility endpoints:

- Feasibility of remote cough data capture (defined as % of analysable data per 24-hour recording)
- Feasibility of hybrid study design (successful completion of all elements of remote visit)

[redacted]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Not applicable, patients did not receive treatment in this trial

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS. Other relevant documentation of details related to iPDs will be included in the CQM minutes

6.3 SUBJECT SETS ANALYSED

The subject analysis set used for reporting is defined as:

Entered Set (ES): those patients who were entered into the study.

The ES will be used for all types of endpoints including:

- Demographic/baseline endpoints
- Primary endpoints
- Secondary [redacted] endpoints
- Safety
- [redacted]

[redacted]

6.5 POOLING OF CENTRES

There will be no statistical model specified for the primary analysis, therefore pooling of centers is not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

The following approaches will be applied in this trial:

- The original results (OR) approach implies the presentation of data exactly as observed (not using time windows as described in Section 6.7 and not setting values to missing). OR analysis will be performed on parameters and endpoints for which it is not meaningful to apply any imputation rule for the replacement of missing values.

- Observed cases (OC) approach will include all collected data, without imputation for any missing data after applying the time windows as described in Section 6.7

Missing or incomplete AE dates are imputed according to BI standards.

Other partial start and stop dates, for example, concomitant medications, non-drug therapies, and IPF diagnoses will be imputed to enable subsequent calculation (but not for display) by the following approach:

- If the day of the end date is missing, then the end date is set to last day of the month (or to the patient's end of study participation from End of Study eCRF. if it is earlier than the last day of the month).
- If the day and month of the end date are missing then the end date is set to 31st of December of the year (or to the patient's end of study participation from End of Study eCRF, if it is earlier than the 31st of December of the year).

- If the day of the start date is missing the start date is set to first day of the month.
- If the day and month of the start date are missing then the start date is set to 1st January of the year.
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general baseline is defined as measurements collected at the Baseline visit. For [redacted] if the value at the Baseline visit is missing the value at the Screening visit will be used.

As this is a low-interventional trial without treatment or other intervention for cough, in cases where the first cough recording or in-office spirometry occurred after the Baseline visit (Visit 2) then the start date of the first cough recoding or first in-office spirometry visit will be considered the Baseline measurement and the time windows below will be applied to the subsequent visits using the respective baseline date as day 1.

Table 6.7: 1 Time windows for assignment of visits for statistical analysis

		Time windows (days)			
Visit name	Visit label	Planned day	Window (relative to planned day)	Start (inclusive)	End (inclusive)
V1	Screening	-7	n/a		
V2	Baseline	1	n/a	-7	1
V3	Day 3[a]	3	-1/+13	2	16
V4	Week 4 [a]	29	-12/+14	17	43
V5	Week 8[a]	57	-13/+13	44	70
V6	Day 82 [a]	83	-13/na	71	One day before last visit (in-office)
V7	Week 12/EoS	85	na/na	Date of last visit (in-office)	Last visit date recorded

[a] Remote visit

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.

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).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

Demographic data and baseline characteristics will be summarised. For some continuous variables, the following categories will be defined and presented according to the number and percentage of patients in each category (Table 7.1: 1):

Table 7.1: 1 Categories for summary of continuous variables

Variable	Categories
Age	< 65 years 65 to <=74 years ≥ 75 years
BMI	< 18.5 kg/m^2 18.5 to <25 $kg.m^2$ 25 to < 30 kg/m^2 ≥ 30 kg/m^2
Time since first diagnosis of Non IPF Pulmonary Fibrosis or IPF	< 1 year 1 to < 3 years 3 to 5 years > 5 years
Time since first diagnosis of Non IPF Pulmonary Fibrosis	< 1 year 1 to < 3 years 3 to 5 years > 5 years

The following demographics and baseline characteristics will be tabulated:

Demographic characteristics:

- Sex
- Gender identity
- Ethnicity
- Race
- Country
- Age(continuous, category)
- Tobacco use
- Weight(continuous, category)
- Height
- Body Mass Index (continuous, category)

Baseline characteristics (including spirometry):

- Time since diagnosis IPF or Non IPF Pulmonary Fibrosis(continuous, category)
- Time since diagnosis Non IPF Pulmonary Fibrosis (continuous, category)
- Underlying ILD diagnosis
- Historical HRCT pattern
- ILD progression information within the last 12 months

- Spirometry:
  - Forced Expiratory Volume in 1 Second (FEV1)
  - Percent Predicted FEV1
  - Forced Vital Capacity (FVC)
  - Percent Predicted FVC
  - FEV1/FVC
  - Percent Predicted FEV1/FVC
  - Forced Expiratory Flow 25-75%
  - Peak Expiratory Flow (PEF)
  - Forced Inspiratory Vital Capacity (FIVC)

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases (i.e. baseline conditions) and concomitant non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medications will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Only descriptive statistics are planned for this section of the CTR. Analyses of concomitant diseases and medications will be based on the TS.

Baseline conditions and diagnosis will be summarised with frequency and percentage of patients by SOC and preferred name.

Concomitant medication use will be summarised with frequency and percentage of patients by ATC3 class and preferred name. The following summaries will be presented by medication used for cough (yes, no):

- Baseline medications: starting prior medication taken any time prior to Day 1 and continuing into the study period
- Concomitant medications: starting any time during the study period

A separate summary of baseline and concomitant anti-tussive medications, angiotensin-converting enzyme (ACE) inhibitors, opiates, and systemic or inhaled (excluding intranasal) corticosteroids will also be produced.

Concomitant procedures/non−drug therapies will be summarised with frequency and percentage of patients.

7.3 TREATMENT COMPLIANCE

Not applicable, no treatment is given in this trial.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

CTP Section 7.2.3: *The cough count (CC) frequency, measured over 4 24-hour recordings in 12 weeks will be analysed as CC/hour and will be log-transformed for data summaries. On each day for which cough monitoring is completed, the log-transformed cough count is calculated as:*

$$\textit{Log-transformed cough count} = \log \frac{\textit{Number of coughs}}{\textit{Length of readable recorded time (hours)}}$$

Cough count for each visit will be reported descriptively. Summary statistics will be tabulated on original scale of CC/hr as well as the geometric mean and 95% confidence intervals after back-transforming the summarized log transformed data. [redacted] *Summary measurements and individual values of CC/hr over time will also be presented graphically.*

Descriptive statistics, including the coefficient of variation (CV), for cough count/hour will be tabulated by visit using the original scale and for the log (natural) transformed values. In cases where 0 coughs are observed during a recording interval (e.g. night time, low activity duration, or over the 24 hour recording period), 0.1/hr will replace 0 in order to allow for the log transformation. Geometric means, coefficients of variation and 95% CIs be presented as well. For these, the summary measures using the log-transformed values will be calculated then back-transformed to the original scale.

Plots of the geometric means and geometric mean ratios over time will be produced. Individual time profiles for CC/hr will also be presented graphically.

The primary endpoints will be summarized in the same fashion as described above by each subgroup level listed in Section 6.4.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.1.1 Primary analysis of the key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

[redacted]

7.5.2 (Other) Secondary endpoint(s)

CTP Section 7.2.3.1: *Secondary endpoints will be summarized descriptively by visit.*

Change from baseline in CC/hr at Week 4, Week 8, and Week 12 will be summarized in terms of absolute changes in CC/hr and in terms of geometric mean ratios. Model based estimates for changes from baseline at Week 12, for example least squares means adjusted for baseline CC/hr or other covariates, may be calculated.

Standard descriptive statistical parameters will be tabulated for all other secondary endpoints.

To assess the relationship between objective cough frequency and FVC (mL), correlations (spearman and Pearson) will be calculated between the following variables:

- *Baseline CC/hr (log-transformed) and Baseline FVC (mL)*
- *Baseline CC/hr (log-transformed) and FVC (mL) at Week 12*
- *Baseline CC/hr (log-transformed) and change from baseline FVC (mL) at Week 12*
- *CC/hr at Week 12 (log-transformed) and FVC (mL) at Week 12*
- *Change in CC/hr at Week 12 (calculated from log-transformed values) and change from baseline in FVC (mL) at Week 12*

Graphical presentations of the secondary endpoints and correlations may also be produced.

Changes from baseline in CC/hr (absolute changes on the original scale and geometric mean ratios calculated from the log transformed values) at each visit will be presented along with the primary endpoints in the descriptive tabulations. Additionally, geometric mean ratios at Weeks 4, 8 and 12, and 95% CIs will be calculated using a statistical model adjusting for the baseline CC/hr. This model can be described as follows:

$$y_{ij} = \mu + v_j + b_i + e_{ij},$$

where

$\mathbf{y_{ij}}$	Log(CC/hr at Visit j) – Log(baseline CC/hr) for patient i,
μ	overall intercept,
v_j	jth Visit (e.g. Week 4, Week 8, Week 12)
b_i	Log(baseline CC/hr) for subject i,
e_{ij}	the random error associated with subject i at visit j.

The adjusted means, standard errors, lower and upper 95% confidence limits from the above model will then be back-transformed and presented as the geometric mean ratios, geometric standard errors and 95% confidence limits.

Study feasibility endpoints:

- Feasibility of remote cough data capture (defined as % of analysable data per 24-hour recording)

  The % of analysable data per 24-hour recording period will be derived from the cough count recording times(Total readable recording time) and defined as:

  $$\frac{\text{Total readable recording time}}{\text{24 (hours)}} \times 100$$

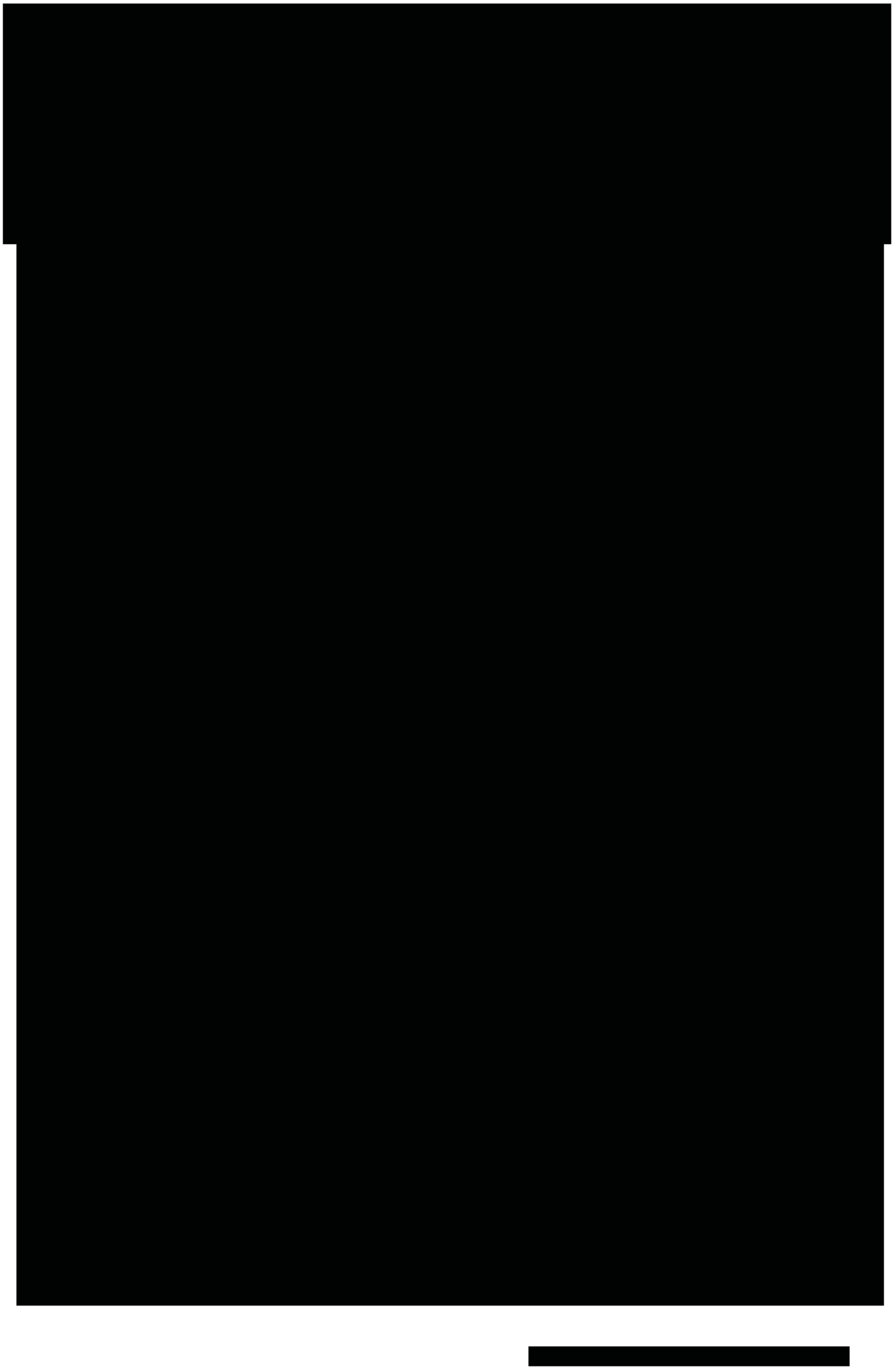
  Descriptive statistics will be produced by visit as well as the number and percentage of patients who have ≥ 80% (19.2 hrs) of analyzable data.

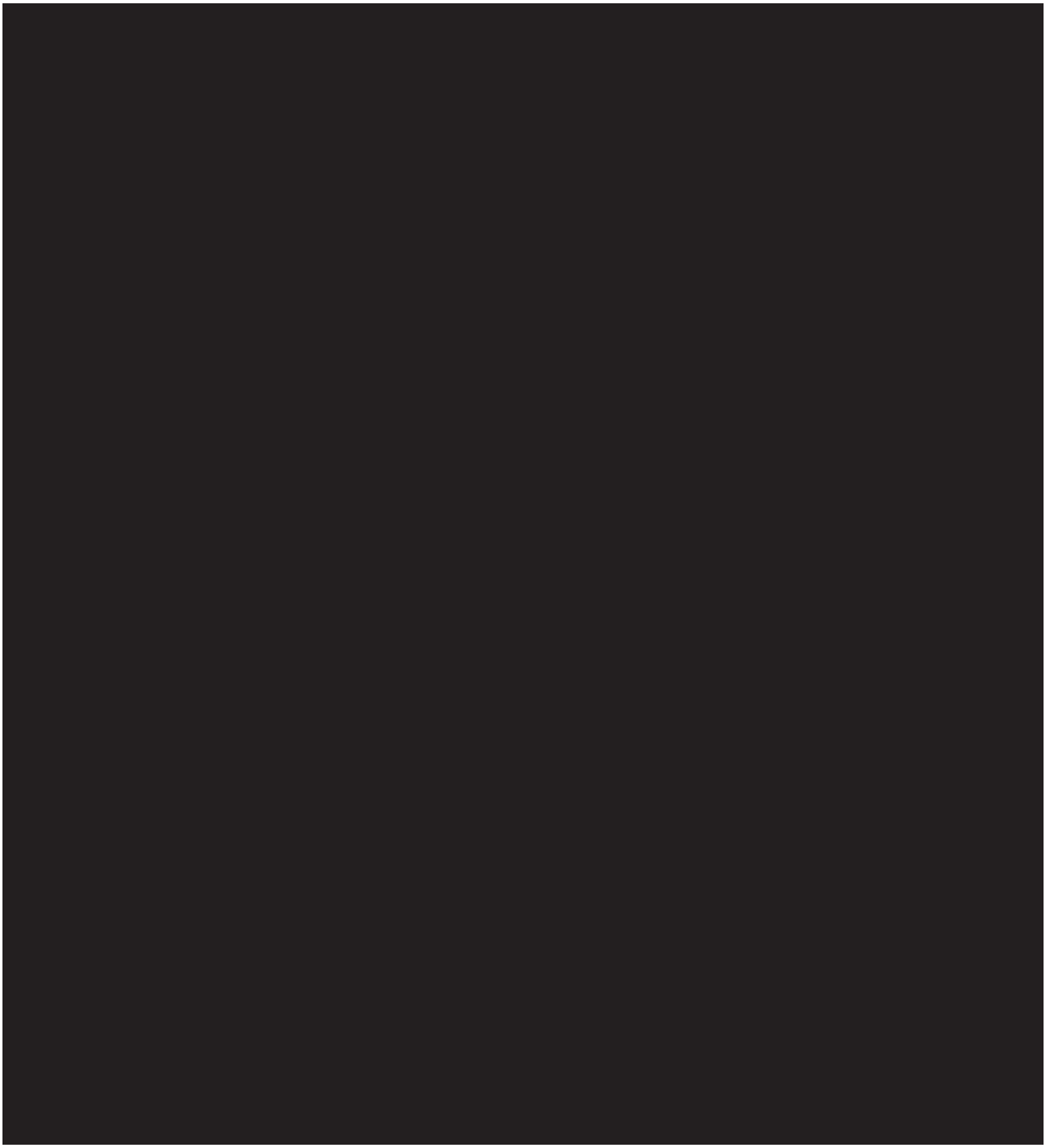
- Feasibility of hybrid study design (successful completion of all elements of remote visit)

  Successful completion of a remote visit will be based on the questions on the home study procedures eCRF:
  - Was home spirometry performed? (Visit 3, Visit 4, Visit 5, Visit 6)
  - Was the videoconference televisit completed? (Visit 4, Visit 5)
  - Was the 24 hour cough recording completed? (Visit 3, Visit 4, Visit 5)

  The number and percentage of patients who complete each element will be tabulated by visit as well as the number an percentage of patients who complete all elements by visit.

Correlation analyses:
Sample Spearman and Pearson correlation coefficients for the pairs of CC/hr and FVC measurements listed above along with the associated p-values to assess the relationship between objective cough frequency and FVC (mL), correlations will be calculated. Scatter plots for the pairs of variables will also be produced.





7.7 EXTENT OF EXPOSURE

Not applicable

7.8 SAFETY ANALYSIS

7.8.1 Adverse Events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

The following AEs occurring during the study period will be tabulated:

- AEs related to study procedures
- AEs or SAEs that fulfill the following criteria:
    - Events leading to lung transplantation
    - COVID-19 Infection
    - Events leading to death

The frequency of subjects with AEs will be summarised by primary system organ class and PT (mention MedDRA levels to be displayed in the tables). A separate table will be provided for subjects with SAEs.

The system organ classes will be sorted by frequency, PTs will be sorted by frequency (within SOC). Customized sorting orders may also be used based on trial needs, e.g. SOC sorted by frequency.

7.8.2 Laboratory data

Not applicable, Safety laboratory parameters are not performed.

7.8.3 Vital signs

Only descriptive statistics are planned for Baseline and EoS visit.

7.8.4 ECG

Not applicable

7.8.5 Others

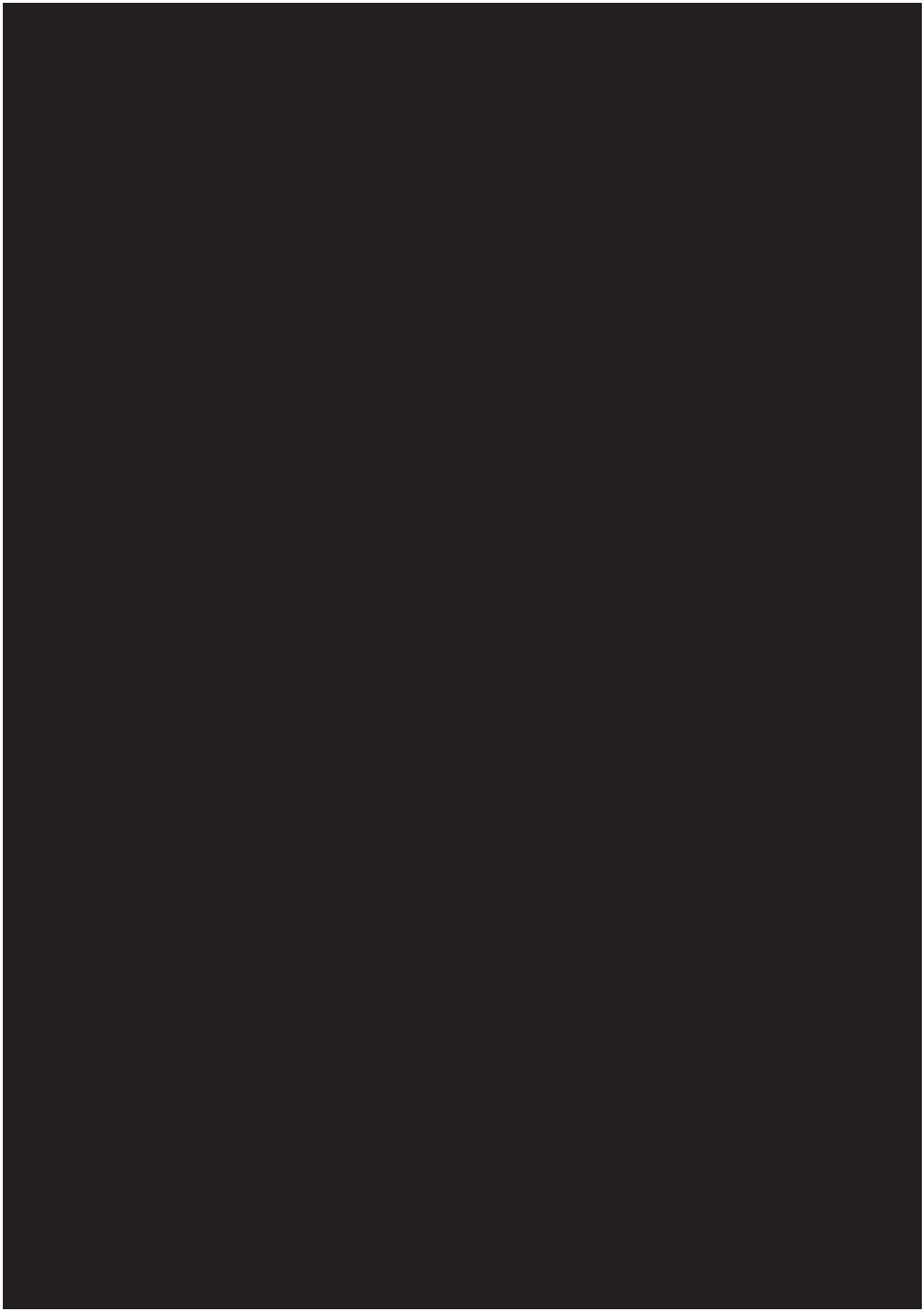
Not applicable

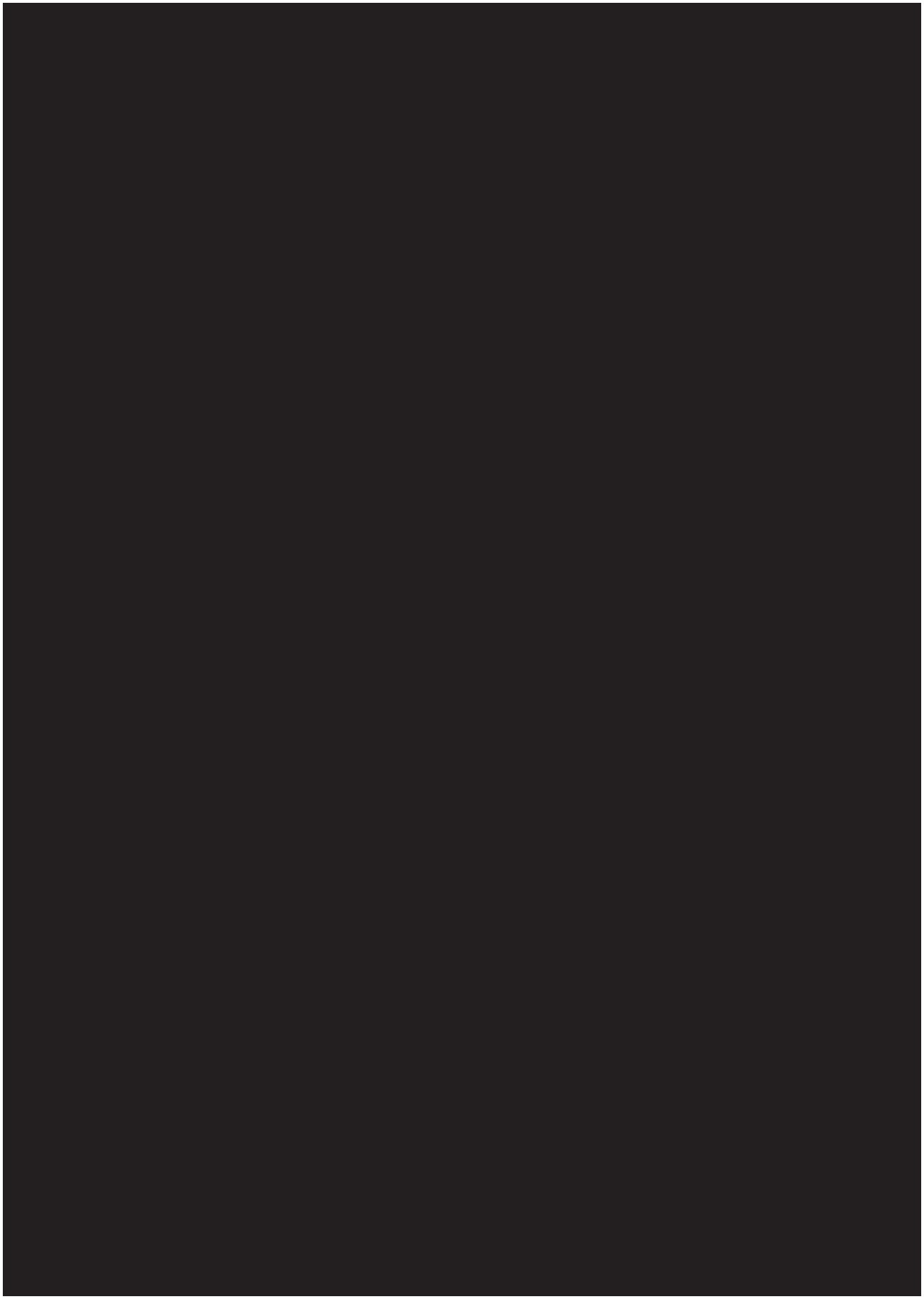
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

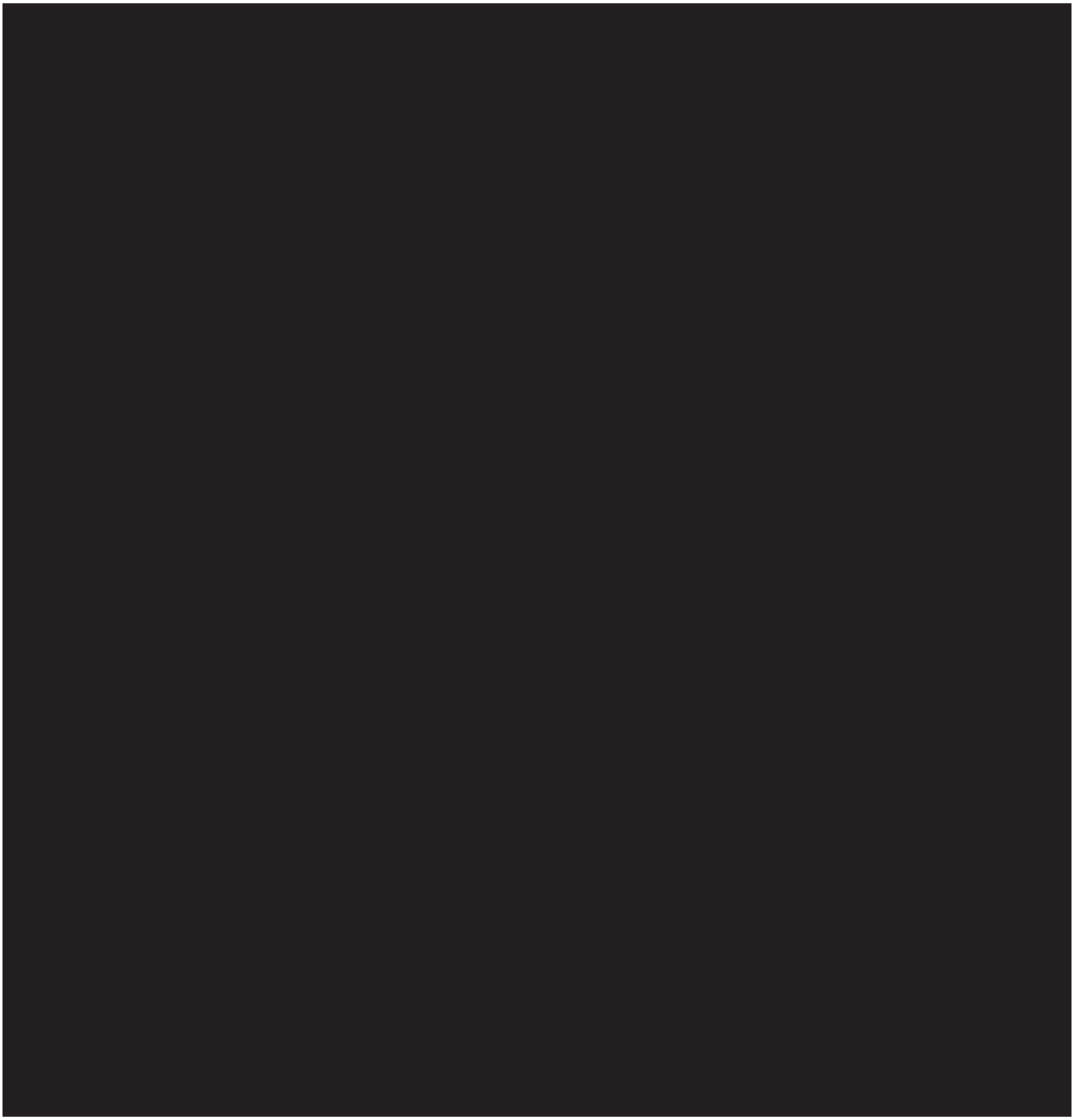
Not applicable

9. REFERENCES

Not applicable







11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**09-APR-24**	[redacted]	None	This is the final TSAP