NOVARTIS

Clinical Development

TBM100/ Tobramycin Inhalation Powder (TIP™)

Study number: CTBM100G2202 / NCT02712983

A randomized, blinded, parallel group, multi-center dose finding study, to assess the efficacy, safety and tolerability of different doses of tobramycin inhalation powder in patients with Non-Cystic Fibrosis Bronchiectasis and pulmonary *P. aeruginosa* infection

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final 3.0

Release date: 21May2019

Number of pages: 79

Document History - Changes compared to previous version

Version	Date	Changes
Draft v1.0	27-Jan-2017	Not applicable – first final version
Draft v2.0	26-Apr-2018	Updated SAP as per protocol amendment version 02 dated 09Feb2018
Draft v3.0	22-Nov-2018	Updated based on the TSC comments after study being terminated due to business (non-safety) reason
Draft v4.0	14-Dec-2018	Updated as per the Novartis comments or response Included forest plot as per the NVS request
Draft v5.0	01Feb2019	Updated exposure categories as per DMC mock Updated Renal safety criteria as per DMC mock [redacted] Updated In-text table as per the request
Final v1.0	15Feb2019	Final version
Final v2.0	19Feb2019	Updated text from "Biotype" to "Morphotype"
	25Feb2019	Updated table 5-4 and table 5-5 as per PD list
	27Feb2019	Removed analysis on local AEs from section 2.7.1
Final v3.0	16May2019	Updated general definition section 2.1.1: Visit consideration for discontinued subject Analysis for exposure adjusted rate of hospitalization due to serious respiratory-related Aes in added
	20 May 2019	Section 5.4 rule for exclusion is modified
	21 May 2019	Table 5.1; compliance rule is updated

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List of abbreviations

ACR	Albumin-creatinine ratio
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUD	Audiology Population
b.i.d.	twice a day
BSI	Bronchiectasis Severity Index
CI	Confidence Interval
CSR	Clinical Study Report
CFUs	Colony Forming Units
DMC	Data Monitoring Committee
DSPC	1, 2-distearoyl-sn-glycero-3-phosphocholine
eGFR	estimated Glomerular Filtration Rate
ENR	Enrolled Set
FAS	Full Analysis Set
FEF_{25-75}	Forced Expiratory Flow at 25-75%
FEV_1	Forced Expiratory Volume at 1 Second
FVC	Forced Vital Capacity
eCRF	electronic Case Report Form
ISC	Independent Study Coordinators
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MIC	Minimum Inhibitory Concentration
o.d.	once a day
PCR	Protein-creatinine ratio
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PKSSAS	Pharmacokinetic Sub-Study Analysis Set
PPS	Per-Protocol Set
PRO	Patient Reported Outcomes
PSD	Premature Subject/Patient Discontinuation
PT	Preferred Term
QoL	Quality of Life
QOL-B	Quality of Life Questionnaire for Bronchiectasis
RAN	Randomized population
SAF	Safety Set
SAP	Statistical Analysis Plan
SOC	System Organ Class

[redacted]	[redacted]
TBL	Total Bilirubin
TD	Study Treatment Discontinuation
TIP	Tobramycin inhalation powder
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) is based on the amended protocol version 02 dated 09th February 2018, and the business decision to close the trial earlier than planned (but not due to safety or efficacy reasons) by the Novartis. Recruitment has been stopped on 02nd October 2018 with 107 patients randomized as against 180 patients initially planned. With this premature closure and reduced sample size, the inferential analysis, regardless if it's pre-defined, can be considered as exploratory, the results obtained should be interpreted with the caution. The plan provides a technical and detailed elaboration of the statistical analyses of the efficacy, safety and tolerability of different doses of tobramycin inhalation powder (TIP) in patients with Non-Cystic Fibrosis Bronchiectasis and pulmonary *P. aeruginosa* infection. The specifications for tables, figures, and listings (TFLs) will be included in a separate document.

A clinical study report (CSR) will be written based on the results of the statistical analyses planned within this SAP. Results will also be used for the various publications.

1.1 Study design

This is a blinded, randomized, dose and regimen finding trial utilizing a 3 treatment cohort design where active TIP, TIP/Placebo cyclical, or placebo in addition to the local standard care within each cohort are delivered once or twice daily (Figure 1). The study will implement a within-cohort blinding approach. This allows assessment of the tolerability (defined as the rate of local AEs) of different doses and regimens of TIP, and also saves the treatment burden that would be imposed for blinding across all arms. Note that all of the patients in the study would need to inhale the maximal dose of 10 capsules every day (5 morning + 5 evening) to maintain the blind between cohorts (different dose levels) and within a cohort (different regimens).

Approximately 180 eligible patients will be randomized to 1 out of the 3 cohorts in a ratio of 1:1:1. The patients within each cohort will be randomized to blinded TIP or placebo with the following randomization scheme: TIP: TIP/placebo cyclical: placebo, in a 2:2:1 ratio.

At Visit 101 (see protocol [Table 6-1 – Assessment schedule]), all eligible patients will be randomized via Interactive Response Technology (IRT) to 1 of the treatment arms with the randomization strata (use of macrolides as part of their standard of care therapy yes/no). To evaluate serum pharmacokinetics (PK) in approximately 16 patients on active treatment, at least 20-22 patients from each cohort (at least 60 total patients) will participate in a PK sub-study. To ensure a balanced distribution across cohorts, this will be captured in IRT. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the user.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The treatment arms distributed among the 3 cohorts are described below. TIP is supplied in hard capsules at 28mg dosage strength, therefore 3 cohorts correspond to 3 different dose

levels of TIP, i.e., 84mg once a day (o.d.), 140mg o.d. and 112mg twice a day (b.i.d.).

Cohort A: 3 capsules o.d.

- **TIP**: 3 capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T-326 Inhaler, for 112 days (on treatment).
- **TIP/placebo cyclical**: patients will take the same doses, i.e. 3 capsules o.d., by alternating TIP 28-days with placebo 28-days for 2 cycles for a total of 112 days.
- **Placebo:** The reference product consists of placebo capsules (DSPC/CaCl2). The dose regimen for the reference product is 3 capsules blinded, inhaled o.d. via the T-326 Inhaler, for 112 days (on treatment).

Cohort B: 5 capsules o.d.

- **TIP**: 5 capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T-326 Inhaler, for 112 days (on treatment).
- **TIP/placebo cyclical**: patients will take the same doses, i.e. 5 capsules o.d., by alternating TIP 28-days with placebo 28-days for 2 cycles for a total of 112 days.
- **Placebo**: The reference product consists of placebo capsules. The dose regimen for the reference product is 5 capsules blinded, inhaled o.d. via the T-326 Inhaler, for 112 days (on treatment).

Cohort C: 4 capsules b.i.d.

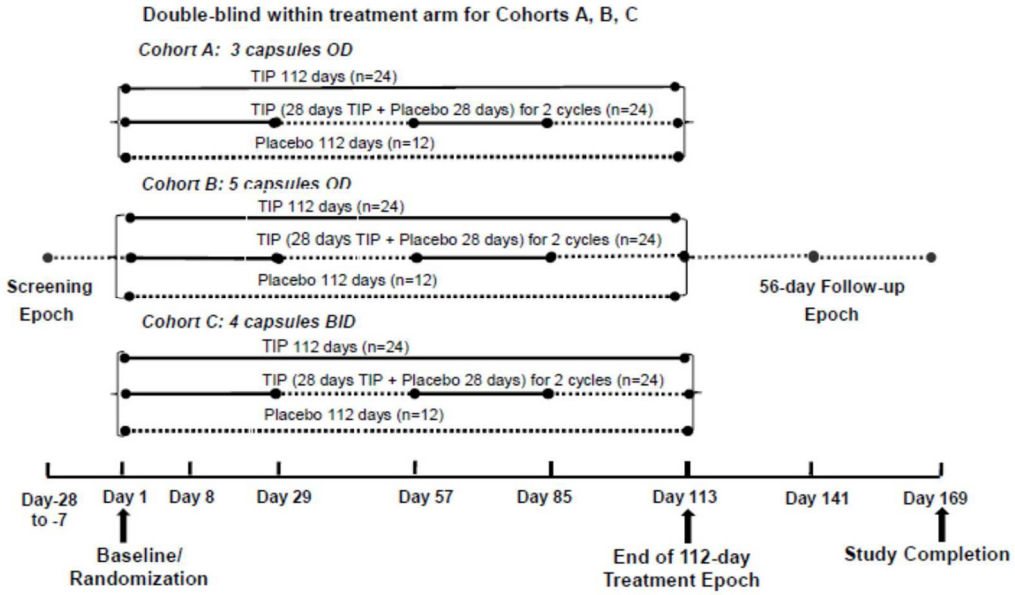
- **TIP**: 4 capsules of blinded TIP at 28 mg dosage strength, inhaled b.i.d. in the morning and in the evening via the T-326 Inhaler, for 112 days of treatment.
- **TIP/placebo cyclical**: patients will take same doses, i.e. 4 capsules b.i.d., by alternating TIP 28-days with placebo 28-days for 2 cycles for a total of 112 days.
- **Placebo**: The reference product consists of placebo capsules. The dose regimen for the reference product is 4 capsules blinded, inhaled b.i.d. via the T-326 Inhaler, for 112 days (on treatment).

There will be 3 study epochs with a total of 9 visits (Figure 1):

- Screening: up to 28 days with 1 clinic visit
- Double-blind treatment (within cohort): 112 days with 6 clinic visits [Visit 101 (Day 1), Visit 102 (Day 8), Visit 103 (Day 29), Visit 104 (Day 57), Visit 105 (Day 85) and Visit 106 or study treatment discontinuation (TD) (Day 113)]
- Follow-up: 56 days with 2 clinic visits [Follow-up Visit 201 (Day 141) and Follow-up Visit 202 or premature subject/patient discontinuation (PSD) (Day 169)

The total duration of the study is expected to be up to 196 days. Patients will be assessed for safety, tolerability and efficacy (see protocol [Table 6-1 – Assessment schedule]).

Figure 1 Study design



The primary efficacy endpoint is the absolute change from baseline to Day 29 of treatment in the bacterial load in sputum in log10 colony forming units (CFUs) of *P. aeruginosa*. Baseline is defined as the last measurement prior to the first dose of blinded study drug.

No interim analysis for efficacy is planned. There is an independent data monitoring committee (DMC) assigned to monitor the safety during the study; further details are defined in the DMC Charter.

1.2 Study objectives and endpoints

1.2.1 Primary objectives

- To evaluate the effect of different doses of TIP, administered o.d. or b.i.d. , on the change in *P. aeruginosa* bacterial load in sputum as assessed by the change in CFUs from baseline to Day 29 of treatment, each compared to placebo.
- To assess the safety and tolerability with different doses of TIP, administered o.d. or b.i.d., and different regimens (TIP and TIP/placebo cyclical) during the treatment epoch (112 days) and during the follow-up epoch (56 days), each compared to placebo.

1.2.2 Secondary objectives

- To assess the effect of different doses of TIP administered o.d. and one b.i.d. dose and different regimens (TIP and TIP/placebo cyclical) on the frequency, rate (by patient months), severity and time to onset of pulmonary exacerbations at the end of the treatment epoch and over the entire study, each compared to placebo.
- To assess the efficacy profile of different doses of TIP administered o.d. and one b.i.d. dose and different regimens (TIP and TIP/placebo cyclical), as measured by the time to first use, proportion of patients requiring anti-pseudomonal antibiotics (overall, oral, parenteral) and the duration of treatment, each compared to placebo.

- To assess the time to first hospitalization, proportion of patients requiring hospitalization and the duration of hospitalization due to serious respiratory-related AEs (other than those regularly scheduled hospitalization that were planned prior to study start).
- To assess the pharmacokinetic concentrations of tobramycin in serum and in sputum from different doses of TIP administered o.d. and one b.i.d. dose and different regimens (TIP and TIP/placebo cyclical).
- To assess the antimicrobial efficacy of TIP over the entire study duration, as measured by the absolute change in *P. aeruginosa* -CFUs in sputum from baseline to each post-baseline treatment visit and during the follow-up visits.
- To evaluate the safety profile of TIP in terms of clinical laboratory results.
- To evaluate the safety profile of TIP in terms of audiology findings throughout the treatment epoch (subgroup of all patients that are in enrolled at sites that are adequately equipped and trained to perform audiologic assessments).
- To evaluate the safety profile of TIP in terms of acute change in forced expiratory volume at 1 second (FEV_1) % predicted values from pre-dose to 30±15 minutes after completion of study drug administration at the clinical site at visits during the treatment epoch.
- To evaluate the impact of treatment with TIP on the Respiratory Symptom Scale Quality of Life Questionnaire for Bronchiectasis (QOL-B) by measuring change from baseline to all post-baseline visits.

Table 1-1 Primary and secondary objectives and related endpoints

Objective	Endpoint	Statistical Analysis
Primary		Section #
To evaluate the effect of different doses of TIP on the change in *P. aeruginosa* bacterial load in sputum at Day 29	Change from baseline to ***Day 29*** in *P. aeruginosa* density in sputum (log10 CFUs)	2.5.2
To assess the safety and tolerability with different doses of TIP and different regimens, on treatment epoch and over entire study duration	Safety: incidence rate of AEs/Serious AEs by MedDRA primary SOC and PT terms Tolerability: incidence and severity of local AEs (eg. cough, bronchospasm, dysgeusia, dry mouth, etc.)	2.7.1
Secondary		
To assess the antimicrobial efficacy of TIP over the entire study duration	Change from baseline to each post-baseline visit in *P. aeruginosa* density in sputum (log10 CFUs)	2.6.3.1
To assess the effect of different doses of TIP and different regimens on pulmonary exacerbation at the end of treatment epoch (Day 113) and over the study period	Time to first pulmonary exacerbation by exacerbation category Duration of pulmonary exacerbations by exacerbation category Exposure adjusted rate of exacerbations Proportion of patients with at least one pulmonary exacerbation by exacerbation category Proportion of patients who permanently discontinued study drug due to pulmonary	2.6.3.2

Objective	Endpoint	Statistical Analysis
	exacerbation	
	Time to permanent study drug discontinuation due to pulmonary exacerbation	
To assess the efficacy profile of different doses of TIP and different regimens as measured by anti-pseudomonal antibiotics usage during the treatment epoch (through Day 113) and the study period	Time to first use (overall, oral, and -parenteral) of anti-pseudomonal antibiotics usage	2.6.3.3
	Proportion of patients used anti-pseudomonal antibiotics usage	
	Duration of anti-pseudomonal antibiotics usage	
To assess the hospitalization (other than those regularly scheduled hospitalization that were planned prior to study start)	Time to first hospitalization due to serious respiratory-related AEs	2.6.3.4
	Number of hospitalizations due to serious respiratory-related AEs	
	Proportion of patients requiring hospitalization due to serious respiratory-related AEs	
	Duration of hospitalization due to serious respiratory-related AEs	
To evaluate the safety profile of TIP in terms of clinical laboratory results	Laboratory results (hematology, serum chemistry, urine dipstick tests): means, mean changes from baseline, frequency/shift tables by visit	2.7.3
To evaluate the audiology safety profile of TIP	Audiology findings (selected centers) by visit	2.7.4.1
To evaluate the safety profile of TIP in terms of bronchial hyperreactivity	Acute change in FEV_1 % predicted values from pre-dose to 30±15 minutes after completion of study drug administration at the clinical site at visits during the treatment epoch	2.7.4.4
To evaluate the treatment effect of TIP on the Respiratory Symptom Scale Quality of Life Questionnaire for Bronchiectasis (QOL-B)	Change from baseline to all post-baseline visits	2.10
Pharmacokinetic concentrations of tobramycin in serum and in sputum	Concentration data at scheduled visits and timepoints	2.8

1.2.3 Exploratory objectives

[redacted]

- To explore the characteristics of the post-inhalational events at all visits during the treatment epoch.

- To explore the impact of healthcare resource utilization of TIP treatment.

Table 1-2 Exploratory objectives and related endpoints

Objective	Endpoint	Statistical Analysis
		

Objective	Endpoint	Statistical Analysis
[redacted]		
To explore the characteristics of the post-inhalational events	Separate summaries for post-inhalation clinical events and post-inhalation adverse events: Proportion of patients experiencing events at each visit Proportion of patients experiencing events that are ongoing at the completion of the visit Proportion of patients experiencing events with an action taken to reduce the event Time of onset of event Duration of event Number of post-inhalation events Event rate adjusted for exposure	2.7.4.3
[redacted]		
To explore the impact of healthcare resource utilization of TIP treatment	All scheduled and unscheduled visits	2.7.4.5
[redacted]		

2 Statistical methods

The study is characterized by 3 cohorts (corresponding to 3 doses). Each cohort consists of TIP, TIP/placebo cyclical, or placebo in a ratio of 2:2:1. Data will be summarized and analyzed by cohort/dose, treatment arms (including combined treatments) and/or pooled by continuous, cyclic and placebo as appropriate. For the efficacy analyses, the placebo patients will be pooled from the 3 cohorts.

2.1 General information

[redacted]. Statistical analyses will be performed using SAS® Version 9.3 (or higher).

In general, all data will be reported as observed. No imputation will be performed for the primary efficacy analysis. Supportive and sensitivity analyses are discussed in Section 2.5.4 to evaluate the robustness of primary analysis results.

Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) will be calculated for continuous data. Minimum and maximum will be presented to the same number of decimal places as reported/collected, 1 additional decimal place for mean and median, and 2 additional decimal places for SD. Derived data will be reported to 1 additional decimal place as the reported data.

Categorical data will be summarized using n and percentages based on the number of non-missing values. Percentages will be presented to 1 decimal place. The number of missing values will be presented as a separate category with no percentage, but only if 1 or more patients are missing data for the summary. Otherwise, all categories will be presented (even if no patients are counted in the category). Counts of zero in any category will be presented without a percentage.

2.1.1 General definitions

Study drug is defined as any single dose of TIP or placebo administered to the patient as part of the required study procedures.

The date of first dose of study drug is defined as the date of first administration of TIP or placebo; the date of last dose of study drug is defined as the date of the last administration of TIP or placebo.

For dates on or after the date of first dose of study drug, study day is defined as [date of interest – date of first dose of study drug] + 1. For dates before the date of first dose of study drug, study day is defined as [date of first study drug – date of interest].

For each visit, the date recorded by the investigators in the eCRF (variable SVSTDTC in the SDTM SV dataset) will be considered as the visit date in all the algorithms and the listings.

In genereal, the nominal visits will be used for the by visits summaries. However, for early treatment discontinued patients, data collected at end of treatment (EOT) visit will be mapped to next planned visits after their last scheduled visits before the discontinuation.

Baseline is defined as the last non-missing result prior to the first administration of study drug.

End/last date of study for each patient is defined by the date of last contact as recorded in the database.

2.1.2 Statistical significance

The step-wise Dunnett procedure will be used for the primary efficacy analysis to control the family-wise type-I error rate (3 dose levels versus placebo) at the 2-sided 5% significance level (Section 2.5.2). Unless otherwise specified, other inferential analyses and confidence intervals (CIs) will be conducted at the 2-sided 5% significance level with no multiplicity adjustment.

2.1.3 Listings

All data collected in the eCRF and diaries will be presented in the listings.

Data will be presented in listings in the order of cohort [Cohort A: 3 capsules OD, Cohort B: 5 capsules OD and Cohort C: 4 capsules BID], treatment arm [TIP, TIP/Placebo Cyclical and Placebo], site/patient identifier, assessment date and assessment (in order collected in the eCRF, unless specified otherwise). AE listings will include the AE start day and AE stop day relative to the first day of study drug. Dates will be presented in format DDMMMYYYY.

2.2 Analysis sets

Safety Set (SAF): The safety set will be used for all safety analyses, which is defined as patients who received at least 1 dose of study drug. Patients will be analyzed according to the actual treatment received.

For the purposes of tables and listings a further 3 populations are defined:

- All enrolled patients (ENR)
- Screening failure patients
- Randomized population (RAN: all randomized patients)

Full Analysis Set (FAS): The full analysis set (FAS) will include all randomized patients who received at least 1 dose of study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment they are assigned to at randomization, which may be different from the actual treatment received. Patients who are mistakenly randomized or who have not taken double blind study drug will be excluded from the FAS. This is the primary analysis set for all efficacy analyses.

Per-Protocol Set (PPS): The per-protocol set (PPS) will include all patients in the FAS without any major protocol deviations.

Criteria for determining protocol deviations will be defined and documented in the protocol deviations section of the data validation specifications. Potential protocol deviators will be identified and reviewed to determine whether they will be excluded from the PPS population. This will take place in a blinded data review meeting prior to database lock. All protocol deviations will be agreed and documented prior to unblinding the study. The PPS will be used for the supportive analysis of the primary efficacy variable.

Pharmacokinetic Analysis Set (PKAS): The pharmacokinetic analysis set (PKAS) will include all patients who are administered TIP, and for whom results of plasma concentrations are obtained for at least one sampling point during the study.

Pharmacokinetic Sub-study Analysis Set (PKSSAS): The pharmacokinetic sub-study analysis set (PKSSAS) will include all patients enrolled in the pharmacokinetic sub-study

who are administered TIP, and for whom results of plasma concentrations are obtained for at least one sampling point during the study.

Audiology Population (AUD): The audiology population is defined as all patients in the safety set with at least one audiology test performed.

2.2.1 Subgroups of interest

Primary endpoint analysis will be repeated in the subgroup of patients with/without macrolide treatment at baseline, only if clinical meaningful difference was observed between the pooled active doses vs placebo.

2.3 Patient disposition, demographics and other baseline characteristics

The number of patients screened and the number of screen failures will be presented (overall).

The number of patients included in each of the Randomized, SAF, FAS, PPS, AUD, PKAS and PKSSAS populations will be summarized for each cohort, treatment arm and overall.

Patients who complete the treatment phase and patients who complete the follow-up phase will be summarized using the FAS. Patients who discontinue from the treatment phase and patients who discontinue the follow-up phase will be summarized overall and by reason for discontinuation using the FAS.

The FAS will be used to summarize the following by cohort and treatment arm:

- Demography: age, age group (< 65 years and >=65 years), gender, race and ethnicity, weight (kg), height (cm), body mass index (BMI).
- Baseline characteristics: baseline spirometry (FEV_1, [redacted]) %predicted values, MIC, macrolide use, bronchodilators, inhaled corticosteroids, tobramycin MIC=>8 at baseline, BSI.
- Medical history - ototoxicity
- History of pulmonary exacerbations
- Bronchiectasis-related medical history
- Spirometry assessed at screening
- Previous hospital admissions and exacerbations
- Other relevant medical history

Age will be calculated as the difference between year of birth and year of informed consent.

[redacted]

The following table will be used to derive the BSI:

Table 2-1 Severity criteria for BSI

Criteria/Point	0	1	2	3	4	5	6
Age	<50		50-69		70-79		80+
BMI (kg/m$^{2)}$	≥18.5		<18.5				
FEV_1 % predicted	>80%	50-80%	30-49%	<30%			
Hospital admissions in the past 2 years	No					Yes	
Exacerbation frequency in the last 12 months	0-2		≥3				
MRC dyspoea	1-3		4	5			
Colonisation status	Not colonised	Chronic colonisation		P.aeruginosa colonisation			
Radiological severity	<3 lobes involved	≥3 lobes or cystic changes					

Medical history recorded in the eCRFs will be reviewed to determine whether a patient had a hospital admission in the past 2 years. The pulmonary exacerbation history eCRF data will be reviewed to determine the exacerbation frequency in the 12 months prior to Screening.

If any individual severity criteria cannot be assessed for a patient due to missing or incomplete data, the BSI total score will not be derived.

Smoking history will be listed in patient listing only.

Listings will be provided to show all demographic and baseline characteristics using the randomized population.

Major protocol deviations will be summarized by cohort and treatment arm using the FAS.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Overall exposure (days) to study treatment will be summarized in terms of treatment duration, defined as the number of days from the date of first dose of study drug taken to the date of the last dose of study drug taken, inclusive, i.e., date of last dose of study drug – date of first dose of study drug + 1.

Assessment of compliance will be based on the number of unused capsules returned per patient assessed by the Independent Study Coordinators (ISC).

Compliance will be derived using the following formula:

Compliance = (number of actual inhaled capsules / number of intended inhaled capsules during the derived treatment period) * 100%

The number of intended inhaled capsules during the treatment period will be derived as follows:

- Cohort A: 3 * treatment duration
- Cohort B: 5 * treatment duration
- Cohort C: 8 * treatment duration

Compliance will also be assessed by visit period. Four specific periods will be defined, i.e., Visit 101 to Visit 103, Visit 103 to Visit 104, Visit 104 to Visit 105, and Visit 105 to Visit 106. This will be used to review the compliance for each on/off active treatment period for the cyclical TIP/placebo treatment arms.
Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented by cohort and treatment arm for the FAS for overall exposure, and both compliance over the treatment period and compliance by visit period. Duration of exposure will be further categorized as <=22 days, 23-28 days, 29-56 days, 57-84 days, 85-112 days, >= 113 days, and the number and percentage of patients by cohort and treatment arm will be presented for each category for the FAS.

The number and percentage of patients with study drug compliance <80% and >=80% over the treatment period and for each visit period will also be summarized by cohort and treatment arm using the FAS.

Overall duration of study (days), defined as the number of days from the date of randomization to the date of study completion, i.e., date of study completion – date of randomization + 1, will be summarized descriptively (n, mean, SD, minimum, median, and maximum) by cohort and treatment arm for the FAS.

2.4.2 Prior, concomitant and post therapies

The latest version available prior to database lock of the World Health Organization (WHO) drug dictionary will be used to classify prior, concomitant and rescue medications by therapeutic class.

Prior medication is defined as any medication with a stop date prior to the date of the first dose of study drug.

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date on or after the date of the first dose of study drug.

Post-treatment medication is defined as any medication with a start date after the date of the last dost of study drug.

Rescue medication for pulmonary exacerbations (including systemic antibiotics) and for bronchospasm is allowed. Use of rescue medication will be recorded on the Concomitant medications/Significant non-drug therapies CRF.

The number and percentage of patients taking prior, concomitant and rescue medications will be summarized by treatment and by Anatomical Therapeutic Classification (ATC) and preferred term. Each prior, concomitant and rescue medication could be classified by more than 1 ATC and will be counted for each. Summary tables will be provided for rescue and concomitant medications started prior to study drug, started on or after the start of study drug and for non-cystic fibrosis bronchiectasis related medications started on or after the start of study drug. Multiple medication usage by a patient in the same category will be counted only once. Summaries will be based on the SAF.

All prior, concomitant and rescue medications and therapies will also be listed.

2.5 Analysis of the primary objective

The analysis of the primary efficacy variable will be based on the FAS.

2.5.1 Primary efficacy endpoint

The primary efficacy variable is the absolute change in the bacterial load in sputum as assessed by the change in log10 CFUs of *P. aeruginosa* from baseline to Day 29 of treatment. The specimens with more than 1 bacterial morphotype, the sum of all bacterial morphotype will be used to calculate change from baseline values.

2.5.2 Statistical hypothesis, model, and method of analysis

The comparisons of 3 doses of active treatment (TIP 3 capsules OD, 5 capsules OD, and 4 capsules BID) versus pooled placebo will be evaluated by testing the following null hypothesis (H0) versus the alternative hypothesis (Ha):

H0: TIP treatment arm is equal to pooled placebo group in bacterial load in sputum at Day 29

Ha: TIP treatment arm is not equal to pooled placebo group in bacterial load in sputum at Day 29

The primary efficacy endpoint will be analyzed using the analysis of covariance (ANCOVA) model. The model will contain treatment, baseline CFU (in log 10 unit), and baseline macrolide use (yes/no). The adjusted means will be displayed together with the associated standard error and 2-sided 95% CI. Pairwise comparisons of TIP dosing groups will be conducted versus placebo. To control the family-wise type-I error rate (3 dose levels vs. placebo) at the 2-sided 5% significance level, the step-wise Dunnett procedure will be used.

For the primary efficacy analysis, patients from treatment arms TIP and TIP/placebo cyclical regimen will be pooled for each cohort. This is possible because all patients within the same cohort on the TIP treatment arms (cyclical or continuous) are receiving the same treatment during the first 28 days. Placebo patients will be pooled across the 3 cohorts, as the number of placebo capsules is not expected to influence the change in *P. aeruginosa* bacterial counts.

The estimated adjusted treatment difference (TIP – placebo) will be displayed along with the associated standard error, 2-sided 95% CI, and p-value (2-sided).

The estimated treatment difference and CI will be displayed in forest plot for the treatment arms TIP and TIP/placebo cyclical regimen pooled for each cohort vs pooled placebo across 3 cohorts.

For other efficacy analyses up to and including Day 29, patients from treatment arms TIP and TIP/placebo cyclical regimen will be pooled for each cohort; placebo patients will be pooled across the 3 cohorts.

If no *P. aeruginosa* isolated (NPAI) are detected, i.e, no growth detected, at a given visit where the laboratory sample was available at that visit, the value will be imputed as 99 based on the lower limit of detection (dilution factor is currently 1/100). Log 10(99) will be used in the analysis.

2.5.3 Handling of missing values/censoring/discontinuations

No imputation will be performed for missing data for the primary endpoint.

2.5.4 Supportive and sensitivity analyses

1. The non-parametric Mann-Whitney-Wilcoxon test will be carried out as a sensitivity analysis due to the potential non-normality of the CFU data.
2. The primary efficacy analysis will be repeated in the PPS as a supportive analysis.

2.6 Analysis of secondary and exploratory efficacy objective(s)

For efficacy analysis, patients assigned to placebo arms will be pooled across the 3 cohorts, as the number of placebo capsules is not expected to impact the efficacy assessments. Unless otherwise specified, the following analysis will be conducted both over the treatment epoch (through Day 113) and over the entire study period (through Day 169).

2.6.1 Secondary endpoints

2.6.1.1 *P. aeruginosa* colony forming units (CFU)

Anti-microbial efficacy of TIP versus placebo over the entire study duration, as measured by the absolute change in log10 CFUs of *P. aeruginosa* in sputum from baseline to each post-baseline visit (Visits 102 (Day 8), 103 (Day 29), 104 (Day 57), 105 (Day 85) and 106 (Day 113)), will be assessed by morphotype and sum of all morphotypes (mucoid, dry, small colony-variants). For patients with a negative *P. aeruginosa* result, i.e, NPAI, the quantitative test result for the analysis will be imputed for each morphotype with log (99) as this represents the detection level for a dilution of 100. Means together with the 95% CIs will be graphically displayed over time. The summaries will be provided by treatment groups Cohort A: TIP, Cohort A: TIP/placebo cyclical, Cohort B: TIP, Cohort B: TIP/placebo cyclical, Cohort C: TIP, Cohort C: TIP/placebo cyclical, Pooled TIP and Pooled TIP/placebo cyclical and pooled placebo. Comparisons between treatment regimens across all cohorts versus pooled placebo will also be analyzed.

The number and percentage for patients with no *P. aeruginosa* in sputum and number and percentage of patients with a positive result of *P. aeruginosa* in sputum will be tabulated by cohort, treatment arm, pooled arms by continuous and cyclic regimens and visit. Percentages will be based on the number of patients for whom microbiology results exist per visit.

The number and percentage of patients with NPAI at 2 consecutive post-baseline visits will also be presented by cohort and treatment arm, pooled arms by continuous and cyclic regimens.

2.6.1.2 Pulmonary exacerbations

Patients with pulmonary exacerbations (pulmonary exacerbation is defined in [Section 6.4.4 of the protocol] will be categorized into the following:

- Category 1: pulmonary exacerbations requiring oral antibiotics only
- Category 2: pulmonary exacerbations requiring parenteral antibiotics and/OR pulmonary exacerbation requiring hospitalization

A patient could be counted in more than 1 exacerbation category.

In addition to the antibiotics listed in Appendix 12 of the protocol, concomitant medication data will be reviewed on an ongoing basis. A list identifying all relevant antibiotics used for the treatment of pulmonary exacerbations will be provided prior to database lock.

Pulmonary exacerbations requiring hospitalization will be identified from the adverse event – pulmonary exacerbations eCRF data.

The following pulmonary exacerbation-related parameters over the treatment epoch (through Day 113) and the study period (unless otherwise stated) will be summarized by cohort and treatment arm. In addition, data will also be pooled and summarized for all three continuous TIP regimens together and all three cyclic TIP regimens together.

- The proportion of patients with at least 1 pulmonary exacerbation overall and by exacerbation category
- Number of pulmonary exacerbations overall and by exacerbation category
- Time to first pulmonary exacerbation overall and by exacerbation category for overall study period
- The exposure adjusted rate of pulmonary exacerbations overall
- Duration of pulmonary exacerbations in days by exacerbation category
- Time to permanent study drug discontinuation due to pulmonary exacerbation for overall study period
- The proportion of patients who permanently discontinued study drug due to pulmonary exacerbation

In addition, the pulmonary exacerbation signs and symptoms lasting for more than 24 hours and 48 hours, respectively, will be summarized separately (see section 2.6.3.2).

2.6.1.3 Anti-pseudomonal antibiotics

The following anti-pseudomonal antibiotics-related parameters will be assessed by cohort and treatment arm and also by pooled three continuous TIP regimens and pooled three cyclic TIP/placebo regimens.

- Proportion of patients requiring anti-pseudomonal antibiotics (overall, oral,parenteral)
- Time to first use of anti-pseudomonal antibiotics across the entire study period
- The exposure adjusted rate of usage of anti-pseudomonal antibiotics across the entire study period
- Duration of anti-pseudomonal antibiotic use across the entire study period

Anti-pseudomonal antibiotics will be identified prior to database lock.

2.6.1.4 Hospitalization

The following hospitalization-related parameters will be assessed by cohort and treatment arm, by pooled three continuous TIP regimens and pooled three cyclic TIP/placebo regimens:

- Time to first hospitalization due to serious respiratory-related AEs across the entire study period
- Duration of hospitalization due to serious respiratory-related AEs across the entire study period
- Number of hospitalizations due to serious respiratory-related AEs across the entire study period
- Proportion of patients requiring hospitalization due to serious respiratory-related AEs across the entire study period

2.6.3 Statistical hypothesis, model, and method of analysis

In general, unless otherwise specified, the following 6 pairwise comparisons will be performed for the secondary endpoints at the 5% significance level without multiplicity adjustment, wherever an inferential analysis is specified:

- TIP 3 capsules OD versus pooled placebo
- TIP/placebo cyclical 3 capsules OD versus pooled placebo
- TIP 5 capsules OD versus pooled placebo
- TIP/placebo cyclical 5 capsules OD versus pooled placebo
- TIP 4 capsules BID versus pooled placebo
- TIP/placebo cyclical 4 capsules BID versus pooled placebo

Descriptive summary statistics by cohort, treatment arm, pooled treatment arm by regimen and pooled placebo will be provided where applicable.

In addition, data will also be summarized for selected endpoints, by pooling continuous TIP regimens together (i.e. TIP 3 capsules OD. from Cohort A + TIP 5 capsules OD from Cohort B+ TIP 4 capsules BID from cohort C) and pooling cyclic TIP regimens together (i.e. TIP/placebo cyclical 3 capsules OD from Cohort A + TIP/placebo cyclical 5 capsules OD. from Cohort B+ TIP/placebo 4 capsules BID cyclical from cohort C) vs pooled placebo.

In addition, the following 2 pairwise comparisons will be performed for the selected endpoints at the 5% significance level without multiplicity adjustment:

- Pooled TIP continuous regimens versus pooled placebo
- Pooled TIP/placebo cyclical regimens versus pooled placebo.

Forest plot will be plotted for below endpoints in addition to the primary endpoint for each treatment arm across 3 cohorts compared with pooled placebo separately and also for the comparison between pooled TIP continuous (pooled from 3 cohorts) with pooled placebo and for

the comparison between pooled TIP/placebo cyclic (pooled from 3 cohorts) with pooled placebo.

- LS Mean difference in log10 CFUs of *P. aeruginosa* in sputum and CI
- For exposure adjusted rate and CI of pulmonary exacerbations during the study
- For incident rate ratio and CI for anti-pseudomonal antibiotics during the study
- Incident rate ratio and CI hospitalization due to serious respiratory-related AEs across the entire study period
- LS Mean difference in QoL-B RSS and CI

2.6.3.1 P. aeruginosa colony forming units (CFU)

The primary efficacy parameter (CFU) will be analyzed using a similar ANCOVA model as used in primary efficacy analysis at Day 85, Day 113 and Day 169. The model will contain treatment, baseline CFU (in log 10 unit), and baseline macrolide use (yes/no).

The analysis will not be performed by the subgroup of morphotypes. Six pairwise comparisons will be evaluated as specified in Section 2.6.3 The estimated adjusted treatment difference for each of the 6 comparisons (TIP–placebo) will be displayed along with the associated standard error, 2-sided 95% CI.. In addition, CFU data will be summarized by morphotype and sum of all morphotypes at each scheduled visit.

2.6.3.2 Pulmonary exacerbations

The proportion of patients reporting pulmonary exacerbations during the treatment period, follow up period and across the entire study period will be summarized by cohort and by treatment arm and by pooled arms by regimen for continuous and cyclic regimen

The proportion of patients in each exacerbation category (as defined in Section 2.6.1.2) will be summarized during the treatment period, follow up period and across the study period by cohort and treatment arm.

Overall and within each pulmonary exacerbation category, the number of events will be summarized during the treatment period and across the study period by cohort and treatment arm.

In addition, summaries of the number and percentage of patients experiencing individual pulmonary exacerbation symptoms will be presented during the treatment period and across the study period by duration of symptoms (> 24 hours and > 48 hours):

- Frequency of each symptom/ finding
- Any two symptoms/ findings that most often occur together and may be combined into one symptom
- Combination of 3 symptoms/findings that occur together in the majority of Pulmonary Exacerbations

Symptoms will be further categorized as follows:

- Sputum/viscosity/purulence > 24h [at least 1 of the 3 symptoms reported as > 24h]
- Malaise/fatigue/lethargy > 24h [at least 1 of the 3 symptoms reported as >24h]
- Shortness of breath at rest/exercise >24 h [at least 1 of the 2 symptoms as >24h]

The number and percentage of pulmonary exacerbations in each category will be presented during the treatment period and across the study period by cohort and treatment arm.

In addition, the number of pulmonary exacerbation signs and symptoms last for more than 48

hours will be summarized separately including below categories.

- Sputum/viscosity/purulence > 48h [at least 1 of the 3 symptoms reported as > 48h]
- Malaise/fatigue/lethargy > 48h [at least 1 of the 3 symptoms reported as >48h]
- Shortness of breath at rest/exercise >48 h [at least 1 of the 2 symptoms as >48h]

Time to first pulmonary exacerbation

The time to first pulmonary exacerbation overall will be analyzed using a Cox regression model stratified by baseline macrolide use. The model will include treatment as a fixed-effect factor, and number of pulmonary exacerbations in the 12 months prior to screening as a covariate. Six pairwise comparisons will be evaluated as specified in Section 2.6.3, in addition two pairwise comparisons will be evaluated between pooled continuous regimens vs pooled placebo and, between pooled cyclic regimens and pooled placebo. The estimated adjusted hazard ratio for TIP over placebo will be displayed along with the associated 2-sided 95% CI. For analyses conducted across the treatment period, patients will be censored at the time of last dose of study drug if they did not have a pulmonary exacerbation during the treatment period. Similarly, for analyses conducted across the study period, patients will be censored at the time of last contact if they did not have a pulmonary exacerbation during the study period.

Kaplan-Meier analysis stratified by cohort and treatment arm and by pooled arms (continuous and alternating regimens) will be also presented and displayed graphically.

The time to first pulmonary exacerbation requiring parenteral antibiotics or hospitalization, and the time to first pulmonary exacerbation requiring hospitalization will also be analyzed using the same approach as described for the time to first pulmonary exacerbation overall.

The exposure adjusted rate of pulmonary exacerbations overall

The exposure adjusted rate of exacerbations will be determined across the treatment period and will be derived as follows:

(Number of pulmonary exacerbations reported during the treatment period / sum of exposure time during the treatment period for all patients during the treatment period) / 365.25

The number of pulmonary exacerbations during the treatment period will be analyzed using a generalized linear model assuming the negative binomial distribution including treatment and baseline macrolide use as fixed-effect factors, and number of pulmonary exacerbations in the 12 months prior to screening as a covariate. The log exposure to treatment in years will be included as an offset variable in the model.

Six pairwise comparisons will be evaluated as specified in Section 2.6.3, in addition two pairwise comparisons will be evaluated between pooled continuous regimens vs pooled placebo and, between pooled cyclic regimens and pooled placebo. The estimated rate ratio along with 2-sided 95% interval will be provided.

The exposure adjusted rate of exacerbations across the entire study period will be derived as follows:

(Number of patients with a pulmonary exacerbation during the study period / sum of study period duration for all patients during the study period) / 365.25.

The number of pulmonary exacerbations during the entire study period will be analyzed in a similar manner as the pulmonary exacerbations during the treatment period; the log time in study in years will be included as an offset variable in the model.

Duration of pulmonary exacerbations overall

The duration of pulmonary exacerbations is defined as the sum of the duration of days recorded as an exacerbation for all exacerbations recorded per patient. This will be derived across the treatment period and across the study period. The duration of pulmonary exacerbations will be analyzed using an ANCOVA model. The model will include treatment as a fixed-effect factor, and number of pulmonary exacerbations in the 12 months prior to screening as a covariate.

Six pairwise comparisons will be evaluated as specified in Section 2.6.3, in addition two pairwise comparisons will be evaluated between pooled continuous regimens vs pooled placebo and, between pooled cyclic regimens and pooled placebo. The estimated adjusted treatment difference for each of the comparisons (TIP–placebo) will be displayed along with the associated standard error, 2-sided 95% CI.

Time to permanent study drug discontinuation due to pulmonary exacerbation

The proportion of subjects who permanently discontinue study drug to pulmonary exacerbation will be summarized by cohort and treatment arm.

The time to permanent study drug discontinuation due to pulmonary exacerbation will be analyzed using a Cox regression model stratified by baseline macrolide use. The model will include treatment as a fixed-effect factor, and number of pulmonary exacerbations in the 12 months prior to screening as covariate. Six pairwise comparisons will be evaluated as specified in Section 2.6.3. in addition two pairwise comparisons will be evaluated between pooled continuous regimens vs pooled placebo and, between pooled cyclic regimens and pooled placebo. The estimated adjusted hazard ratio for TIP over placebo will be displayed along with the associated 2-sided 95% CI.

Patients will be censored at the time of last dose of study drug if they did not discontinue study drug due to a pulmonary exacerbation.

Kaplan-Meier analysis stratified by treatment arm will be also presented and displayed graphically.

2.6.3.3 Anti-pseudomonal antibiotics

Proportion of patients requiring anti-pseudomonal antibiotics

The proportion of patients requiring anti-pseudomonal antibiotics across the treatment epoch and across the entire study period will be summarized by treatment arm and by route of administration (overall, oral and parenteral).

Time to first use of anti-pseudomonal antibiotics across the entire study period

The time to first use of anti-pseudomonal antibiotics by route of administration (overall, oral and parenteral) will be analyzed using a Cox regression model stratified by baseline macrolide use. The model will include treatment as a fixed-effect factor, and number of pulmonary exacerbations in the 12 months prior to screening as a covariate. Six pairwise comparisons will be evaluated as specified in Section 2.6.3. in addition two pairwise comparisons will be evaluated between pooled continuous regimens vs pooled placebo and, between pooled cyclic regimens and pooled placebo. The estimated adjusted hazard ratio for TIP over placebo will be displayed along with the associated 2-sided 95% CI.

The exposure adjusted rate of usage of anti-pseudomonal antibiotics across the entire study period

The number of anti-pseudomonal antibiotics across the entire study period will be analyzed by route of administration (overall, parenteral and oral) using a generalized linear model assuming the negative binomial distribution including treatment and baseline macrolide use as fixed-effect factors, and number of pulmonary exacerbations in the 12 months prior to screening as a covariate. The log time in study in years will be included as an offset variable in the model. Six pairwise comparisons will be evaluated as specified in Section 2.6.3, in addition two pairwise comparisons will be evaluated between pooled continuous regimens vs pooled placebo and, between pooled cyclic regimens and pooled placebo. The adjusted rate of usage will be provided for each treatment arm. The estimated rate ratio together with the 2-sided 95% interval will be provided.

Duration of anti-pseudomonal antibiotic use across the entire study period

The duration of anti-pseudomonal antibiotic use (days) across the entire study period will be summarized by cohort, treatment arm and pooled cyclic and continuous regimens and by route of administration (overall, parenteral and oral).

2.6.3.4 Hospitalization

Proportion of patients requiring hospitalization due to serious respiratory-related AEs

The proportion of patients requiring hospitalization due to serious respiratory-related AEs across the treatment period, follow up period, and across the entire study period will be summarized by treatment arm and by pooled continuous and cyclic regimen. The number of events will also be summarized.

The time to first hospitalization due to serious respiratory-related AEs

The time to first hospitalization due to serious respiratory related AEs will be analyzed using a Cox regression model stratified by baseline macrolide use. The model will include treatment as a fixed-effect factor, and number of pulmonary exacerbations in the 12 months prior to screening as covariate. Six pairwise comparisons will be evaluated as specified in Section 2.6.3, in addition two pairwise comparisons will be evaluated between pooled continuous regimens vs pooled placebo and, between pooled cyclic regimens and pooled placebo. The estimated adjusted hazard ratio for TIP over placebo will be displayed along with the associated 2-sided 95% CI.

Kaplan-Meier analysis stratified by treatment arm will be also presented and displayed graphically.

If a small number of events occur after pooling events, only the Kaplan-Meier estimation of time to first hospitalization due to serious respiratory-related AEs will be provided.

Duration of hospitalization due to serious respiratory-related AEs

The duration of hospitalization due to serious respiratory-related AEs (days) across the entire study period will be summarized by treatment arm and pooled arms by continuous and cyclic regimens. Summaries will be event driven and not patient driven.

Number of hospitalizations due to serious respiratory-related AEs

The number and percentage of patients with 0, 1, 2, >2 hospitalizations due to serious respiratory-related AEs across the entire study period will be summarized by treatment arm

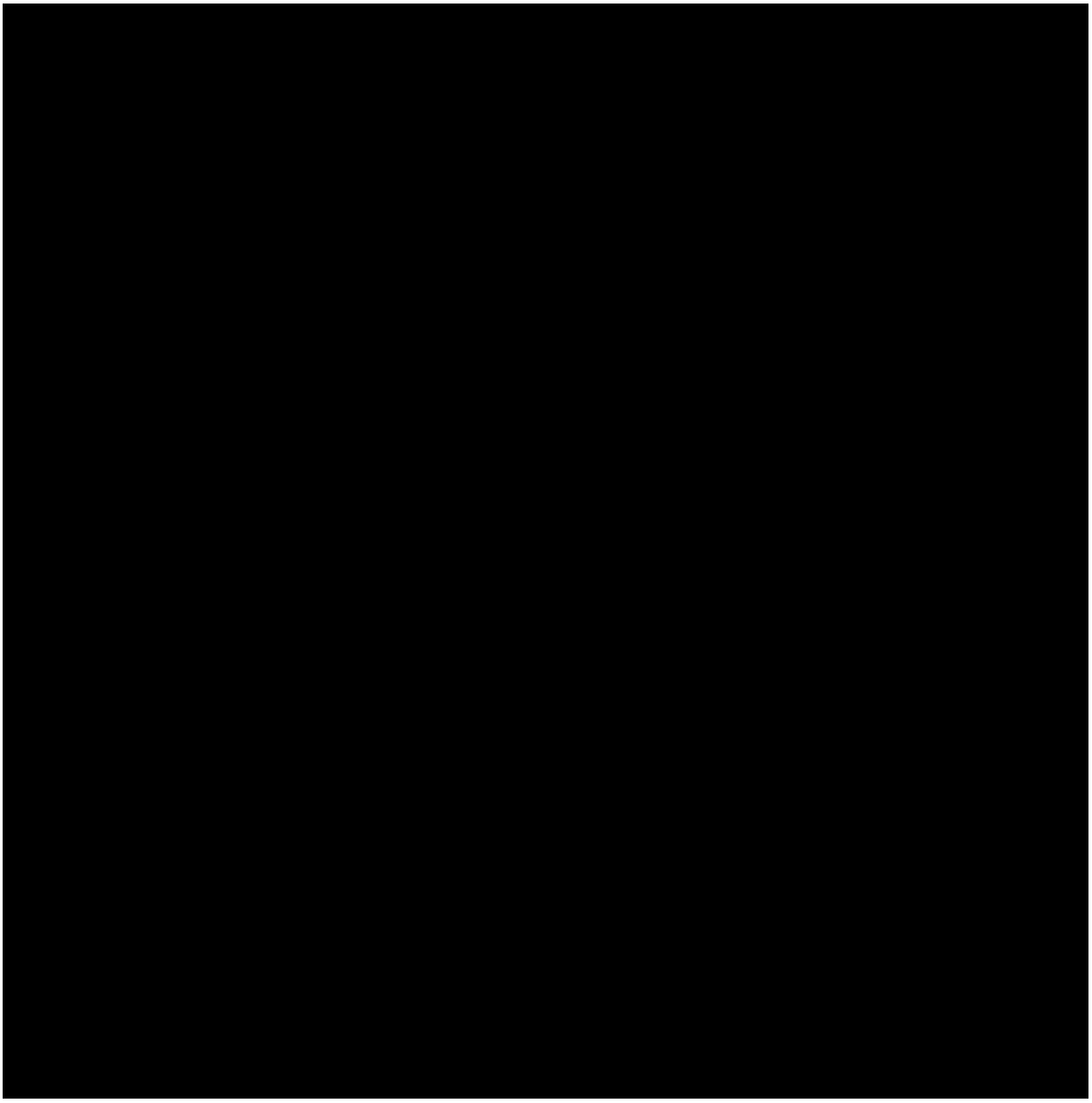
and pooled arms by continuous and cyclic regimens.

The exposure adjusted rate of hospitalization due to serious respiratory-related AEs

The exposure adjusted rate of hospitalization due to serious respiratory-related AEs will be determined across the study period.

The number of hospitalization due to serious respiratory-related AEs during the study period will be analyzed using a generalized linear model assuming the negative binomial distribution including treatment and baseline macrolide use as fixed-effect factors, and number of pulmonary exacerbations in the 12 months prior to screening as a covariate. The log exposure to treatment in years will be included as an offset variable in the model.

Six pairwise comparisons will be evaluated as specified in Section 2.6.3, in addition two pairwise comparisons will be evaluated between pooled continuous regimens vs pooled placebo and, between pooled cyclic regimens and pooled placebo. The estimated rate ratio along with 2-sided 95% interval will be provided.



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2.6.4 Handling of missing values/censoring/discontinuations

For time to event analyses, patients not experiencing that event will be censored at either the time of last dose of study drug (if the analysis is across the treatment period) or the date of last follow-up visit (if the analysis is across the entire study period).

2.7 Safety analyses

All safety analyses will be performed using the SAF, and will be presented by cohort and treatment arm (TIP, TIP/placebo cyclical, placebo and pooled placebo).

Baseline for safety analyses is defined as the last measurement prior to the first dose of study drug in the study.

Appropriate summary statistics will be provided for laboratory test results, audiology, bronchial hyperreactivity and vital signs.

Safety data will be presented in the individual patient data listings based on the SAF. Only descriptive analysis of safety will be performed (i.e., no statistical hypothesis testing will be performed).

Table 2-2 shows the safety parameters (e.g., raw value, change from baseline, incidence, and clinical abnormalities) that will be summarized for AEs/Serious AEs (SAEs), laboratory data (serum chemistry/hematology, urinalysis), 12-lead ECG and vital signs.

For the non-AE safety evaluations, raw values, and changes from baseline will be summarized as indicated in Table 2-2. For example, an "X" under the raw value column (second column) means that the raw values for the safety evaluation will be summarized; an "X" under the change column (third column) means that change will be summarized.

Throughout this section, "change" refers to absolute change from baseline.

Table 2-2 Summaries of safety data

Safety Assessment	Incidence	Raw Value	Change	Clinical Abnormalities
AEs*	X			Not applicable
Serum Chemistry/Hematology		X	X	X
Urinalysis	X	X	X	X
12-lead ECG		Present in listing only		
Vital signs		X	X	Not applicable

ECG: electrocardiogram; X: safety assessment will be summarized in tables.
*AEs, SAEs and other significant AEs or AEs of special interest, see Section 2.7.1

2.7.1 Adverse events (AEs)

An AE will be classified as a treatment emergent AE (TEAE) if it starts on or after the date of the first dose of study drug until study completion.

TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) using the latest Medical Dictionary for Drug Regulatory Affairs (MedDRA) available at the time of database lock.

The number and percentage of patients experiencing TEAEs, SAEs, AEs suspected to be related to study drug, AEs leading to study drug discontinuation and AEs leading to death will be summarized by treatment arm and overall.

The number and percentage of patients experiencing TEAEs will be summarized by treatment arm by SOC and PT, and by SOC, PT and maximum severity. In addition, the number and percentage of patients experiencing AEs suspected to be related to study drug will be summarized by treatment arm by SOC and PT.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on TEAEs which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT using the SAF.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

AEs of special interest (AESIs):

The number and percentage of patients with AEs regarding ototoxicity and/or hemoptysis and renal events will be summarized. Specific AE terms will be collected on the AESI electronic case report forms (eCRFs). These data include symptoms, medical history and relevant local assessment.

In addition, post-inhalational adverse events will be summarized as instructed 2.7.4.3.

2.7.2 Deaths

AEs leading to death will be listed.

2.7.3 Laboratory data

Laboratory parameters will be recorded at Visit 1 (Screening), Visit 101 (Day 1), Visit 102 (Day 8), Visit 103 (Day 29), Visit 104 (Day 57), Visit 105 (Day 85), Visit 106 or TD (Day 113), Follow-up Visit 201 (Day 141) and Follow-up Visit 202 or PSD (Day 169).

Laboratory data (hematology, serum chemistry), including changes from baseline, will be summarized descriptively (n, mean, SD, median, minimum and maximum).

Hematology

Hematology parameters include hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

Serum chemistry

Serum chemistry parameters include urea (or BUN), creatinine, glucose, total bilirubin (TBL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase, sodium, potassium, chloride, calcium, bicarbonate, phosphate, total protein, albumin, and uric acid.

All continuous laboratory variables will be classified according to the normal ranges (low, normal, high) and shift tables of the categories at baseline versus the last available post-baseline visit will be generated. In addition hematology and serum chemistry value shifts from baseline to above upper/below lower of normal will be tabulated with number and percentage of patients by visit and at any time post-baseline.

Urine dipstick tests

Results of the urine dipstick tests (specific gravity, protein, glucose, blood) will be presented with number and percentage of patients with negative values and trace categories. WBC and RBC sediments result will be summarized in the same manner as described above for continuous laboratory parameters.

Note: a urine pregnancy test will be performed at Visit 2 (Screening 2) and Follow-up Visit 202 or PSD (Day 169). These data will be listed only.

Proportion of patients with liver events at any post-baseline visit

Elevated liver function test cases will be classified according to the following grading system:

- ALT or AST > 3 × upper limit of normal (ULN)
- ALT or AST > 5 × ULN
- ALT or AST > 8 × ULN
- ALT or AST > 10 × ULN
- ALT or AST > 20 × ULN
- ALP > 1.5 × ULN
- ALP > 2 × ULN
- ALP > 5 × ULN
- TBL > ULN
- TBL > 1.5 × ULN
- TBL > 2 × ULN
- ALT or AST > 3 × ULN and TBL > 1.5 × ULN
- ALT or AST > 3 × ULN and TBL > 2 × ULN
- ALT or AST > 3 × ULN and TBL > 2 × ULN without ALP > 2 × ULN

In addition, 3 x ULN < ALT / AST <= 5 x ULN will be evaluated.

For the above mentioned events patient listings will be provided (ALT, AST, TBL, ALP) , by visit, for all visits.

Renal safety

Renal safety will be determined using the following classifications using the central laboratory data provided:

- Serum creatinine increase from baseline 25% - <50%
- Serum creatinine increase from baseline >=50%
- BUN increase from baseline >=1.5 x ULN, if it was normal at baseline
- Estimated glomerular filtration rate (eGRF) of 50 mL/min/1.73m2 or less
- Dipstick proteinuria >=3+ (not present at baseline)

- Albumin-creatinine-ratio (ACR) >=30 mg/g or >=3 mg/mmol
- Protein-creatinine-ratio (PCR)>=150 mg/g or >=15 mg/mmol
- Dipstick hematuria >=3+ (not present at baseline)

For the above mentioned renal safety laboratory parameters, patient listings will be provided (creatinine, eGFR, proteinuria, ACR, PCR) , by visit, for all visits.

2.7.4 Other safety data

2.7.4.1 Audiology testing

Audiology testing will be conducted at selected sites at Visit 2 (prior to dosing), Visit 102 (Day 8), Visit 103 (Day 29), Visit 104 (Day 57), Visit 105 (Day 85), Visit 106 or TD (Day 113), Follow-up Visit 201 (Day 141) and Follow-up Visit 202 or PSD (Day 169). Certain patient sub-groups are required to have audiology testing during the screening period.

The results of audiology testing will be summarized at each visit by the number and percentage of patients. Patients with the following decreases in consecutive frequencies will be presented for audiology safety: any frequencies decreased, 2 consecutive frequencies decreased, >=10 dB decrease in >=3 consecutive frequencies, >=15 dB decrease in >=2 consecutive frequencies, >=20 dB decrease in at least 1 frequency. Events can be observed in either ear.

Results of the bone conduction test will be summarized with the number of patients who performed the test; the number and percentage of conductive, neurosensory and mixed hearing loss in left, right or both ears will also be given.

Summaries will be based on the AUD.

2.7.4.2 Vital signs

Systolic/diastolic blood pressure, radial pulse rate (over a 30s interval), respiratory rate and body temperature will be recorded at Visit 1 (screening), Visit 101 (start of treatment), Visit 106 or TD (Day 113) and Follow-up Visit 202/PSD (Day 169).

Vital signs data, including changes from baseline, will be summarized for each visit using descriptive statistics (n, mean, SD, minimum, median, and maximum).

2.7.4.3 Post-inhalation events

Events occurring within 5 minutes after inhalation of the study treatment (post-inhalation events) will be observed at the site by site personnel at Visit 101 (start of treatment), Visit 102 (Day 8), Visit 103 (Day 29), Visit 104 (Day 57), Visit 105 (Day 85) and Visit 106 or TD (Day 113). If the event is determined to be an adverse event, this should be recorded on the Adverse Event eCRF. In addition, event details will also be captured in the Post-inhalation Adverse Event eCRF. For post-inhalation events that are determined not to be an adverse event, event details will be recorded in the Post-inhalation clinical events eCRF.

The number and percentage of patients experiencing post-inhalation events occurring at a site visit within 5 minutes (yes/no), experiencing post-inhalation events that are ongoing at the completion of a site visit (yes/no), experiencing post-inhalation events which have an action taken to reduce the event (yes/no) will be presented for each visit. The number and percentage of patients for each time of onset category (≤30 sec, >30 sec-1min, >1-2min, >2-5min, >5min) will be presented for each visit.

Descriptive statistics including mean, SD minimum, median and maximum will be provided for the duration of the events in minutes for each visit.

Summaries of post-inhalation events will be conducted for the 2 types of events, i.e., post-inhalation clinical events and post-inhalation adverse events. The number of patients with post-inhalation events will be summarized by treatment. In addition, the number of these events and the event rate adjusted for exposure will be displayed by treatment.

An AE occurring after 5 minutes post-inhalation will be reported as an AE.

2.7.4.4 Bronchial hyperreactivity

Bronchial hyperreactivity will be measured as the acute relative change from pre-dose to 30±15 minutes post-dose in FEV_1% predicted at Visit 101 (start of treatment), Visit 102 (Day 8), Visit 103 (Day 29), Visit 104 (Day 57), Visit 105 (Day 85) and Visit 106 or TD (Day 113). A change of 20% or more is considered a clinically significant indicative of bronchospasm/bronchial hyperreactivity. This change will be summarized with the number and percentage of patients who experienced no change, a decrease/increase of >0-<10%, a decrease/increase of 10-<20% or a decrease/increase >=20%. Both summaries will also be performed for the patients who did the post-dose spirometry test in a 60 minute time window.

2.7.4.5 Resource utilization

Data as reported on the resource utilization eCRF will be listed for all patients with data.

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2.8 Pharmacokinetic endpoints

The serum and sputum pharmacokinetic properties of tobramycin will be assessed by evaluating tobramycin concentrations in serum and sputum collected from non-CF BE population post administration of o.d. or b.i.d. doses of TIP.

Serum specimens for PK tobramycin concentration will be assessed at Visit 101 (start of treatment) 0-1 and 1-2 h post-dose and Visit 103 (Day 29) 0-1 and 1-2 h post-dose.

Sputum specimens for PK tobramycin concentration will be assessed at Visit 101 (start of treatment) 0-1 and 1-2 h post-dose, Visit 102 (Day 8) 0-2 h post-dose, Visit 103 (Day 29) 5-6 h post-dose and Visit 105 (Day 85) 3-4 h post-dose

Tobramycin concentrations in serum and sputum specimens will be summarized descriptively (n, mean, SD, minimum, median and maximum) by scheduled visit and timepoint for the PAS.

A separate PK sub-study is included in this study which collects additional PK samples. Patients included in this sub-study will provide 1 serum specimen per specified interval at Visit 101 (start of treatment) and Visit 103 (Day 29): pre-dose, 0-1, 1-2, 3-4 and 5-6 h. Descriptive statistics (n, mean, SD, minimum, median and maximum) will be provided for the PSSAS by scheduled visit and time point.

All PK data will be presented in individual patient data listings.

2.9 PD and PK/PD analyses

The independent bio-analytical report (including PK model and if possible PK/PD model) will be done by Ventiv or Novartis and is not covered in this SAP.

2.10 Patient reported outcomes

Quality of Life Questionnaire-Bronchiectasis (QoL- B)

QoL-B is assessed at Visit 2 (Baseline), Visit 102 (Day 8), Visit 103 (Day 29), Visit 104 (Day 57), Visit 105 (Day 85), Visit 106 or TD (Day 113), Follow-up Visit 201 (Day 141) and Follow-up Visit 202 or PSD (Day 169).

The QoL-B consists of 37 items across 8 domains: Physical, Role Functioning, Vitality, Emotional Function, Social Functioning, Treatment Burden, Health Perception and Respiratory Symptoms. Each of the 37 items is scored from 1 to 4.

Items in the questionnaire are expressed either ‘negatively’ or ‘positively’, therefore a number of items must be recorded before the scores for each of the domains are calculated. The score is calculated by adding the score obtained for each item of a domain (scale), after any necessary recoding. Scoring for each domain can be computed only if at least half the items have been completed. If not, then the domain should not be scored and should be considered missing for that particular person who filled out the questionnaire.

Descriptive statistics will be provided for each domain score for all applicable visits for the FAS by treatment arm and pooled arms by continuous and cyclic regimens. Changes from baseline to each post-baseline visit will also be summarized. For the QoL-B Respiratory Symptom Score (RSS), further summaries will be provided for:

- Patients with/without pulmonary exacerbations during the treatment period
- Patients with overall study drug compliance >=80%

The change from baseline in QoL-B RSS will be analyzed using a linear repeated measure model. The model will contain treatment, baseline macrolide use, visit (visits 102 to 202), and treatment-by-visit interaction as fixed effects with baseline QoL-B RSS, baseline-by-visit interaction as covariates. The within-patient correlation will be modeled using the unstructured covariance matrix in the mixed model. If the model does not converge, then the compound symmetry covariance structure will be used. The restricted maximum likelihood method will be used.

QoL-B correlation with other patient reported outcome measures will be performed by RTI health solutions; consequently these are not detailed within this SAP.

Details on deriving the domain scores can be found in Section 5.5.

[redacted]

[redacted]

2.12 Interim analysis

No interim analysis of efficacy is planned for this study.

The final analysis will be performed after the database is locked, the treatment assignments are unblinded using the actual randomization, and the database released.

An independent DMC is set-up to review safety data and provide the Sponsor with guidance on safety issues. SAE listings generated from the Novartis safety database, ARGUS, will be reviewed monthly by the DMC. The DMC will also perform a pre-planned review of AE and additional pre-defined safety data when approximately 50% of patients have completed the 28 days of treatment.

The membership of the DMC and the responsibilities of the DMC, [redacted] will be defined in a separate 'DMC Charter' document. The DMC Charter will include information about data flow, purpose and timings of DMC meetings, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

3 Sample size calculation

Sample size estimation was based on a difference of 2.0 log10 CFU/g, with standard deviations of 2.0 log10 CFU/g. The assumptions were based on conservative estimates from published results (Konstan et al 2011a, Konstan et al 2011b, Barker et al 2000, and Wilson et al 2013).

As there are 3 primary comparisons between the 3 doses versus placebo, the Bonferroni multiplicity adjustment has been used (0.05/3) for sample size calculation. Using α=1.67% (2-sided) and 90% power, the sample size estimation yielded n = 36 patients per treatment arm as valid for intent-to-treat (ITT) analyses. This takes into account an approximate 20%-discontinuation rate. For the primary efficacy analysis, patients from TIP continuous and TIP cyclical regimen within the same cohort will be pooled as they receive exactly the same treatment during the first 28 days. Placebo patients will be pooled across the 3 cohorts, as the number of placebo capsules is not expected to influence the change in *P. aeruginosa* bacterial counts. With the current study design, the power is 94% to detect a reduction of 2.0 log10 CFU/g for each dose level versus placebo.

For calculation of sample size, NQuery Advisor version 7.0 module MTTO-1 was used.

4 Change to protocol specified analyses

The annual rate of pulmonary exacerbations will be summarized overall. Analyses on the number of pulmonary exacerbations will only be performed overall and not by exacerbation category.

5 Appendix

5.1 Imputation rules for complete or partial missing dates

5.1.1 Study drug

When the date of the last dose of study drug is missing for a patient in the SAF, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when study drug was returned will be used in the calculation of treatment duration.

5.1.2 Adverse event start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(D) No convention	(D) No convention	(D) No convention	(D) No convention
YYYY < TRTY	(D) Before Treatment Start	(D) Before Treatment Start	(D) Before Treatment Start	(D) Before Treatment Start
YYYY = TRTY	(o) Uncertain	(o) Before Treatment Start	(o) Uncertain	(o) After Treatment Start
YYYY > TRTY	(D) After Treatment Start	(D) After Treatment Start	(D) After Treatment Start	(D) After Treatment Start

Before imputing AE start date, find the AE start reference date.

- If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
- Else AE start reference date = treatment start date

Impute AE start date -

- If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.

- If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
- If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
- Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
- If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
- If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
- Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
- If the AE start date year value is equal to the treatment start date year value:
  - And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
  - Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
  - Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Adverse event end date imputation

- If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
- If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
- If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.4 Relative day of AE onset and AE end imputations

The relative day of AE onset will be calculated as follows:

- AE start date - date of first dose of study drug (if AE start date is completely known)
- missing (if AE onset date is incomplete or unknown)

The relative day of AE end will be calculated as follows:

- AE end date – date of first dose of study drug (if AE end date is completely known)
- missing (if AE end date is incomplete or unknown)

The duration of an AE will be calculated as follows:

- AE end date – AE start date + 1 (when both dates are completely known)

- Date of end of study completion/discontinuation – AE start date + 1 (when the AE onset date is fully known but the AE is not resolved at the end of the trial): in this case the duration will be presented as ">x days" in the listing rather than "x days"
- missing (when the AE start date is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date, or when the AE onset date is > date of end of completion/discontinuation and the AE is not resolved)

5.1.5 Concomitant medication start date imputation

The following table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(D) Uncertain	(D) Uncertain	(D) Uncertain	(D) Uncertain
YYYY < TRTY	(o) Before Treatment Start	(o) Before Treatment Start	(o) Before Treatment Start	(o) Before Treatment Start
YYYY = TRTY	(o) Uncertain	(o) Before Treatment Start	(o) Uncertain	(o) After Treatment Start
YYYY > TRTY	(o) After Treatment Start	(o) After Treatment Start	(o) After Treatment Start	(o) After Treatment Start

- If the CM start date year value is missing, the imputed CM start date is set to 1 day prior to treatment start date.
- If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
  - If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
  - Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
- If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
  - If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).

- Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

- If the CM start date year value is equal to the treatment start date year value:
  - And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to 1 day prior treatment start date.
  - Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
  - Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.6 Concomitant medication end date imputation

- If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
- If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
- Only include if ongoing records will have an imputed CM end date. If CM day/month/year is missing then use the treatment end date + 1 day as the imputed CM end date.

If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.6.1 Prior therapies date imputation

Not applicable

5.1.6.2 Post therapies date imputation

Not applicable

5.1.6.3 Other imputations

Not applicable

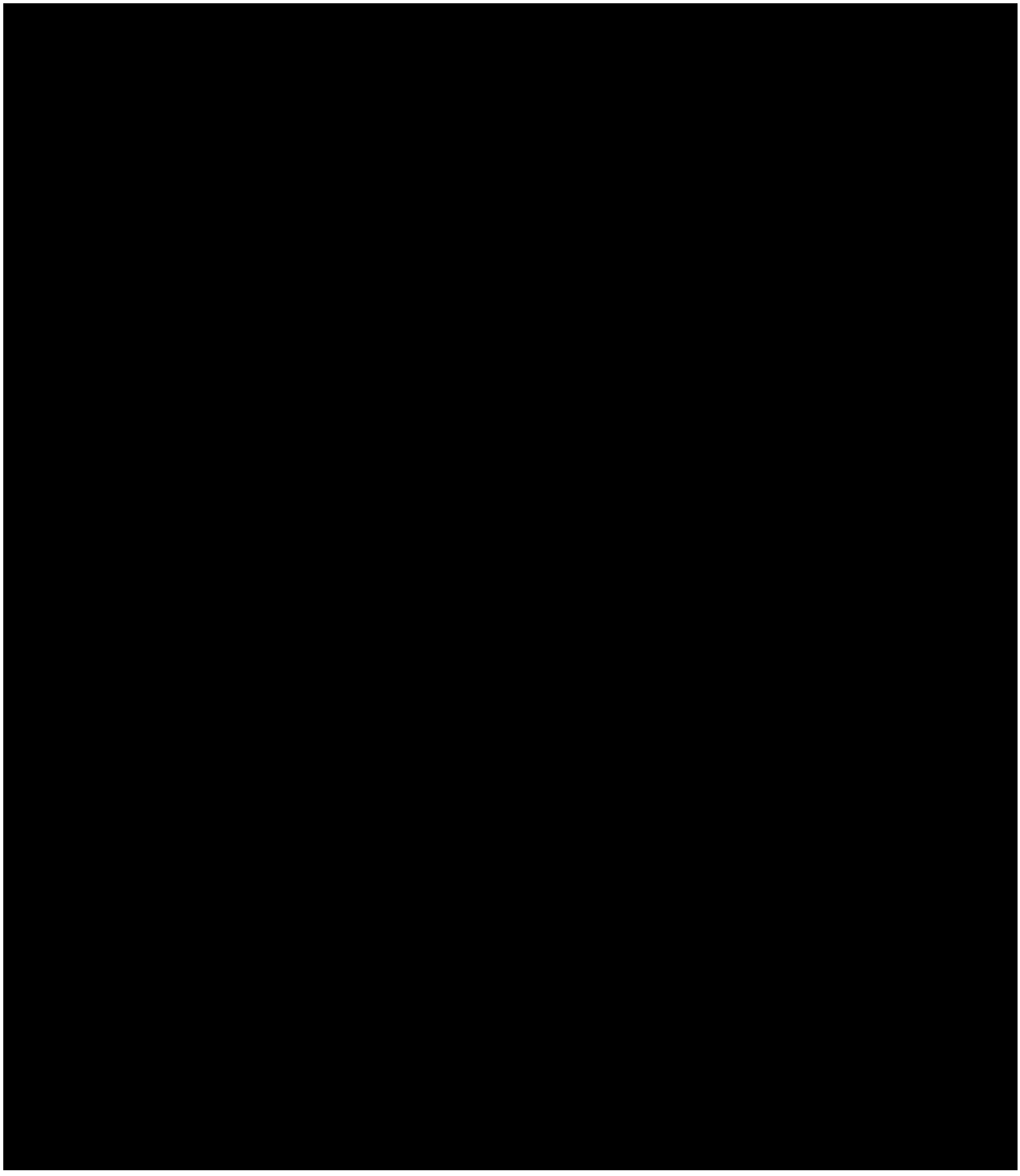
5.2 Laboratory parameters derivations

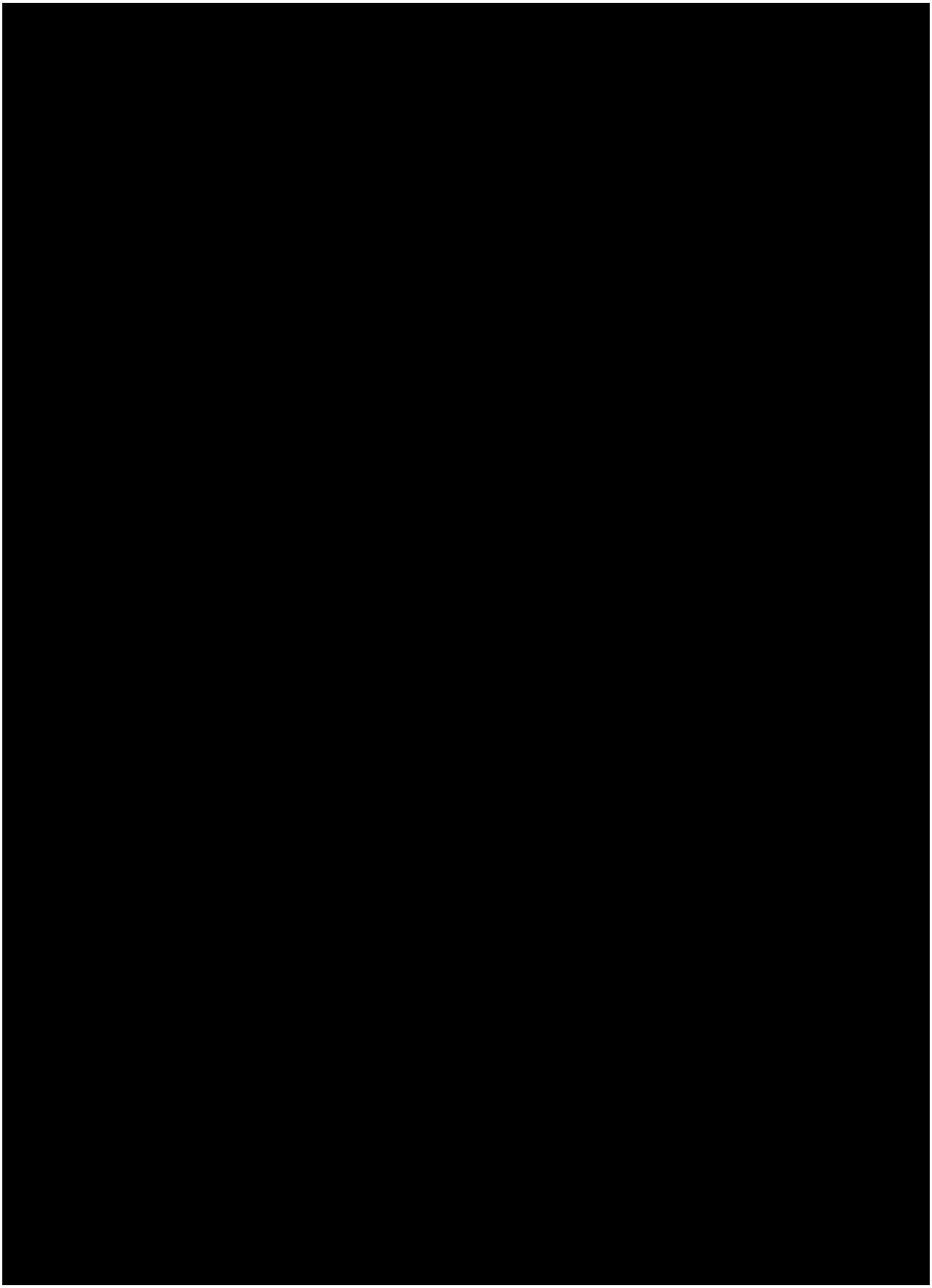
Table 5-1 Criteria for potentially clinically important laboratory tests

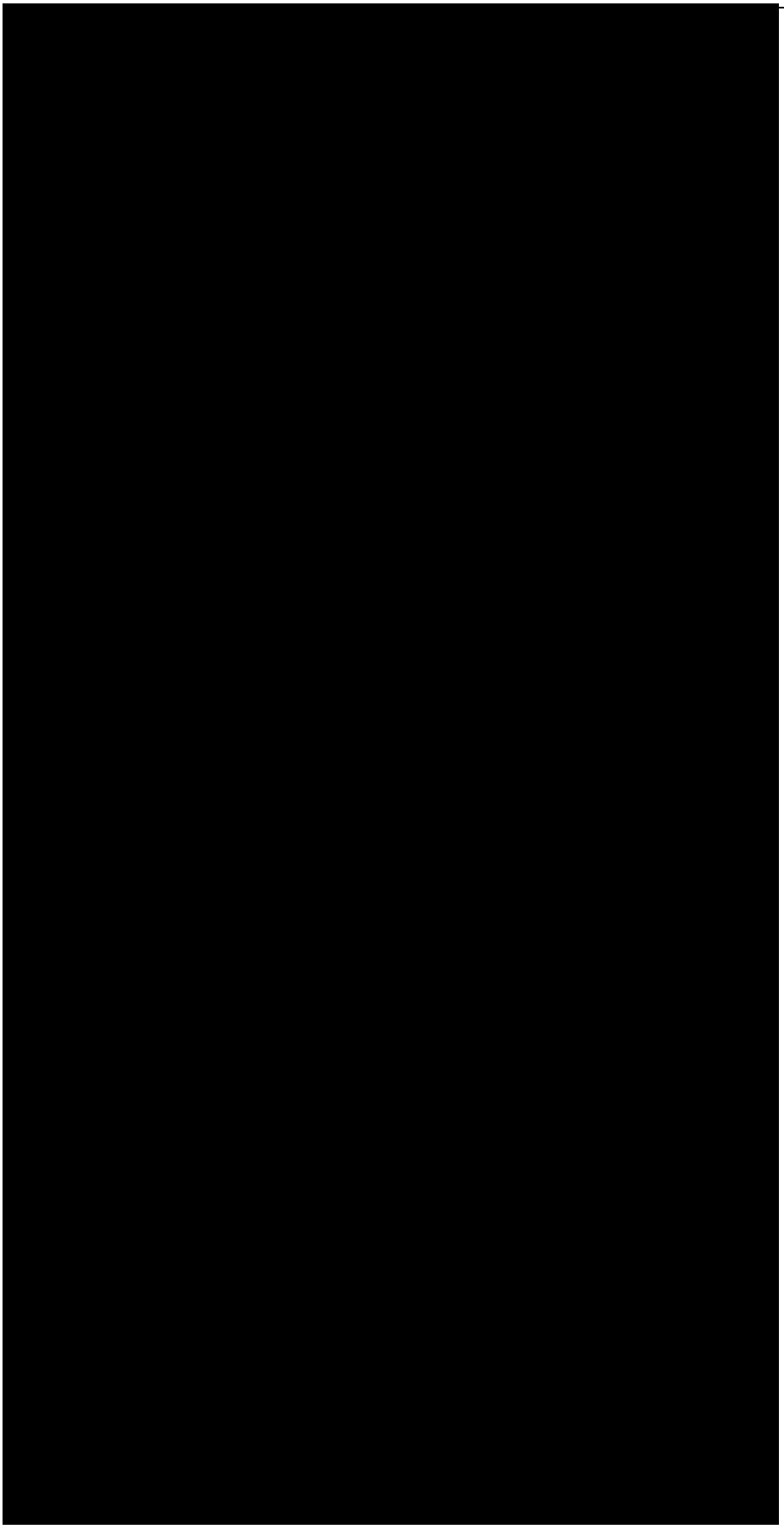
Parameter	SI Unit	Lower Limit < or =	Higher Limit > or =
Hematology			
WBC	x10^9/L	2.50	30.00

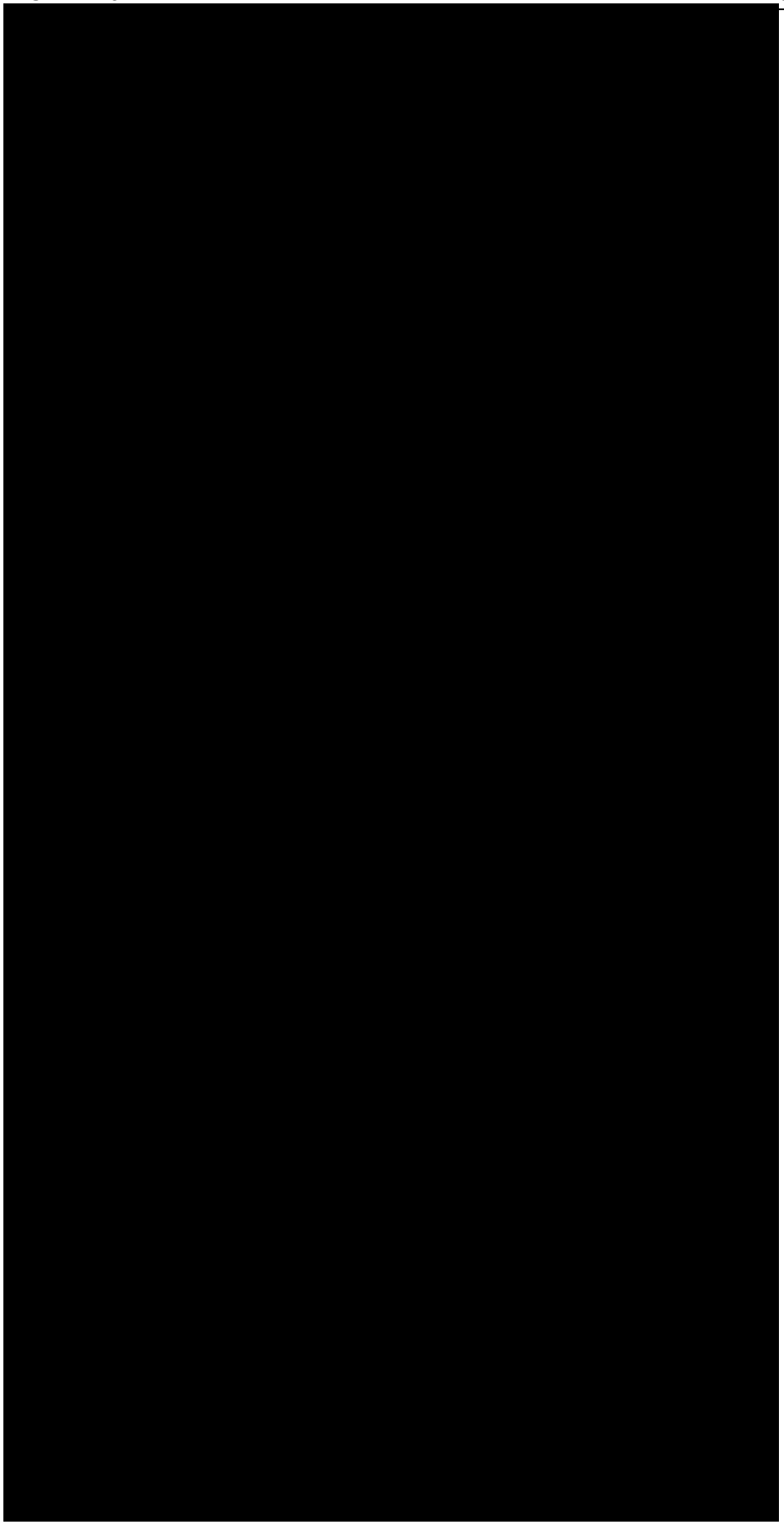
HGB	g/dL	8.0	18.0
Platelets	x10^9/L	50	1,000
Platelets, Na Citrate	x10^9/L	39	914
Chemistry			
Calcium	mmol/L	1.50	3.50
Potassium	mmol/L	2.5	6.5
Fasting Glucose, Serum	mmol/L	2.20 (Female) 2.80 (Male)	22.20
Random Glucose, Serum	mmol/L	2.20 (Female) 2.80 (Male)	22.20
Urea (BUN)	mmol/L		> 1.5 x ULN
Creatinine Enzymatic	umol/L		> 1.25 x ULN
Creatinine Kinase	U/L		850 (Female) 975 (Male)
Total Bilirubin	umol/L		57.0
eGFR by MDRD	mL/min/SSA	50	
Endocrinology			
HCG (Quantitative)	IU/L		5.01 (Female)
Urinalysis			
Protein, Urine	mg/dL		30
Glucose, Urine	mg/dL		250
Blood, Urine			Small
Albumin-Creatinine Ratio	mg/g		30
Protein-Creatinine Ratio	Ratio		0.15

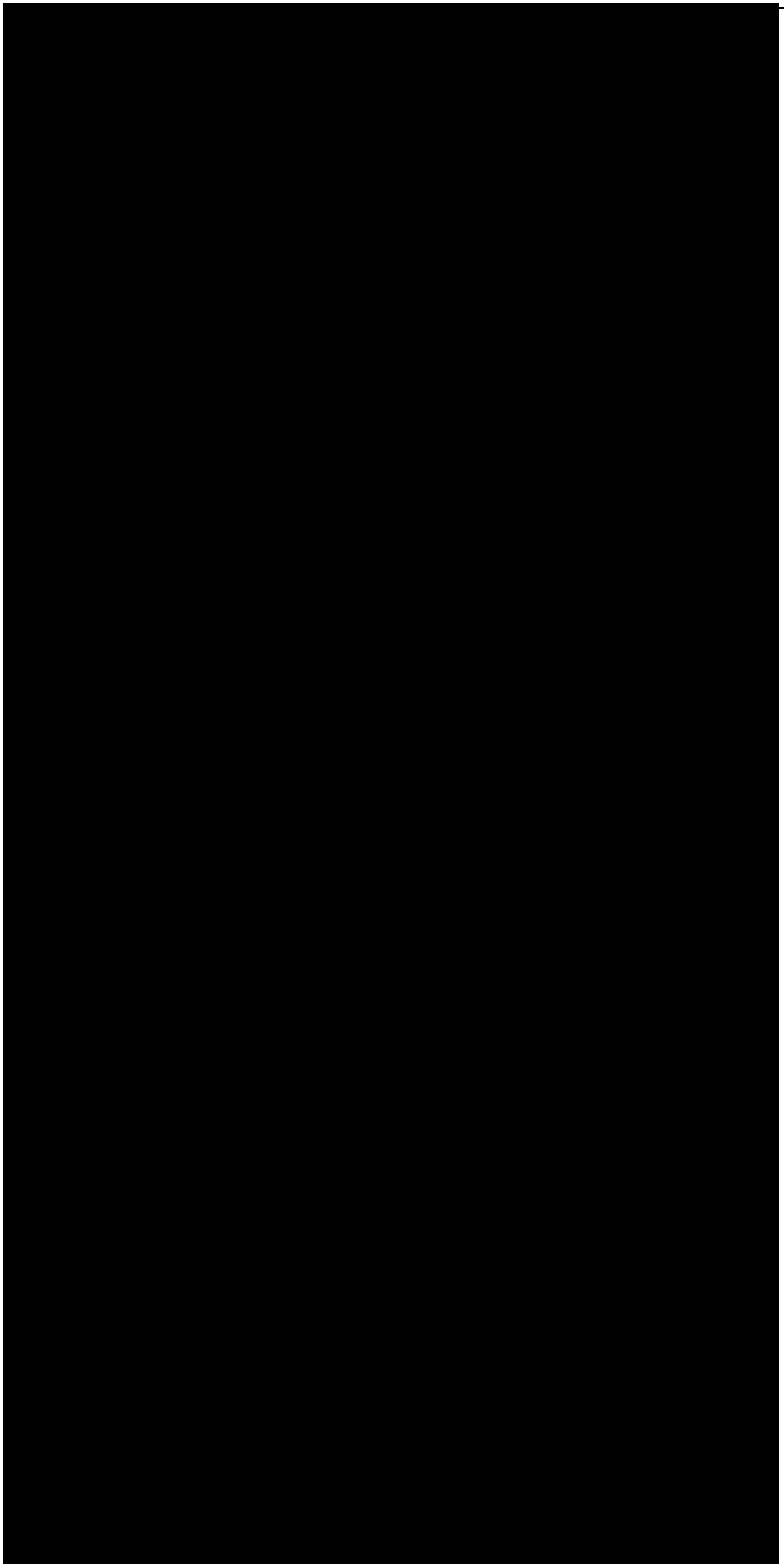
LLN: Lower limit of normal value provided by the laboratory
ULN: Upper limit of normal value provided by the laboratory

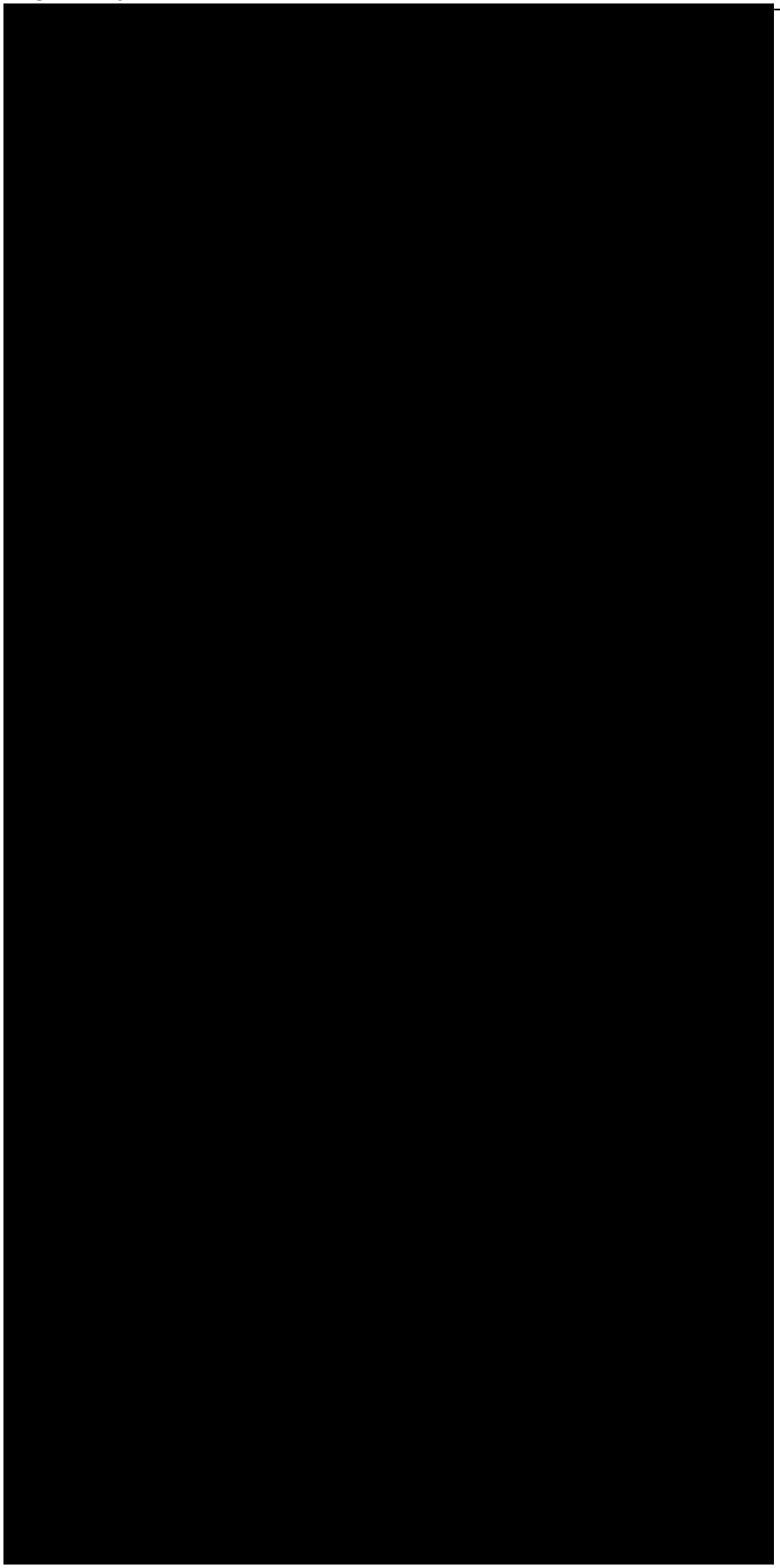


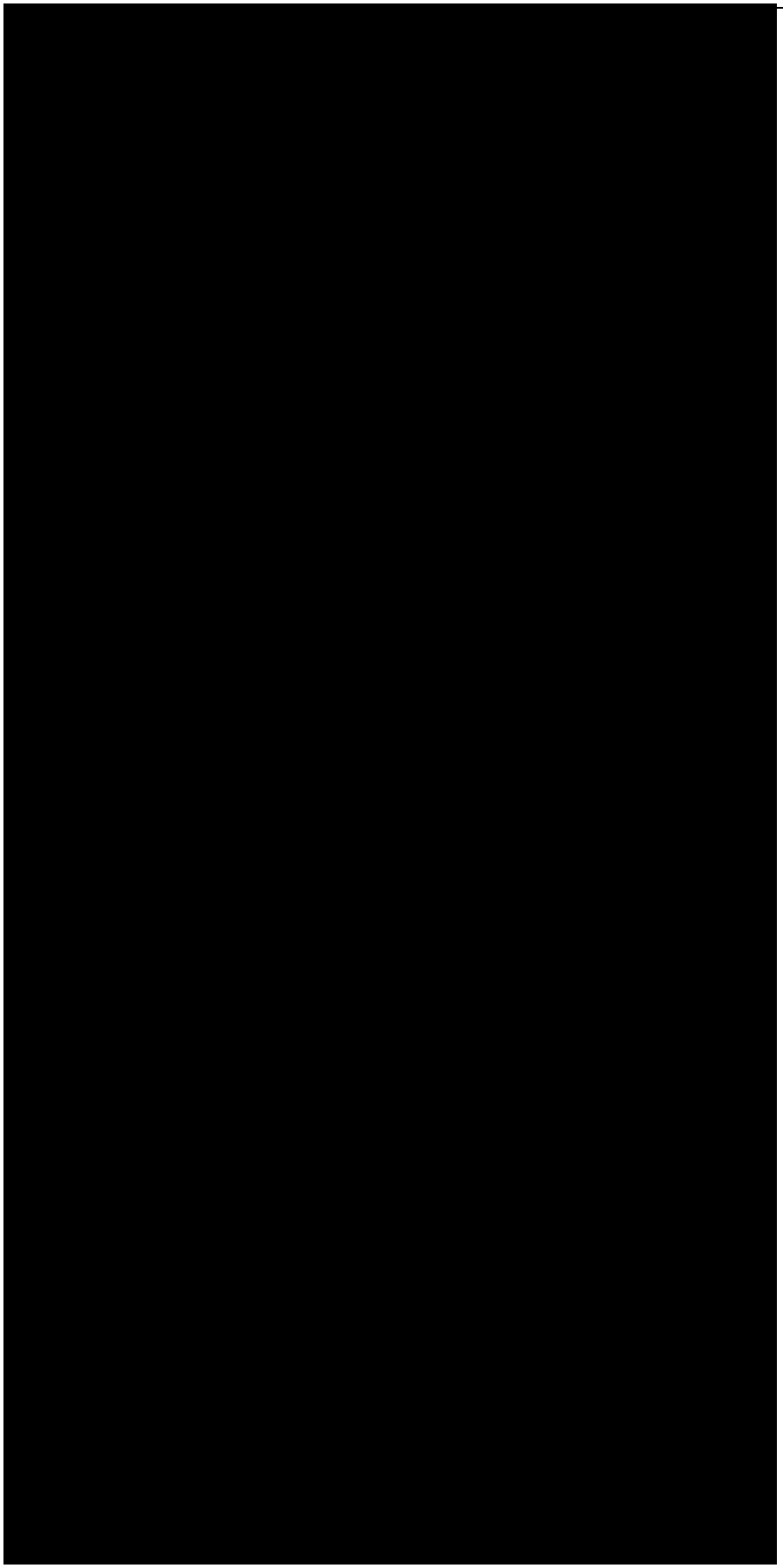


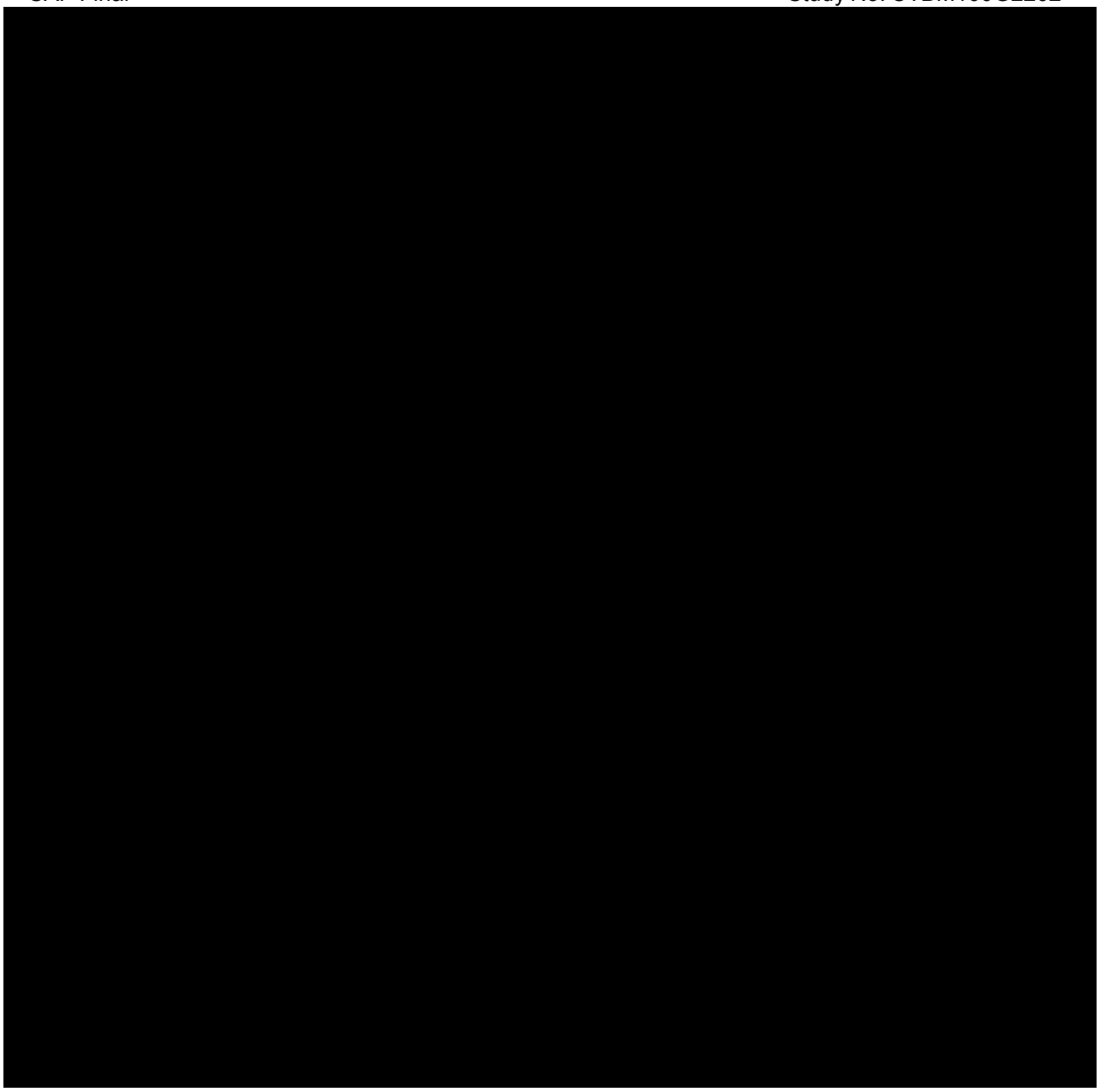


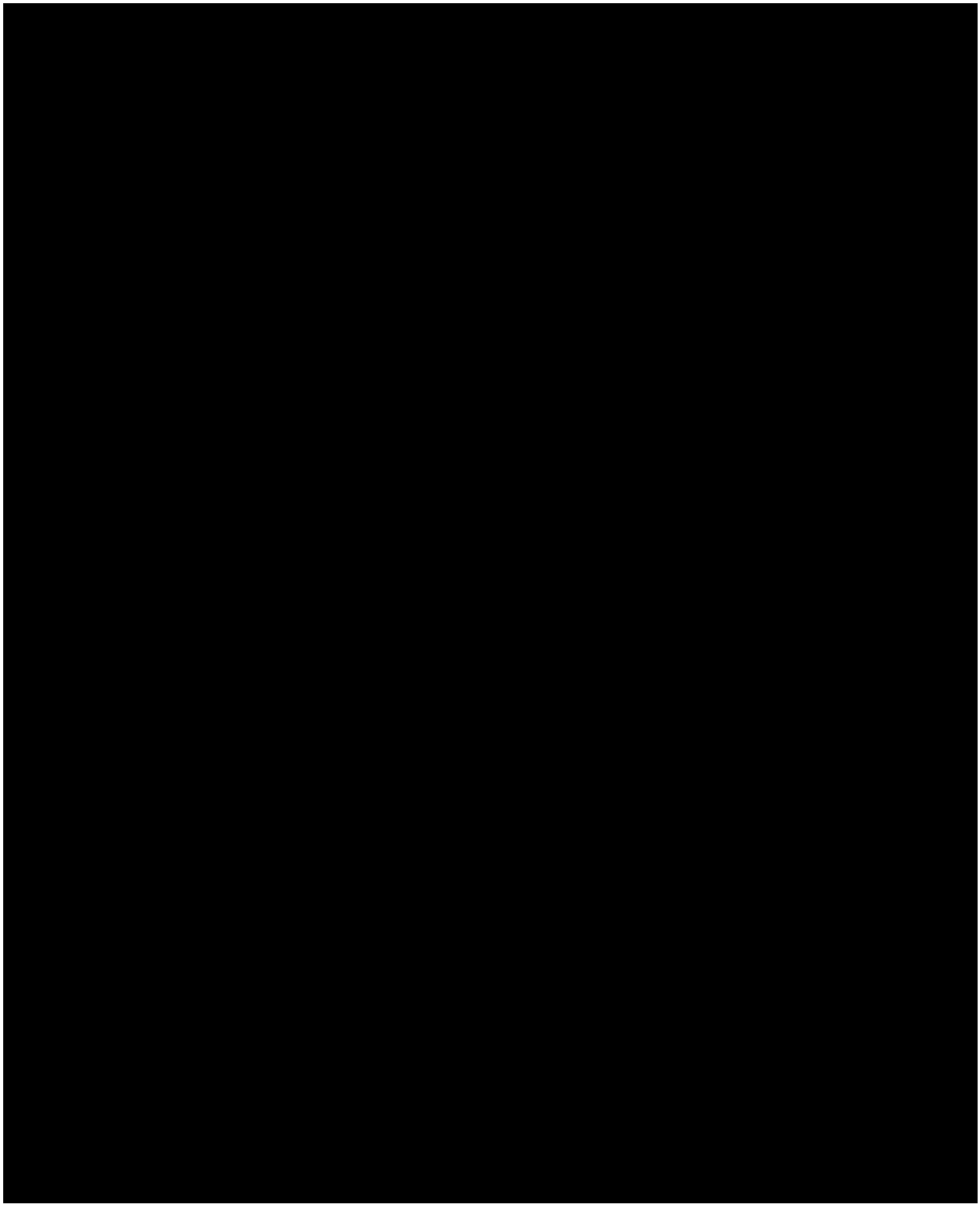


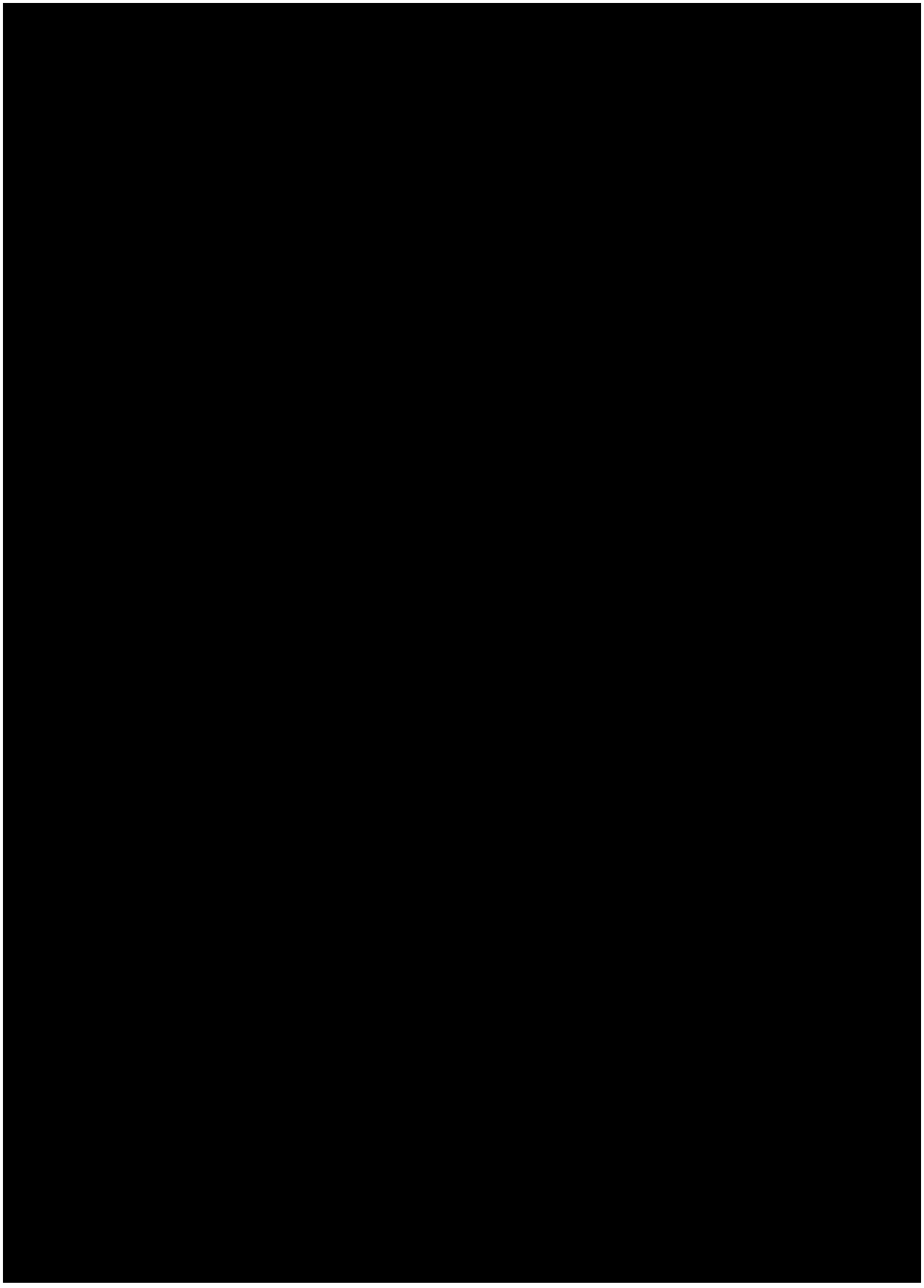


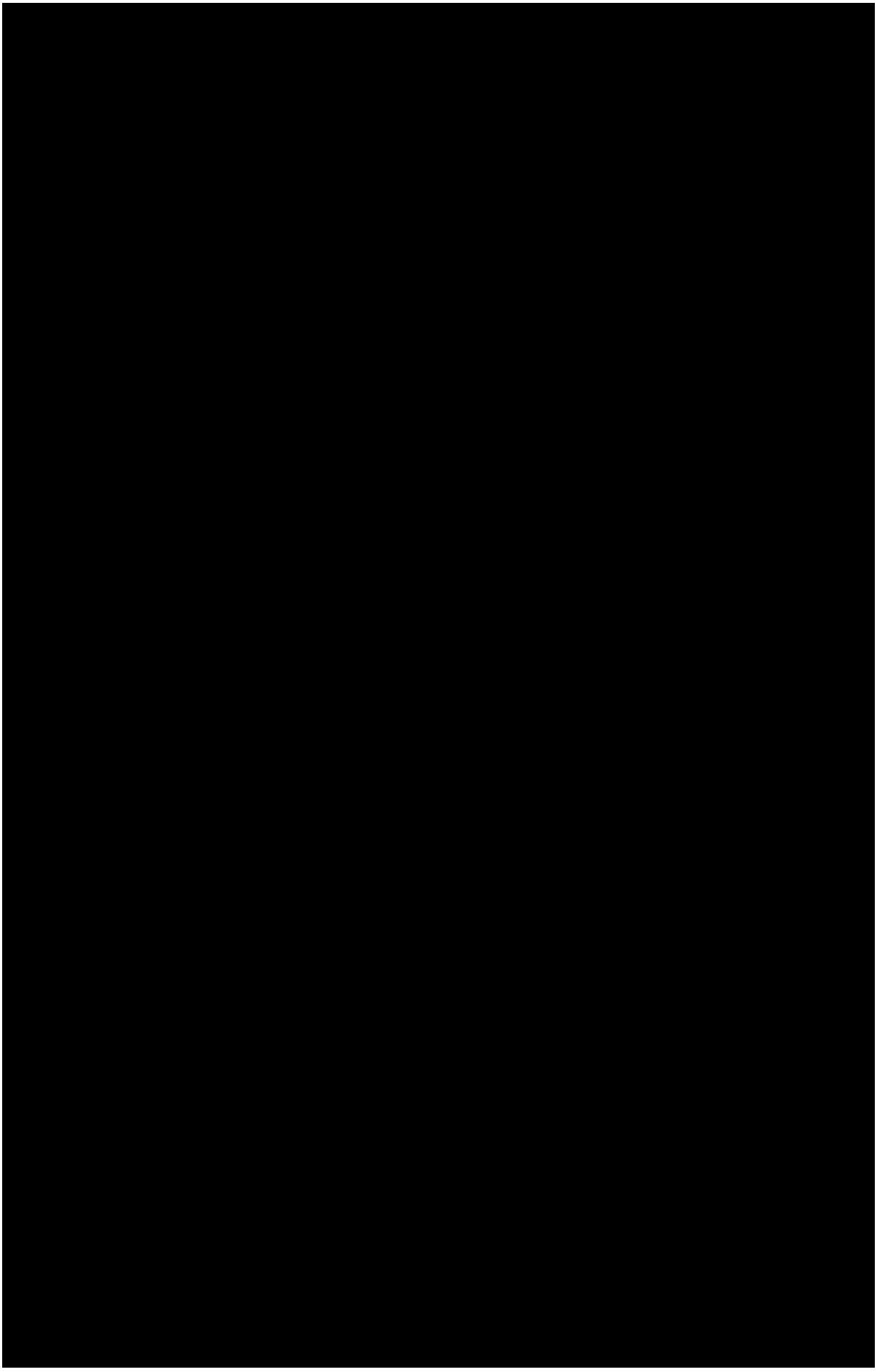


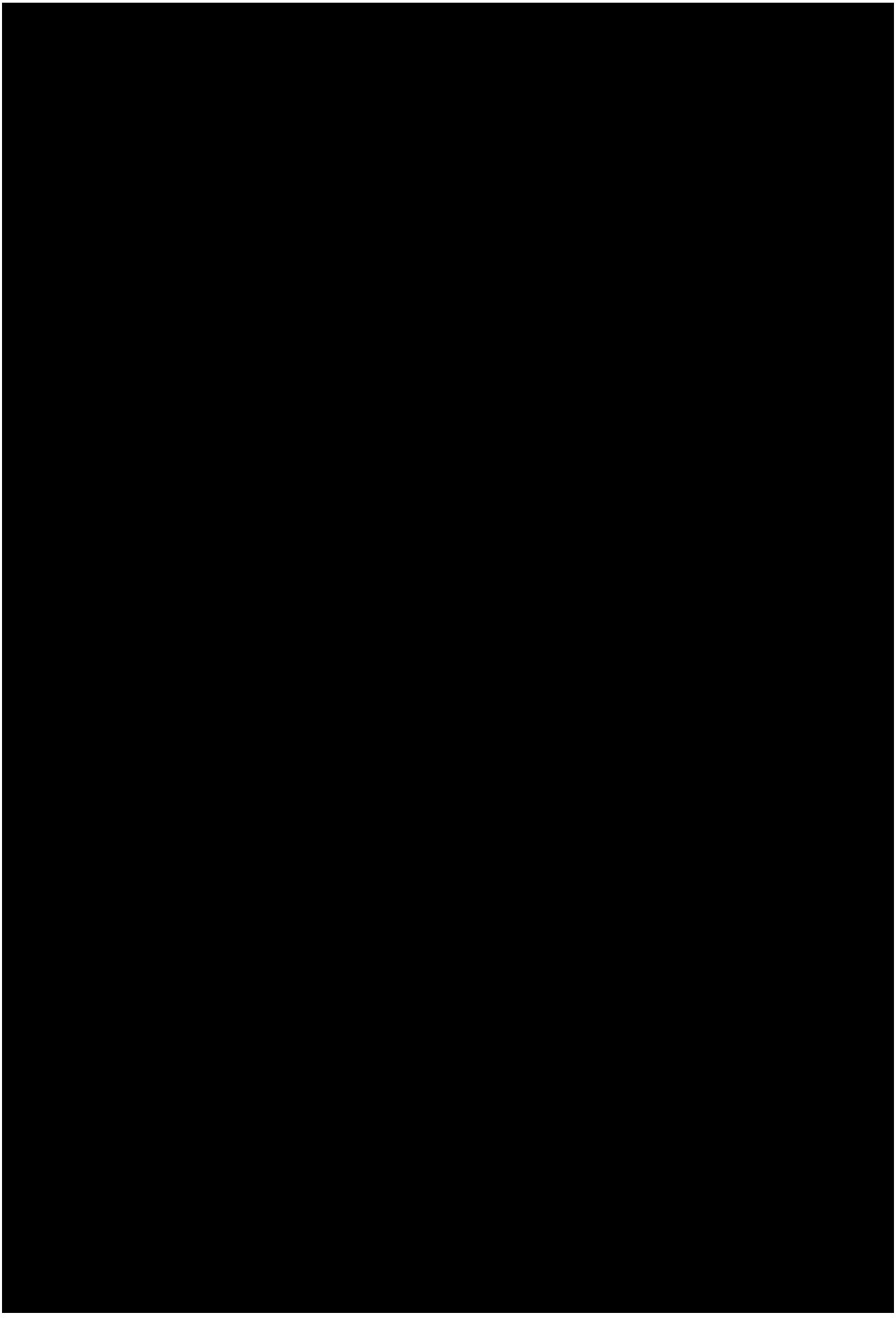












5.5 Patient reported outcomes – questionnaires

QoL-B

Step 1: Item-by-item responses

The values assigned to participants' responses for each question are listed below.

For questions 1 – 4: A lot of difficulty = 1, Moderate difficulty = 2, A little difficulty = 3, No difficulty = 4

For questions 5 – 11: Always = 1, Often = 2, Sometimes = 3, Never = 4

For questions 12 – 15: Use the assigned number designated for each specific response

For questions 16 – 26: Completely true = 1, Mostly true = 2, A little true = 3, Not at all true = 4

For question 27: Use the assigned number designated for each specific response

For question 28: Always = 1, Often = 2, Sometimes = 3, Never = 4

For questions 29 – 31: A lot = 1, A moderate amount = 2, A little = 3, Not at all = 4

For question 32: Clear = 1, Clear to yellow = 2, Yellowish-green = 3, Brownish-dark = 4, Green with traces of blood = 4, Don't know = 6

For questions 33 – 37: Always = 1, Often = 2, Sometimes = 3, Never = 4

Step 2: Scoring multiple responses or skipped questions

If two responses are marked and there is no opportunity to ask the respondent which one is correct, the worst response should be selected for data entry and scoring. This provides a conservative estimate of their response to this item. For example, item #29 asks: "Have you felt congestion in your chest?" The response choices range from "A lot" to "Not at all." If the respondent marks "a lot" and "a moderate amount" you should enter "a lot" for this question.

Please note that some items are reverse-keyed and therefore, the worst response is not necessarily the lower number.

If participants skip a question, do not assign a response value (i.e. leave it blank).

Step 3: Scaling item 32 and reverse coding

Item 32 (resp32) has 5 possible answers that are scored and all other items on the QOL-B questionnaire have only 4 possible answers. Possible scores for resp32 are 1, 2, 3, 4, 5 and 6, whereas for other questions the possible scores are 1, 2, 3, and 4. Resp32 and eight other items are also reverse coded; because of the wording for these particular items, reverse coding is necessary to make higher scores correspond to better health outcomes. Reverse coding is conducted for resp32, and for health5, vital8, treat12, treat14, health15, role20, health24, and role27.

For item 32: Original value = Reverse-coded value

1 = 4
2 = 3
3 = 2
4 = 1
6 = Not scored

For item 19: "doesn't apply" = Not scored

For items 5, 8, 12, 14, 15, 20, 24, 27: Original value = Reverse-coded value

1 = 4
2 = 3
3 = 2
4 = 1

Step 4: Preparing to calculate scaled scores and missing values

If the responses are missing for more than half the items in a scale, the score for that scale should not be calculated. Missing values are not imputed. Note that missing responses within a scale will change the number of points corresponding to a change of one answer category for one item for that respondent.

Step 5: Calculate the scaled scores

Calculate scores for the eight QOL-B domains

Physical Functioning Domain (5 items)

1. _____
2. _____
3. _____
4. _____
16. _____

If 3 or more responses are missing, do not score this domain. Scaled score = [((mean of responses)-1)/3] x 100

Role Functioning Domain (5 items)

17. _____
20. _____
25. _____
27. _____
28. _____

If 3 or more responses are missing, do not score this domain. Scaled score = [((mean of responses)-1)/3] x 100

Vitality Domain (3 items)

6. _____
8. _____
9. _____

If 2 or more responses are missing, do not score this domain. Scaled score = [((mean of responses)-1)/3] x 100

Emotional Functioning Domain (4 items)

7. _____
10. _____
11. _____
23. _____

If 3 or more responses are missing, do not score this domain. Scaled score = [((mean of responses)-1)/3] x 100

Social Functioning Domain (4 items)

18. _____
19._____(* "doesn't apply" = Not scored)
22. _____
26. _____

If 3 or more responses are missing, do not score this domain. Scaled score = [((mean of responses)-1)/3] x 100

Treatment Burden Domain (3 items)

12. _____
13. _____

14. _____

If 2 or more responses are missing, do not score this domain. Scaled score = [((mean of responses)-1)/3] x 100

Health Perceptions Domain (4 items)

5. _____
15. _____
21. _____
24. _____

If 3 or more responses are missing, do not score this domain. Scaled score = [((mean of responses)-1)/3] x 100

Respiratory Symptoms Domain (9 items)

29. _____
30. _____
31. _____
32. _____
33. _____
34. _____
35. _____
36. _____
37. _____

If 5 or more responses are missing, do not score this domain. Scaled score = [((mean of responses)-1)/3] x 100

QOL-B

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Understanding the impact of your illness and treatments on your everyday life can help your doctor monitor your health and adjust your treatments. For this reason, we have developed a quality of life questionnaire specifically for people who have bronchiectasis. Thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Demographics *Please fill-in the information or check the box indicating your answer.*

A. What is your date of birth?
Date ☐☐/☐☐/☐☐☐☐
Mo Day Year

B. What is your gender?
☐ Male ☐ Female

C. During the past week, have you been on vacation or out of school or work for reasons **NOT** related to your health?
☐ Yes ☐ No

D. What is your current marital status?
☐ Single/never married
☐ Married
☐ Widowed
☐ Divorced
☐ Separated
☐ Remarried
☐ With a partner

E. Which of the following best describes your racial background?
☐ Caucasian
☐ African American
☐ Hispanic
☐ Asian/Oriental or Pacific Islander
☐ Native American or Native Alaskan
☐ Other (please describe) _____
☐ Prefer not to answer this question

F. What is the highest grade of school you have completed?
☐ Some high school or less
☐ High school diploma/GED
☐ Vocational school
☐ Some college
☐ College degree
☐ Professional or graduate degree

G. Which of the following best describes your current work or school status?
☐ Attending school outside the home
☐ Taking educational courses at home
☐ Seeking work
☐ Working full or part time (either outside the home or at a home-based business)
☐ Full time homemaker
☐ Not attending school or working due to my health
☐ Not working for other reasons/ Retired

Continue to Next Page

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Section I. Quality of Life *Please check the box indicating your answer.*

During the past week, to what extent have you had difficulty:	A lot of difficulty	Moderate difficulty	A little difficulty	No difficulty
1. Performing vigorous activities, such as gardening or exercising	☐	☐	☐	☐
2. Walking as fast as others (family, friends, etc.)	☐	☐	☐	☐
3. Carrying heavy things, such as books, groceries, or shopping bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐

During the past week, indicate how often:	Always	Often	Sometimes	Never
5. You felt well	☐	☐	☐	☐
6. You felt tired	☐	☐	☐	☐
7. You felt anxious	☐	☐	☐	☐
8. You felt energetic	☐	☐	☐	☐
9. You felt exhausted	☐	☐	☐	☐
10. You felt sad	☐	☐	☐	☐
11. You felt depressed	☐	☐	☐	☐

Are you currently on any treatments (such as oral or inhaled medications, PEP or Flutter® device, chest PT, or Vest) for bronchiectasis?

☐ Yes ☐ No (Go to Question 15 on the next page)

Please circle the number indicating your answer. Please choose only one answer for each question.

12. To what extent do your treatments for bronchiectasis make your daily life more difficult?
    1. Not at all
    2. A little
    3. Moderately
    4. A lot

13. How much time do you currently spend each day on your treatments for bronchiectasis?
    1. A lot
    2. A moderate amount
    3. A little
    4. Almost none

14. How difficult is it for you to fit in your treatments for bronchiectasis each day?
    1. Not at all
    2. A little
    3. Moderately
    4. Very

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QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Please circle the number indicating your answer. Please choose only one answer for each question.

15. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

Thinking about your health during the past week, indicate the extent to which each sentence is true for you.

	Completely true	Mostly true	A little true	Not at all true	Doesn't apply
16. I have to limit vigorous activities, such as walking or exercising	☐	☐	☐	☐	
17. I have to stay at home more than I want to	☐	☐	☐	☐	
18. I am worried about being exposed to others who are sick	☐	☐	☐	☐	
19. It is difficult to be intimate with a partner (kissing, hugging, sexual activity)	☐	☐	☐	☐	☐
20. I lead a normal life	☐	☐	☐	☐	
21. I am concerned that my health will get worse	☐	☐	☐	☐	
22. I think my coughing bothers others	☐	☐	☐	☐	
23. I often feel lonely	☐	☐	☐	☐	
24. I feel healthy	☐	☐	☐	☐	
25. It is difficult to make plans for the future (vacation, attending family events, etc.)	☐	☐	☐	☐	
26. I feel embarrassed when I am coughing	☐	☐	☐	☐	

Please circle the number or check the box indicating your answer.

During the past week:

27. To what extent did you have trouble keeping up with your job, housework, or other daily activities?
1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

	Always	Often	Sometimes	Never
28. How often does having bronchiectasis get in the way of meeting your work, household, family, or personal goals?	☐	☐	☐	☐

Continue to Next Page

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Section II. Respiratory Symptoms

Please check the box indicating your answer.

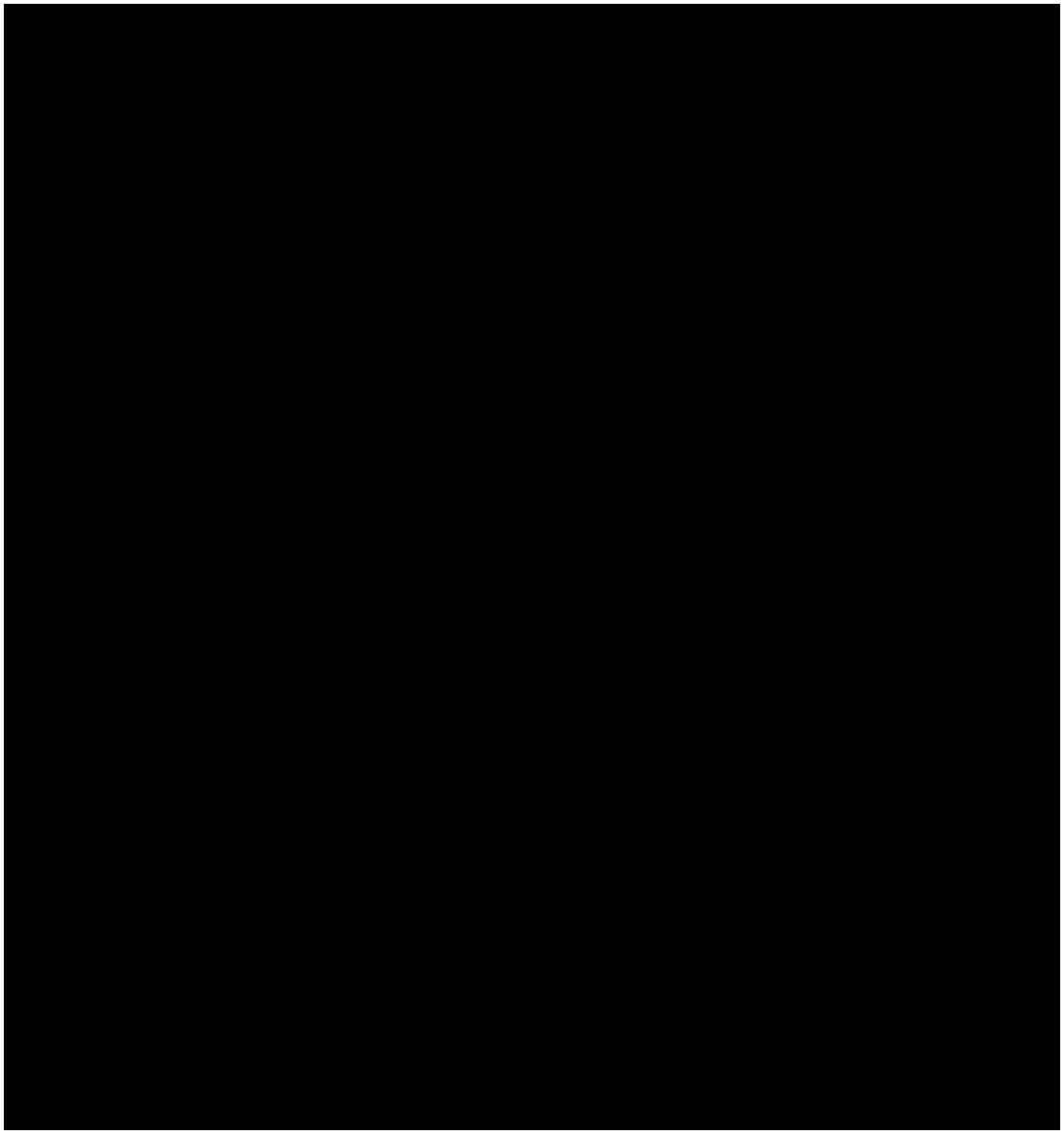
Indicate how you have been feeling during the past week:	A lot	A moderate amount	A little	Not at all
29. Have you felt congestion in your chest?	☐	☐	☐	☐
30. Have you been coughing during the day?	☐	☐	☐	☐
31. Have you had to cough up mucus?	☐	☐	☐	☐

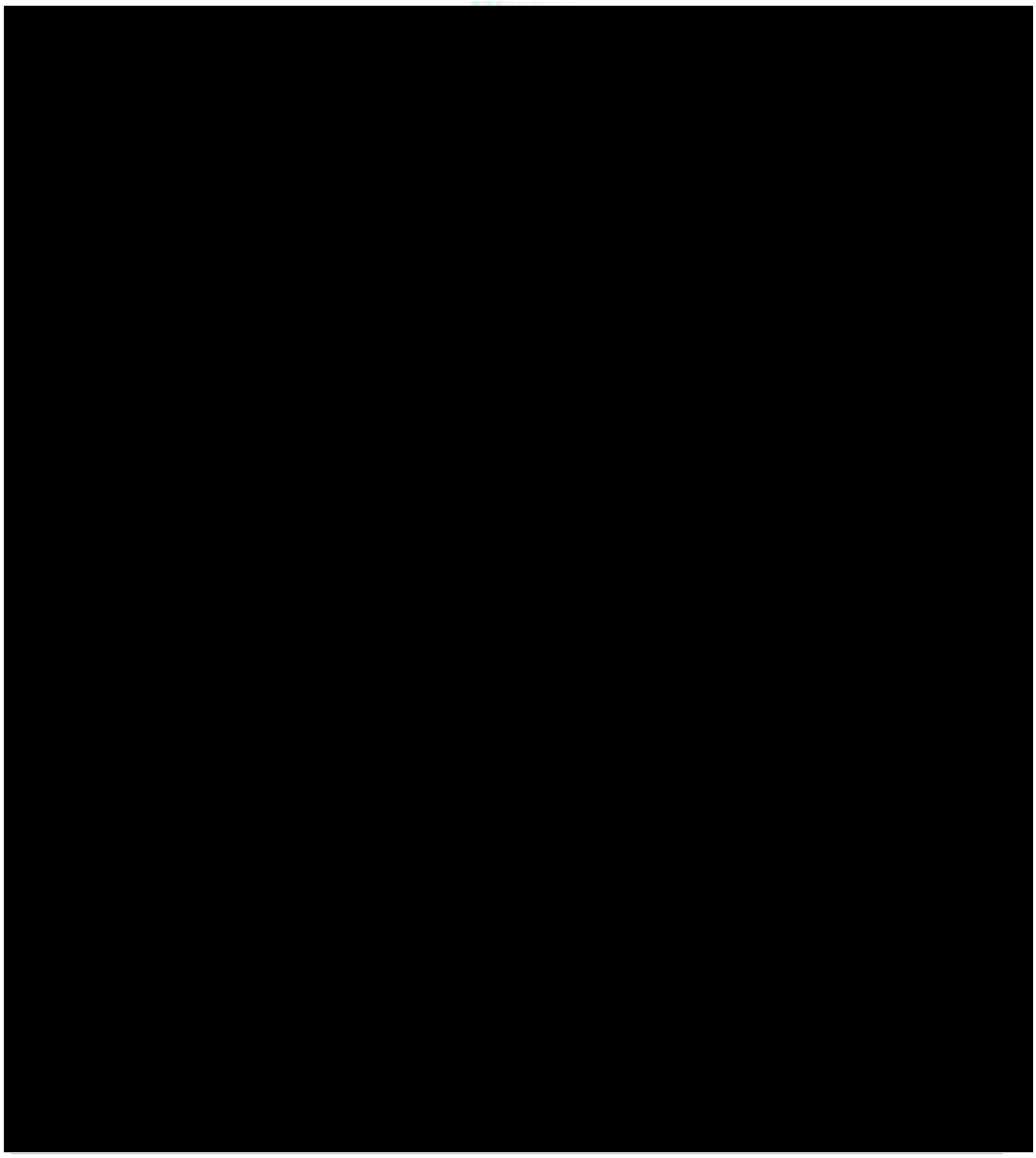
32. Has your sputum been mostly:
☐ Clear ☐ Clear to yellow ☐ Yellowish-green
☐ Brownish-dark ☐ Green with traces of blood ☐ Don't know

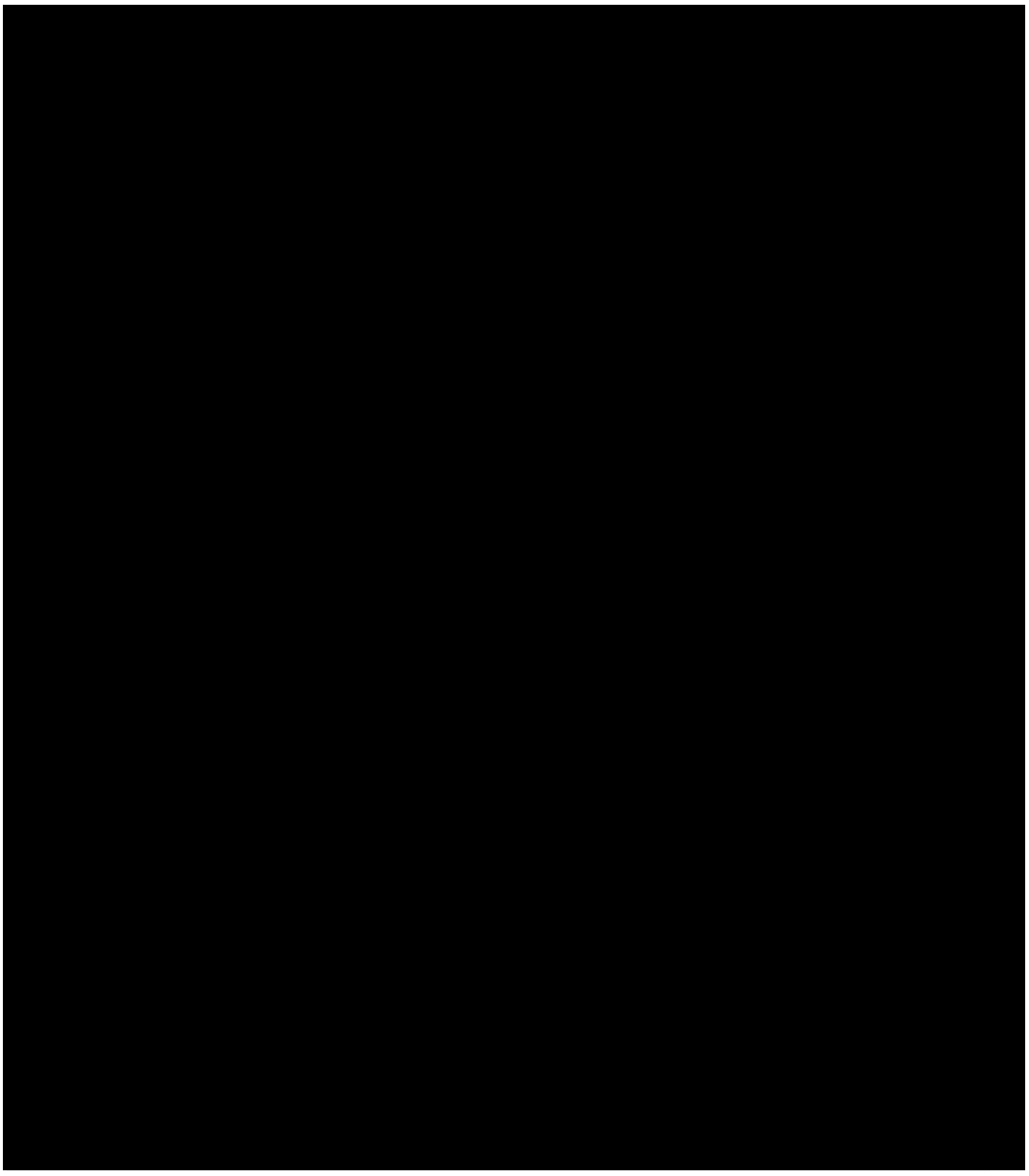
How often during the past week:	Always	Often	Sometimes	Never
33. Have you had shortness of breath with greater activity, such as housework or yardwork?	☐	☐	☐	☐
34. Have you been wheezing?	☐	☐	☐	☐
35. Have you had chest pain?	☐	☐	☐	☐
36. Have you had shortness of breath when talking?	☐	☐	☐	☐
37. Have you woken up during the night because you were coughing?	☐	☐	☐	☐

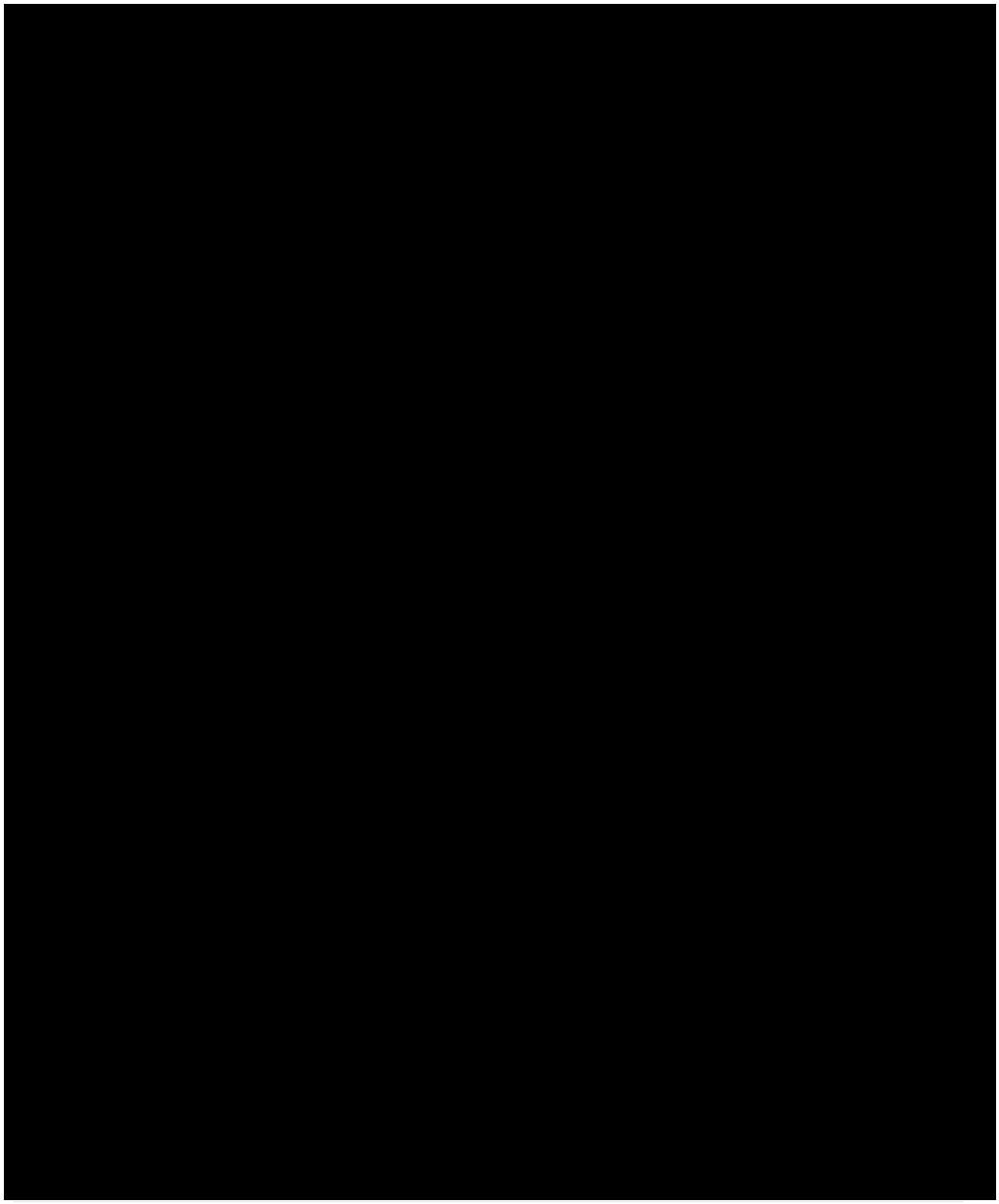
Please be sure you have answered all the questions.

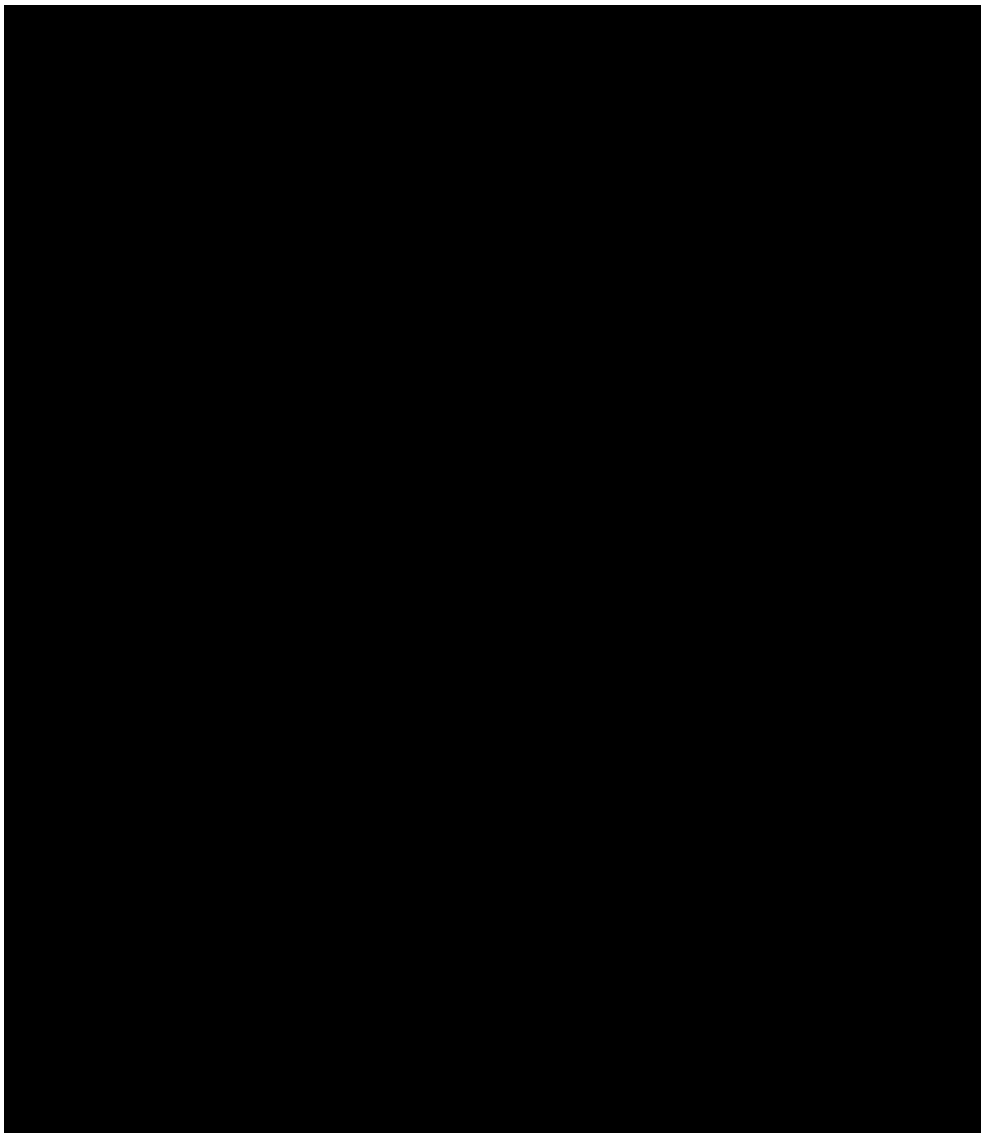
THANK YOU FOR YOUR COOPERATION!

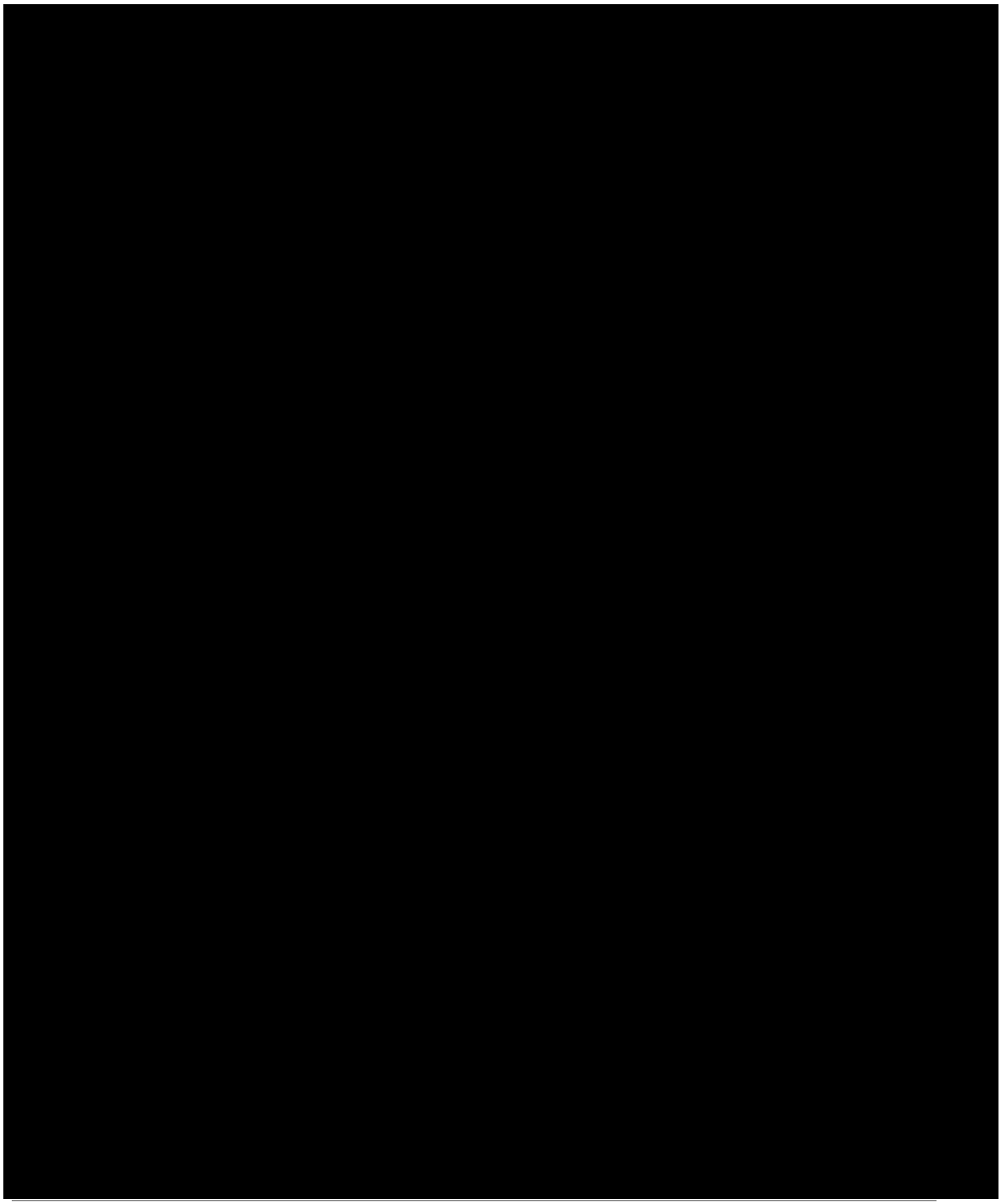


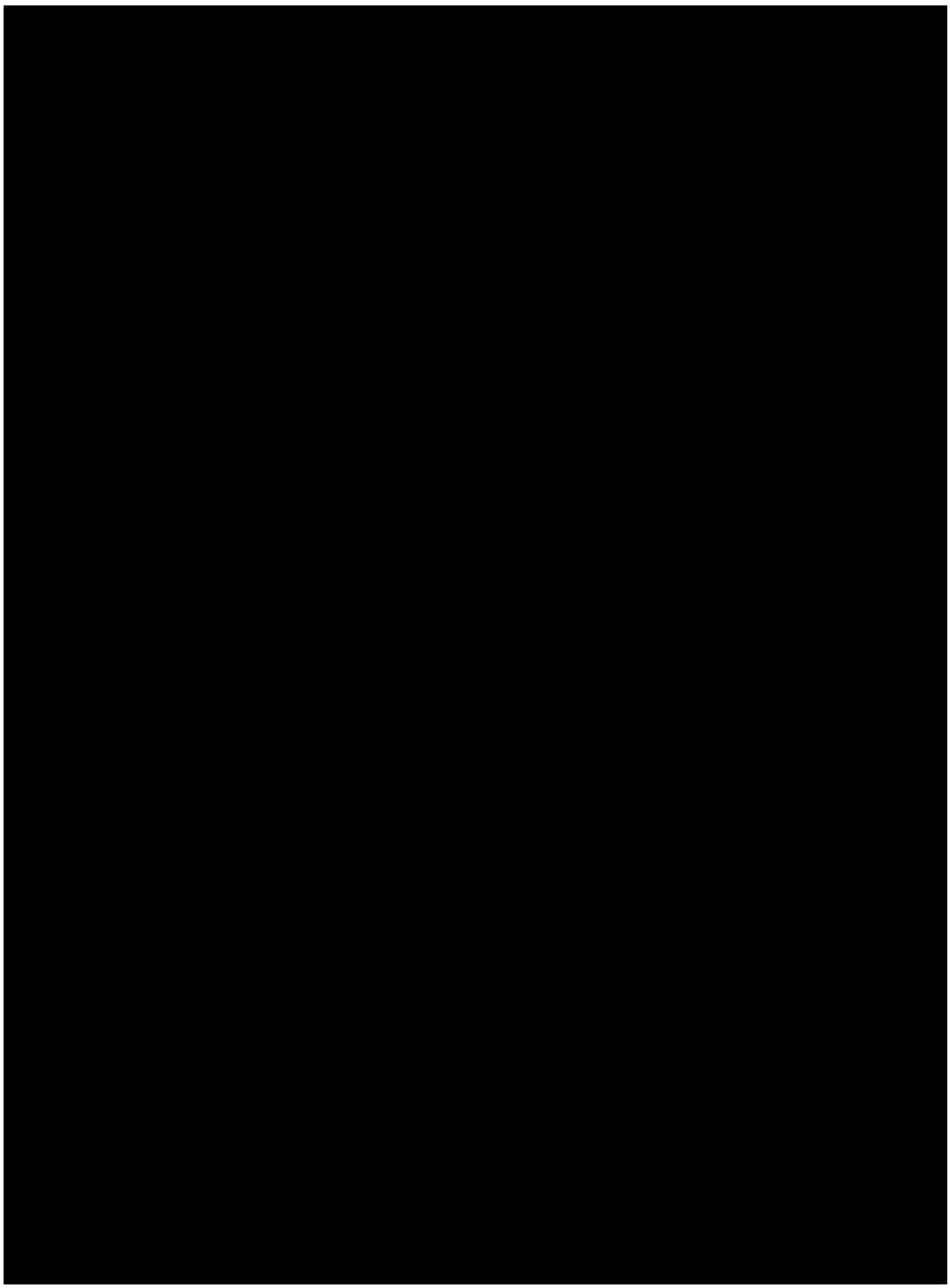












6 References

[Barker AF, Couch L, Fiel SB, et al (2000)] Tobramycin Solution for Inhalation Reduces Sputum Pseudomonas aeruginosa Density in Bronchiectasis. Am J Respir Crit Care Med; 162:481-5.

[Konstan MW, Geller DE, Minic P, et al (2011a)] Tobramycin inhalation powder forP. aeruginosa infection in cystic fibrosis: the EVOLVE trial. Pediatr Pulmonol; 46(3):230-8.

[Konstan MW, Flume PA, Kappler M, et al (2011b)] Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. J Cyst Fibros; 10(1):54-61.

[redacted]

[Wilson R, Welte T, Polverino E, et al (2013)] Ciprofloxacin dry powder for inhalation in noncystic fibrosis bronchiectasis: a phase II randomised study. Eur Respir J; 41(5):1107-15.

[The European Bronchiectasis Registry] Calculation of the bronchiectasis severity index (BSI).