Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product OPC-167832

Protocol No. 323-201-00003
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A Phase 1/2, Active-controlled, Randomized, Open-label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Multiple Oral Doses of OPC-167832 Tablets in Subjects with Uncomplicated, Smear-positive, Drug-susceptible Pulmonary Tuberculosis

Statistical Analysis Plan

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{24h}	Area under the concentration-time curve from zero to 24 hours
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_{τ}	Area under the concentration-time curve calculated over the dosing interval at steady-state
AUC_t	Area under the concentration-time curve from time zero to time t (the last observable concentration)
BDQ	Bedaquiline
CRF	Case report form
CFU	Colony-forming unit
CRO	Clinical Research Organization
CLss/F	Apparent clearance of drug from plasma at steady-s
Cmax	Maximum (peak) plasma concenration
Cmax,ss	Cmax during the dosing interval at steady-state
CYP	Cytochrome P450
DAIDS	Division of AIDS
DNA	Deoxyribonucleic acid
EBA	Early bactericidal activity
ECG	Electrocardiogram
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
Emax	Maximum effect
ET	Early Termination
EU	European Union
EudraCT	European Clinical Trial Data Base
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
hCG	Human chorionic gonadotropin
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigative new drug
IRB	Institutional review board
IRE	Immediately reportable event
LAM	Lipoarabinomannan

M2	N-monodesmethyl metabolite
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	Mycobacteria Growth Indicator Tube®
MIC	Minimum inhibitory concentration
MITT	Modified Intent to Treat
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamic
PE	Physical examination
PK	Pharmacokinetic(s)
PQC	Product quality complaint
QD	Once daily
QTcB	Corrected QT interval using Bazett's method
QTcF	Corrected QT interval using Fridericia's method
RBC	Red blood cell
RHEZ	Rifampicin, isoniazid, ethambutol, and pyrazinamide
SAD	Single ascending dose
SAE	Serious adverse event
SD	Standard Deviation
t1/2,z	Terminal-phase elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TTD	Time to detection
US or USA	United States or United States of America
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential
XDR	Extensively drug-resistant

1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for the analysis of clinical trial data of trial 323-201-00003 for compound OPC-167832. The original protocol was dated 26 Feb 2018. Amendment 1, 2, 3, 4 and 5 of the protocol occurred on 29 Jan 2019, 25 Oct 2019, 20 Dec 2019, 17 August 2020, and 21 May 2021. All amendments to the protocol are taken into consideration in the SAP.

There is a separate PK plan with details on the analyses of the PK endpoints.

2 Trial Objectives

2.1 Primary Objective

2.1.1 Stage 1

To evaluate the efficacy, pharmacokinetics (PK), safety, and tolerability of multiple ascending oral doses of OPC-167832 compared with the administration of RHEZ in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB.

2.1.2 Stage 2

- To evaluate the safety and tolerability of multiple oral doses of OPC-167832 when administered with delamanid and/or bedaquiline (BDQ) compared with the administration of RHEZ alone in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB.
- To evaluate the PK of OPC-167832 and delamanid, and/or BDQ after coadministration.

2.2 Secondary Objectives

2.2.1 Stage 1

- To evaluate the relationship between OPC-167832 exposure and efficacy determined by changes of sputum lipoarabinomannan (LAM) and Mycobacteria Growth Indicator Tube® (MGIT) time to detection (TTD), after multiple ascending oral doses of OPC-167832.
- To evaluate the relationship between QT interval and plasma concentrations of OPC-167832.

2.2.2 Stage 2

- To evaluate the efficacy of OPC-167832 when administered with delamanid and/or BDQ compared with the administration of RHEZ alone in subjects with uncomplicated, smear-positive, drug susceptible pulmonary TB.
- To evaluate the relationship between OPC-167832 exposure and efficacy determined by changes of sputum LAM and MGIT time to detection after OPC-167832 when administered with delamanid and/or BDQ.
- To evaluate the relationship between QT interval and plasma concentrations of OPC-167832 when administered with delamanid and/or BDQ.

- To evaluate the PK of DM-6705 after coadministration of OPC-167832 and delamanid and/or BDQ.

2.2.3 Stage 1 and Stage 2

To evaluate the efficacy, safety, and tolerability of OPC-167832 when administered with delamanid and/or BDQ (data derived from stage 2) compared with the administration of OPC-167832 alone (data derived from stage 1).

3 Trial Design

3.1 Type/Design of Trial

3.1.1 Stage 1

Stage 1 will be a randomized, open-label, active controlled, multiple ascending dose stage in approximately 72 subjects. Dosing is planned to be conducted in 4 sequential cohorts of 18 subjects each:

- Cohort 1: 10 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects)
- Cohort 2: 30 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects)
- Cohort 3: 90 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects)
- Cohort 4: 3 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects)

Subjects who signed the informed consent form (ICF) will be admitted to the trial site at screening. Subjects will be screened for up to 4 days (Days -6 to -3) prior to the start of the Day -2 assessments. Screening can be extended up to 7 days. Subjects randomized to OPC-167832 will receive once daily (QD) oral doses of investigational medicinal product (IMP; OPC 167832) from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20.

Subjects will be discharged on Day 20 once all safety assessments have been completed and all PK samples have been collected.

The safety, tolerability, PK, and efficacy (results from Otsuka TB LAM enzyme-linked immunosorbent assay [ELISA] only) data from each cohort will be reviewed by the trial review team at the end of each cohort. Once all the data for dose selection for the next cohort is available, the data collected from each cohort will be provided to the trial review team. The data will be evaluated to determine if (i) the dose level for the next cohort will be escalated, (ii) the dose level from the previous cohort will be repeated, or (iii) the dose level will be decreased. The dose of OPC-167832 will not exceed the highest tolerated dose studied in the single ascending dose trial, i.e., 480 mg.

Decisions to proceed to the next dose level should be based on, but not limited to, the following safety aspects:

- No death assessed as related to OPC 167832
- No more than 2 subjects with Grade 4/5 AEs ("Division of AIDS [DAIDS] Table for Grading the Severity of Adult and Pediatric AEs[1]") assessed as related to OPC 167832.

3.1.2 Stage 2

The dose of OPC-167832 for Stage 2 has been determined based on the safety, tolerability, PK and efficacy data from Stage 1 of this trial. Based on the Stage 1 PK/PD analysis of OPC-167832 plasma concentrations and reduction in $\log_{10}$CFU/mL, a dose lower than the current 30 mg specified in the protocol may be considered, provided it can offer similar potential for efficacy as the 30 mg dose.

Stage 2 will be a randomized, open-label, active-controlled, parallel group comparison stage comprising of 46 subjects (subjects who were randomized in stage 1 cannot enroll in stage 2).

Subjects who signed ICF will be admitted to the trial site at screening. Subjects will be screened for 4-7 days prior to the start of Day -2 assessments. Eligible subjects will be housed at the trial site until discharge or early termination. All subjects enrolled during this stage of the trial will be randomized prior to first dosing on Day 1 to one of the following 4 treatments in a ratio of 14:14:14:4:

- 30 mg OPC-167832 and 300 mg delamanid QD (14 subjects)
- 30 mg OPC-167832 and 400 mg BDQ QD (14 subjects)
- 30 mg OPC-167832 and 300 mg delamanid and 400 mg BDQ QD (14 subjects)

- RHEZ QD (4 subjects)

Subjects receiving BDQ will take a loading dose of 700 mg BDQ on Day 1 and 500 mg on Day 2. The dose of BDQ will be 400 mg QD for days 3 to 14.

Subjects will be centrally randomized through an interactive voice response system with no stratification.

Subjects randomized to OPC-167832 and/or delamanid and/or BDQ will receive QD oral doses of IMP (OPC-167832 and/or delamanid and/or BDQ) from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20.

Subjects will be discharged on Day 20 once all safety assessments have been completed and all PK samples have been collected.

3.2 Trial Treatments

3.2.1 Investigational Medicinal Products

3.2.1.1 Stage 1

Subjects randomized to OPC-167832 will receive QD oral doses of IMP (OPC-167832) from Day 1 through Day 14.

The planned dose escalation steps of OPC-167832 for Cohorts 1 to 4 are 10, 30, 90, and 3 mg, respectively. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature, within 5 minutes after the completion of a meal.

3.2.1.2 Stage 2

Subjects randomized to 30 mg OPC-167832 and 300 mg delamanid or 30 mg OPC-167832 and 400 mg BDQ, or 30 mg OPC-167832 and 300 mg delamanid and 400 mg BDQ will receive QD oral doses of IMP (OPC-167832 and/or delamanid and/or BDQ) from Day 1 through Day 14. Subjects receiving BDQ will take a loading dose of 700 mg BDQ on Day 1 and 500 mg on Day 2. The dose of BDQ will be 400 mg QD for days 3 to 14.

Delamanid (300 mg) should be administered orally once daily (QD), within 5 to 10 minutes after the completion of a meal.

OPC-167832 (30 mg QD) and BDQ should be administered orally, approximately 30 minutes after administration of delamanid.

The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature.

Based on the Stage 1 PK/PD analysis of OPC-167832 plasma concentrations and reduction in log_{10}CFU/mL, a dose lower than the current 30 mg specified in the protocol maybe considered, provided it can offer similar potential for efficacy as the 30 mg dose.

3.2.2 Reference Product

3.2.2.1 Stage 1 and Stage 2

Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20.
Subjects will receive Rifafour® single-dose combination tablets. Each RHEZ tablet contains 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide, and 275 mg ethambutol. Subjects will receive the following number of Rifafour tablets per day based on their pretreatment body weight:

- Subjects weighing 30 to 37 kg will receive 2 tablets per day.
- Subjects weighing 38 to 54 kg will receive 3 tablets per day.
- Subjects weighing 55 to 70 kg will receive 4 tablets per day.
- Subjects weighing > 70 kg will receive 5 tablets per day.

RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal.

3.3 Trial Population

Approximately 118 male or female subjects with newly diagnosed, uncomplicated, smear-positive, drug susceptible pulmonary TB who meet all the inclusion criteria and none of the exclusion criteria will be enrolled and randomized into this trial. In Stage 1, approximately 72 subjects will be enrolled and randomized to 1 of 4 cohorts (18 subjects per cohort). Approximately 46 subjects will be enrolled and randomized in Stage 2. Subjects who randomized to Stage 1 cannot enroll in Stage 2.

3.4 Trial Visit Window

There is no visit window for trial visits on/before Day 20. The follow up visit can be target day plus or minus 3 days.

4 Sample Size

The trial is not powered for formal statistical hypothesis testing or comparisons. The sample size is based on sample sizes from several similar trials in the literature. It is planned to enroll 72 (18 in each cohort) subjects in stage 1 in 14:4 ratio. Stage 2 will enroll 46 patients in 14:14:14:4 ratio.

5 Statistical Analysis Sets

5.1 Efficacy Analysis Set

Efficacy analyses will be conducted based upon the Modified Intent-to-Treat (mITT) Analysis Set. The mITT Set will include randomized subjects who are agar media culture positive at baseline (either at day -2 or at day -1, or both), have taken any dose of IMP, and have available at least one post-baseline CFU count value.

Randomized Analysis Set includes subjects who are randomized into the study.

5.2 Safety Analysis Set

Safety Analysis Set includes subjects who are randomized and take any dose of IMP (OPC-167832 or Delamanid or Bedaquiline or RHEZ).

5.3 Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects who took at least one dose of IMP with adequate data for deriving the PK parameters accordingly to clinical pharmacology requirement.

5.4 Handling of Missing Data

Missing data in PK blood sample result and efficacy data will not be imputed for this study unless specified in individual sections. The imputation of missing colony forming units or LAM results will be discussed in corresponding sections.

6 Primary and Secondary Outcome Variables

6.1 Primary Outcome Variables

6.1.1 Efficacy - Stage 1

Efficacy will be assessed by the change in *Mycobacterium tuberculosis* bacterial (MTB) load in sputum as a measure of EBA. Bacterial load in sputum at each collection time point will be measured by colony-forming unit (CFU) counts on agar media culture. The

EBA will be measured as the slope of the change in log_{10}CFU/mL on agar media from baseline (baseline is defined as the log_{10} of the mean of Day -2 and Day -1) to Day 14.

6.1.2 Pharmacokinetics - Stage 1

The following PK parameters will be determined for plasma OPC-167832:

- Day 1: Maximum (peak) plasma concentration (C_{max}), time to C_{max} (t_{max}), and area under the concentration-time curve (AUC) from time zero to time t (the last observable concentration) (AUC_t).
- Day 14: C_{max} during the dosing interval at steady-state ($C_{max,ss}$), t_{max}, terminal-phase elimination half-life ($t_{1/2,z}$), apparent clearance of drug from plasma at steady-state (CL_{ss}/F), AUC_t, AUC calculated over the dosing interval at steady-state (AUC_τ), accumulation ratio of C_{max} (R_{CMax}), and accumulation ratio of AUC (R_{AUC}), C_{max} normalized to dose (C_{max}/Dose), and AUC_τ normalized to dose (AUC_τ/Dose).

6.1.3 Pharmacokinetics - Stage 2

The following PK parameters will be determined for plasma OPC-167832, delamanid and BDQ:

- Day 1: C_{max}, t_{max}, and AUC_t.
- Day 14: $C_{max,ss}$, t_{max}, $t_{1/2,z}$, CL_{ss}/F, AUC_τ, R_{CMax}, R_{AUC}, and C_{max} normalized to dose (C_{max}/Dose), and AUC_τ normalized to dose (AUC_τ/Dose).

6.1.4 Pharmacokinetics/Pharmacodynamics - Stage 1

The maximum effect (E_{max}) and exposure producing 80% of E_{max} (EC_{80}) for OPC-167832, regardless of dose level, will be determined from an exposure-response analysis of the decline of log_{10}CFU/mL counts on agar media. The results can be found in a separate population PK/PD analysis report.

6.1.5 Pharmacokinetics/Pharmacodynamics - Stage 2

The E_{max} and EC_{80} for OPC-167832 in combination with delamanid and/or BDQ will be determined from an exposure-response analysis of the decline of log_{10}CFU/mL counts on agar media. The results can be found in a separate population PK/PD analysis report.

6.1.6 Safety and Tolerability - Stage 1 and Stage 2

6.2 Secondary Outcome Variables

6.2.1 Efficacy

Stage 1 and Stage 2

The slope of the change in log_{10}LAM pg/mL values and the change in time to detection (TTD) in the Mycobacteria Growth Indicator Tube® (MGIT) system will be assessed from baseline to Day 14.

Stage 2

Efficacy will be assessed by the change in bacterial load in sputum as a measure of EBA. Bacterial load in sputum at each collection time point will be measured by CFU counts on agar media. The EBA will be measured as the slope of the change in log_{10}CFU/mL from baseline (baseline is the log_{10} of the mean of the values from Day -2 and Day -1 with more details in Section 8.1) to Day 14 and compared with the administration of 30 mg OPC-167832 alone (data derived from Stage 1). Similar analyses are performed for log_{10}LAM pg/mL and MGIT TTD endpoints.

6.2.2 Pharmacokinetics

Stage 1

Plasma concentrations of rifampin and isoniazid at 2 and 6 hours postdose will be determined for compliance.

Stage 2

The following PK parameters will be determined for plasma DM-6705 (metabolite of delamanid) and M2 (metabolite of BDQ):

- Day 1: C_{max}, t_{max}, and AUC_t.
- Day 14: $C_{max,ss}$, t_{max}, $t_{1/2,z}$, and AUC_t.

Plasma concentrations of rifampin and isoniazid at 2 and 6 hours postdose will be determined for compliance.

6.2.3 Pharmacokinetics/Pharmacodynamics - Stage 1 and Stage 2

The maximum effect and EC_{80} for OPC-167832, regardless of dose level, will be determined from an exposure-response analysis of the results from the Otsuka TB ELISA LAM. The results can be found in a separate population PK/PD analysis report.

The relationship between QT interval and plasma concentrations of OPC-167832 (stage 1) and OPC-167832 when administered with delamanid and/or BDQ (Stage 2) will be evaluated. The results can be found in a separate population PK/PD analysis report.

6.2.4 Safety and Tolerability - Stage 1 and Stage 2

Safety and tolerability of OPC-167832 when administered with delamanid and/or BDQ (data derived from stage 2) will be compared with the administration of OPC-167832 alone (data derived from stage 1). Safety and tolerability will be assessed based on the incidence of AEs and the incidence of abnormal findings in clinical laboratory tests (serum chemistry, hematology, urinalysis, and coagulation), vital signs, ECGs and physical examinations.

7 Disposition and Demographic Analysis

7.1 Subject Disposition

Number of patients screened, randomized, included in safety analysis or efficacy analysis, completed, early terminated will be summarized by count and percentage within each treatment group. Enrolment by country and by age group will also be summarized.

The frequency and percentages will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

7.2 Demographic and Baseline Characteristics

Summary statistics (mean, standard deviation, median, minimum and maximum) will be presented for continuous baseline characteristics. Frequency and percentage of discrete baseline variables will also be presented. Summaries will be presented by treatment groups based on the Randomized Analysis Set.

Demographic and baseline characteristics variables include:

- Age
- Sex
- Race
- Ethnicity
- Weight, Height, BMI
- Baseline CFU/mL count (Actual X1000)
- Baseline CFU/mL count (log_{10})

- Baseline x-ray
- Baseline HIV Screen
- Baseline FSH
- Baseline Urine/Blood alcohol
- Baseline Urine test for isoniazid (only applicable to protocol dated 26 Feb 2018)

The baselines for lab tests, ECG, vital sign and overnight sputum culture results are summarized with post-baseline results and will be described in later sections.

The analysis will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

7.3 Medical History

Medical history will be presented by count and frequency for each system organ class and preferred term for each treatment group. The summary will be based on the Randomized Analysis Set.

The frequencies and percentages will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

7.4 Treatment Compliance

Plasma concentrations of rifampin and isoniazid at 2 and 6 hours postdose will be determined for compliance. The time and dose of IMP and RHEZ administration during the trial will be recorded in eCRF and be listed. No analysis will be performed on compliance.

7.5 Prior and Concomitant Medication

The proportion of subjects taking concomitant medications will be tabulated by drug classification using the WHO drug dictionary WHODRUG B3G March 2019 for Safety Analysis Set. Concomitant medications taken prior to the study medication treatment period, during study medication treatment period and after the study treatment will be tabulated. The study medication treatment period is defined as days from first IMP till the last dose of OPC-167832 and/or delamanid and/or bedaquiline in non-RHEZ groups. For RHEZ group, Day 14 (study date – first RHEZ date +1) is used as end point for “IMP dosing period” period. Concomitant medications will be listed. Anti-TB concomitant medications and other general concomitant medications will be summarized separately.

The analysis will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

7.6 Protocol Deviations

Frequency of protocol deviations (PDs) collected from CRF will be summarized by type of deviation (e.g., deviations in entry criteria, dosing, prohibited concomitant medication, procedural, met withdrawal criteria but was not withdrawn). The analysis will be presented by treatment group for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2. In addition, a subject listing for non-COVID-19 related PDs will be provided. COVID-19 related PDs will be listed separately.

8 Efficacy Analyses

8.1 Primary Efficacy Endpoint Analyses

8.1.1 Stage 1

Overnight sputum will be collected starting from 3pm to 7am next day starting on Day -2, -1, 2, 4, 6, 8, 10, 12 and Day 14. *Mycobacterium tuberculosis* bacterial load in sputum at each collection time point will be measured by CFU counts on solid media culture. Two agar media bi-plates will be inoculated with 0.1 mL sputum sample per side (total of 0.2 ml per whole plate) at each visit. Each sample was diluted to $1, 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}$ times of the original concentration, represented by the values of dilution factor collected from CRF in 0, 1, 2, 3, 4, 5. The number of colonies from each plate collected in the CRF will be converted to CFU per mL using the formula: $Number\ of\ colonies\ collected\ from\ CRF\ \times 10^{dilution\ factor\ collected\ in\ CRF+1}$. Because of the initial 10-fold dilution factor during sputum sample preparation, 1 is added to the power of 10. The CFU value reported from the laboratory is set to missing if the qualitative culture result is "Negative for MTB Complex" or "Contaminated". Because two results are collected per visit, the method to derive the analysis value for CFU for a visit day is described as follows:

If only one CFU result is available, then the available result is used as the CFU/mL value from that visit. If both CFU results are available, the average CFU/mL is taken as the value for that visit. If both sputum samples have missing CFU result, then the qualitative test result from SOLID MICROBIAL CULTURE will be taken into consideration. If both of the SOLID tests are "negative for MTB Complex", or if one of the SOLID results is "negative for MTB complex" and the other is "CONTAMINATED", the CFU for that visit is set to 5 CFU/mL, since the lower detection limit of the agar media is 5 CFU/mL. If both SOLID tests are "CONTAMINATED", then the CFU/mL for that visit is still treated as missing.

The baseline value derived for the analyses is as follows.

The study day of baseline is set to be 0 no matter whether the baseline comes from Day -2 or Day -1 or the average. The derived analysis CFU is $\log_{10}$ transformed in the calculations of decline in bacteria load. The early bactericidal activity (EBA) is determined by the rate of decline in $\log_{10}$CFU/mL during the first 14 days of treatment. The rate of decline will be estimated using both a two-point calculation (day 14 and day 0 (baseline)) as well as a linear-regression based approach as discussed in Section 8.1.1.1.1 and Section 8.1.1.1.2.

The effect size for EBA for IMP-1 group relative to that of IMP-2 group is expressed as the ratio of EBA as shown in formula (1). Either Fieller's method or Delta method as described in Sections 8.1.1.2 [2] will be used in the estimation of the confidence interval of the ratio

$$\frac{EBA_{0-14,IMP1}}{EBA_{0-14,IMP2}} \quad (1)$$

8.1.1.1 Estimation of Day 14 Early Bactericidal Activity (EBA)

8.1.1.1.1 Two-time Point Early Bactericidal Activity Calculation

The change from baseline in log_{10}CFU/mL count will be summarized using descriptive statistics (mean, standard error, median, min, max) at each visit by treatment group. The change from baseline in log_{10}CFU/mL is calculated as the value post-baseline minus the value from baseline. Endpoints log_{10}LAM pg/mL and MGIT TTD will also be analyzed in the same way.

A simple two-point EBA estimate is obtained by taking a negative sign for the change from baseline in log_{10}CFU/mL at visit Day 14 divided by the number of days since first IMP ((Baseline log_{10}CFU/mL – Postbaseline log_{10}CFU/mL)/(Days since first IMP at Visit Day 14)). A positive value of 14-Day EBA indicates reduction in bacteria load. The study is an inpatient study, and the nominal visit equals to the analysis visit day.

The mean and standard error for 14-Day EBA for each treatment group can be obtained from SAS PROC MEAN procedure, and will be used in the formulas in Sections 8.1.1.2 to calculate the confidence intervals of the ratio between treatment groups.

8.1.1.1.2 14-Day EBA Estimate Through Linear Mixed Effects Modeling

Another way to estimate the 14-Day EBA is through a linear mixed effect model, using log10CFU/mL as outcome variable, treatment group, [redacted] and intercept and slope for day includes a random component for each subject.

The model can be specified in formula as follows:

[redacted]

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[redacted]

The model can be fit using SAS PROC MIXED procedure.

The estimated EBA is obtained by taking the negative sign of the slopes for each treatment group. Either the Fieller's method or Taylor's method described in Sections 8.1.1.2 will be used in estimating 95% CI for the EBA ratios between treatment groups. The parameters needed as input for the two algorithms include negative slope and the variance covariance matrix for the slopes, represented using symbols $\hat{\theta}_1$, $\hat{\theta}_2$ $\hat{\sigma}_{11}$, $\hat{\sigma}_{22}$.

Similar analyses will be performed for $\log_{10}$LAM pg/mL and TTD endpoints (in greater detail in Section 8.2) except that, in estimating the EBA for TTD, a negative sign is not applied to the slope for TTD. For Stage 2, the same model is used, with the groups for Stage 2 being Stage 1 + Stage 2 RHEZ, OPC + DLM, OPC + BDQ, OPC + DLM + BDQ.

8.1.1.2 Confidence Interval Estimation for EBA Ratio Between OPC and RHEZ

The treatment mean and standard error (the square of which is the estimated $\hat{\sigma}_{11}$, $\hat{\sigma}_{22}$) calculated using methods in Section 8.1.1.1 will be used to estimate EBA ratio using Fieller's or Taylor's methods described in this section.

8.1.1.2.1 Estimate EBA Ratio with Fieller's method

Let $r = \theta_1/\theta_2$ and θ_1 and θ_2 stands for the 14-Day EBA for two treatment groups. It is assumed that the estimators $(\hat{\theta}_1, \hat{\theta}_2)$ follow a bivariate normal distribution with mean (θ_1, θ_2) and estimated variance covariance $\hat{\sigma}_{11} = var(\hat{\theta}_1), \hat{\sigma}_{22} = var(\hat{\theta}_2), and\ \hat{\sigma}_{12} = cov(\hat{\theta}_1, \hat{\theta}_2)$. For two-point estimate from Section 8.1.1.1.1, the parameter estimates $\hat{\theta}_1$, $\hat{\theta}_2$, $\hat{\sigma}_{11}$, $\hat{\sigma}_{22}$ comes from summary statistics (mean and square of the standard errors), and covariance between EBA for two treatment groups $\hat{\sigma}_{12}$ [redacted]

[redacted] A Fieller's method SAS macro is provided in Appendix 5 for reference.

8.1.1.2.2 Estimate EBA Ratio with Taylor's (Delta) method

Formula (2) can be used to estimate the $100(1-\alpha/2)$ CI for the EBA ratio (IMP-1 divided by IMP-2). For two-point estimate from Section 8.1.1.1.1, the parameter estimates $\hat{\theta}_1$, $\hat{\theta}_2$, $\hat{\sigma}_{11}$, $\hat{\sigma}_{22}$ come from summary statistics (mean and square of the standard errors), and covariance between EBA for two treatment groups $\hat{\sigma}_{12}$[redacted] The $\hat{\theta}_1$, $\hat{\theta}_2$, $\hat{\sigma}_{11}$, $\hat{\sigma}_{22}$, $\hat{\sigma}_{12}$ can be estimated using the same method from Section 8.1.1.2.1.

$$\frac{\hat{\theta}_1}{\hat{\theta}_2} \pm t_q \frac{\hat{\theta}_1}{\hat{\theta}_2}\sqrt{\frac{\hat{\sigma}_{11}}{\hat{\theta}_1^{\,2}} + \frac{\hat{\sigma}_{22}}{\hat{\theta}_2^{\,2}} - \frac{2\hat{\sigma}_{12}}{\hat{\theta}_1\hat{\theta}_2}} \quad (2)$$

8.2 Secondary Efficacy Endpoint Analyses

The analyses of the secondary endpoints of the slope of change in $\log_{10}$LAM pg/mL values and change in Time to detection (TTD) in stage 1 will be conducted in a way similar to comparisons of change in $\log_{10}$CFU/mL specified in Section 8.1.1.1 for Stage 1.

Stage 2 EBA analyses will be based on $\log_{10}$CFU/mL, $\log_{10}$LAM pg/mL (raw and processed) and TTD.

Treatment group comparisons in Stage 2 are:

[redacted]

[redacted]

The same analysis methods as described in Section 8.1.1 will be used for the comparisons of (1) and (2) above mentioned. Only the data of these three treatment groups in all efficacy analysis set in Stage 2 will be included in this analysis (that is, Stage 2 RHEZ arm, and Stage 1 arms are not included in the analysis).

LAM and TTD analyses:

The change from baseline in LAM and TTD will be analyzed using the same methods specified for CFU.

LAM:

More details of analysis data derivation for LAM is provided as follows.

Two LAM assessments are available at each visit, one on raw sputum (LAM(raw)), and one on processed decontaminated sputum (LAM(processed)). Baseline LAM is calculated as the average of Day -2 and Day -1 and the $\log_{10}$ of the average is used in EBA derivation. If one sample has a missing value then the nonmissing sample is used. The lower limit of quantification (LLoQ) of LAM test is 15 pg/mL. If a sample result has a reported value below the LLoQ (< 15 pg/mL) and does not indicate "NO RESULT", the value 15 pg/mL is used in the analyses for that visit.

TTD:

TTD is the time from start of inoculation of a sputum sample until a MGIT machine detects a positive signal during the 42-day incubation period. One TTD measurement, reported in days and hours, is taken at each of the visits at Days -2, -1, 2, 4, 6, 8, 10, 12 and 14.

The TTD values in Days will be calculated as "days + hours/24" to be used in deriving the analysis values of TTD. Pure MTB positive MGIT culture is MTB confirmed with no growth of contaminants.

Baseline TTD will be derived using the Day -2 and Day -1 MGIT culture with a pure positive result for *Mycobacterium tuberculosis*. If both days are pure positive, the average of Day -2 and Day -1 will be used as baseline TTD. If only one day is pure positive, the

TTD from that day is used as baseline. If neither day is pure positive, the baseline TTD is set to missing.

The postbaseline TTD analysis values from Day 1 and later will be derived based on the MGIT culture result as follows:

1. When a MGIT culture result is negative for MTB complex, TTD is set to 42 days (the value for time-to-result with negative culture).
2. If the MGIT culture is pure positive for MTB, but for some reason the TTD took longer than 42 days, TTD will be capped at 42 days.
3. TTD values from MGIT cultures with the following qualitative results will be set to missing:
    - Contaminated
    - Positive for MTB complex and contaminated
    - No TB growth but positive for other mycobacteria
    - Unknown.

All analyses will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

[redacted]

[redacted]

9 Safety Analyses

Safety data will be summarized by randomized treatment using descriptive statistics (number, median, mean, SD, minimum, and maximum) for numeric variables and frequency and count for discrete variables.

9.1 Extent of Exposure

In Stage 1, subjects randomized to OPC-167832 will receive once daily oral doses of IMP (OPC-167832) from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward. Subjects randomized to RHEZ will receive once daily oral doses of RHEZ from Day 1 through Day 20.

In Stage 2, subjects randomized to IMP (OPC-167832 and/or delamanid and/or BDQ) will receive once daily oral doses of IMP from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward. Subjects randomized to RHEZ will receive once daily oral doses of RHEZ from Day 1 through Day 20.

Exposure to IMP is considered to be the exposure of OPC, DLM or BDQ (for the three OPC-containing regimens) in study days 1-14. For comparison purposes, for the RHEZ arm also, exposure to IMP will be taken to be the exposure to any treatment with RHEZ in days 1-14, and will be tabulated for the first 14 days only. The total exposure to IMP or reference product (RHEZ) in days will be divided to time intervals (No exposure, 1-2 days, 3-4 days, etc.) and the number and percentage of patients whose durations of exposure are in each interval will be presented for each treatment group. The duration of exposure is calculated as the last date of IMP (within 14 study days) – first date of IMP +1. For patients who are lost to follow-up, the last known date of taking IMP or RHEZ (within 14 study days) will be used for missing last date.

Patients randomized to RHEZ will receive once daily oral doses of RHEZ from Day 1

through Day 20. For the RHEZ group, the exposure table will summarize the exposure to RHEZ within the first 14 days of treatment only

All analyses will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

The summaries will be based on the Randomized Analysis Set. IMP dosing will be listed. The dosing of RHEZ will be listed in the anti-TB concomitant medication listing.

9.2 Adverse Events

All AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA; Version 22 or newest available) system organ class and preferred term. Treatment-emergent AEs (TEAE) are defined as AEs that occurs after the initiation of trial treatment; or an event or pre-existing medical problem that has changed adversely in nature or severity from baseline in a subject while receiving trial treatment.The frequency and percentage of subjects with the following events will be summarized by SOC, MedDRA preferred term, severity and treatment:

- Treatment-emergent AEs (TEAEs)
- TEAEs potentially causally related to the IMP or RHEZ
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuations of the IMP
- TEAEs by DAIDS grading
- non-serious TEAEs (NSAE)

All AEs will be presented in a listing. The listing of death due to AE, serious AE and TEAE leading to discontinuation will also be provided. In addition, the number and frequency of TEAE incidences will be summarized for serious TEAE, serious study medication related TEAE and non-serious TEAE. The analyses on AEs will be performed separately for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

9.3 Clinical Laboratory Data

Clinical hematology, chemistry, coagulation and urinalysis are tested at screening, Day -1, Day 4, Day 7, Day 14 and Day 20/ET for both Stage 1 and Stage 2.

For clinical laboratory tests data, baseline is defined as the last non-missing value obtained on or before Day −1.

The incidence of clinical laboratory test abnormalities, as defined in the "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events[1]will be summarized by grade and treatment group and listed by test. The DAIDS criteria for laboratory test results are listed in Appendix 1.

Shift tables assessing status (low, normal, or high based on the clinical laboratory normal ranges) changes from baseline will be presented by treatment group based on the Safety Analysis Set. All cases of lab results where ALT (alanine aminotransferase) or AST (aspartate aminotransferase) are ≥ 3 times the normal upper limit and at the same time the total bilirubin is ≥ 2 times normal upper limit. All clinical laboratory test data will be listed.

In case of a repeated lab test, the last repeat test on the same visit will be used for the value at that visit. Unscheduled lab test data will not be included in the mean change from baseline summary but will be included when searching for laboratory test abnormalities in the incidence and shift analyses.

When lab parameter values are recorded as < or > a cutoff value, then the lab value is set as 50% of the cutoff value in the case of < and 150% in the case of > when used as a continuous variable. In data listing the originally collected format will be presented.

All analyses will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

9.4 Vital Sign Data

Vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be assessed at screening and on Day −1, Day 1 (predose and at 1, 2, 4, 8, and 12 hours postdose), Days 2 through 6 (predose and 2 and 4 hours postdose), Day 7 (predose and 1, 2, 4, 8, and 12 hours postdose), Days 8 through 13 (predose and 2 and 4 hours postdose), Day 14 (predose and 1, 2, 4, 8, and 12 hours postdose), and Days 15 through 20 or at ET. At screening, blood pressure and heart rate will be taken with the subject in the supine (performed first) and sitting position after remaining for ≥ 3 minutes in each position and temperature and respiratory rate will be taken with the subject in the supine position for at least 1 minute. At all other time points, vital signs will be obtained after the subject has been at rest in the supine position for 1 to 3 minutes. Vital signs will be obtained prior to the ECG and PK blood draw at the nominal time points, where applicable. The post-dose

vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints.

The baseline of vital sign is defined as data collected at Day 1 predose. If Day 1 predose is missing, then baseline can be taken from Day -1 or screening.

Change from baseline in vital signs will be summarized for each post-baseline timepoints. The "last visit" in the summaries includes last observed non-missing data collected at post-baseline visits. The incidence of vital signsas based on the tablein Appendix 2, specifying potentially clinically relevant abnormalities, will be summarized for all visits. Also incidence of vital signs based on the "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events" as listed out in Appendix 3 will also be summarized by grade and treatment group and will be listed.

When vital sign is repeated, the last repeat value will be used in the summary for that visit. Unscheduled vital sign data will not be summarized in the change from baseline analysis, but will be included in incidence of clinical relevance analysis.

All analyses will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

9.5 Physical Examination Data

Complete physical examinations will be performed at screening and on Day −1. Targeted physical examinations will be performed on Days 1 through 14 (predose and 4 hours postdose) and Days 15 through 20 or at ET. The 4-hour post-dose targeted physical examination could be performed ±30 minutes around the expected post-dose timepoint.

Baseline is defined as Day 1 predose. If Day 1 predose is missing, then Day -1 or screening can be used as baseline.

Frequency of percentage of subjects for each physical examination outcome will be presented by visit and treatment group.

All analyses will be presented by treatment groups for Stage 1 and Stage 2 separately, and with a combined RHEZ group from Stage 1 and Stage 2.

9.6 Electrocardiogram Data

Standard 12-lead ECGs will be collected in triplicate (5 minutes apart) at screening and on Day −1, Day 7 (predose), and Day 14 (predose). The ECGs will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the first ECG and subjects will remain supine through the final ECG. Electrocardiograms will be obtained prior to the PK blood draw and after vital signs at the nominal time points, where applicable.

Heart rate, ventricular rate, RR interval, PR interval, QRS duration, and QT intervals will be recorded. The QTcF and corrected QT interval using Bazett's method (QTcB) will be calculated.

ECGs are available in triplicates at each nominal timepoint, but may appear as a single or duplicate assessment. All (single, duplicate or triplicate) ECGs at each nominal time point will be averaged and the average will be used in descriptive summary statistics and frequency and percentages. Baseline of ECG is defined as the averaged measurement on Day -1. If the measurement from Day -1 is missing, the screening ECG is taken as baseline.

Summary and change from baseline for ECG will be presented for continuous ECG parameters by visit and treatment group.

Incidence and percentage of potentially clinically significant ECG parameters as defined in Appendix 4 will be presented for each treatment group. All post baseline visit till end of study will be included in incidences of significant change or value. For criteria that involves change from baseline, the subject must have a baseline value to be included in the analysis. For absolute criteria the complete Safety Set will be included.

Incidence of potentially clinically significant QT increases will also be summarized by treatment groups.

In summarizing the incidence of abnormalities, a patient must have had an evaluation that met abnormality criteria by the end of trial, i.e. last contact date. Incidence rate is calculated as the number of patients having at least one abnormality within a trial period divided by the number of patients who are both exposed to trial medication and have an on-treatment evaluation within that trial period.

When the ECG is repeated, the last repeat value will be used in the summary for that visit. Unscheduled ECG data will not be summarized in the change from baseline descriptive analysis but will be included in the incidence of clinically relevant table.

All analyses will be presented by treatment groups for Stage 1, and Stage 2 with a combined RHEZ group from Stage 1 and Stage 2.

9.7 Other Safety Data

NA.

10 Pharmacokinetic Analyses

In general, pharmacokinetic concentrations and parameters will be summarized by treatment using descriptive statistics (number, median, mean, standard deviation (SD),

percent coefficient of variation, minimum, and maximum). Pharmacokinetic concentrations and parameters will also be listed by subject. The individual, mean, and median plots of plasma concentrations and other PK analyses will be detailed in the clinical pharmacology report.

In Stage 1, dose proportionality for steady-state (eg, Day 14) PK exposure ($C_{max,ss}$ and AUC_{τ}) of OPC-167832 will be analyzed using the random intercept power model, with subjects as a random effect, using the following equation:xx

$$ln\ (AUC_{\tau}\ or\ C_{max,ss}) = \alpha + \beta\ ln\ (dose)$$

where α is the intercept and β is the slope parameter. Dose proportionality will be assumed if β is close to 1 and its 90% confidence interval (CI) is entirely contained within the 80% to 125% interval corrected for dose range.xx

Population PK modeling will be performed on OPC-167832 PK data from both stages, and the details can be found in a separate Population PK/PD analysis plan.

11 Pharmacokinetic/Pharmacodynamic Analyses

Exposure-response modeling will be performed in both stages for OPC-167832 PK measures versus bacterial load using LAM and CFU counts on agar media.

The relationship between QT interval (Holter data) and plasma concentrations of OPC-167832 (stage 1) and OPC-167832 when administered with delamanid and/or BDQ (stage 2) will be examined using an exposure-response analysis.

The details can be found in a separate population PK/PD analysis plan.

12 Pharmacogenomic Analyses

There were no pharmacogenomic analyses in this trial.

13 Interim Analysis

An interim analysis of safety, tolerability, PK and efficacy of OPC-167832 is planned after the end of stage 1. All analyses specified in this SAP for Stage 1 will be provided at the interim analysis.

14 Changes in Planned Analysis

There is no deviation from the planned analysis.

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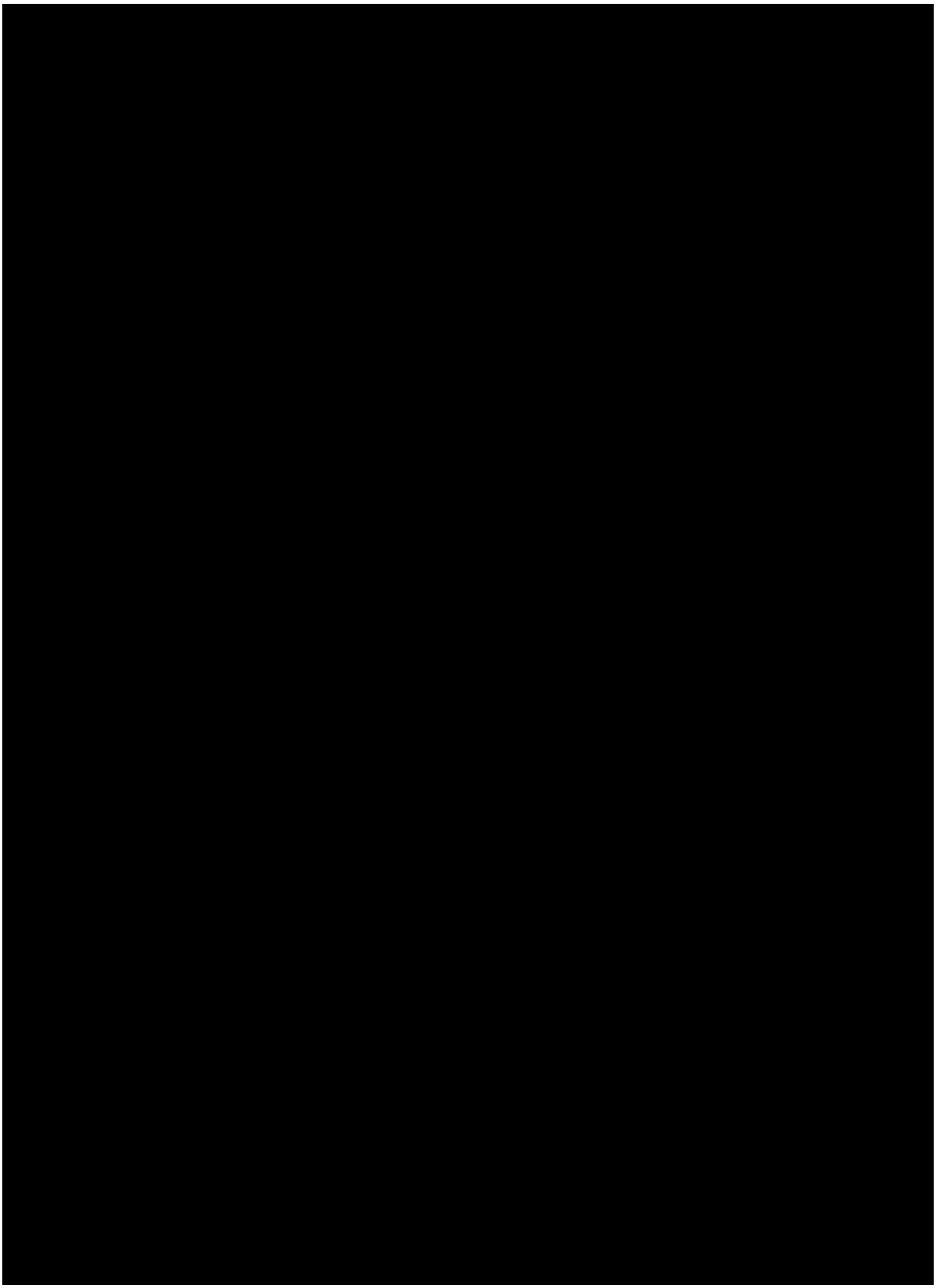
15 Document History



16 References

1. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.1. July 2017
2. Ratios: A short guide to confidence limits and proper use. Franz, Volker H. http://www.ecogsci.cs.uni-tuebingen.de/pub/publications_abstracts.php#Franz_fieller_07, 2007.
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4. Smith BP, Vandenhende FR, Desarte KA, Farid NA, Welch PA, Callaghan JT, et al. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000;17(10):1278-1283.

Appendix 1 Definition of Grades in Serum Chemistry, Hematology and Urinalysis Lab Test Results in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

							Clinically Significant	
LAB GROUP	TEST	UNITS	SEX	AGE Group	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Chemistry	Albumin, Low	g/dL	Male/Female	All	3.0 to < LLN	≥2.0 to < 3.0	< 2.0	NA
Chemistry	Albumin, Low	g/L	Male/Female	All	30 to < LLN	≥20 to < 30	< 20	NA
Chemistry	Alkaline Phosphatase, High		Male/Female	All	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Chemistry	ALT or SGPT, High		Male/Female	All	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Chemistry	AST or SGOT, High		Male/Female	All	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Chemistry	Total Bilirubin, High		Male/Female	> 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Chemistry	Calcium, High	mg/dL	Male/Female	≥ 7 days of age	10.6 to < 11.5	11.5 to < 12.5	12.5 to < 13.5	≥ 13.5
Chemistry	Calcium, High	mmol/L	Male/Female	≥ 7 days of age	2.65 to < 2.88	2.88 to < 3.13	3.13 to < 3.38	≥ 3.38
Chemistry	Calcium, Low	mg/dL	Male/Female	≥ 7 days of age	7.8 to < 8.4	7.0 to < 7.8	6.1 to < 7.0	< 6.1
Chemistry	Calcium, Low	mmol/L	Male/Female	≥ 7 days of age	1.95 to < 2.10	1.75 to < 1.95	1.53 to < 1.75	< 1.53
Chemistry	Creatinine, High		Male/Female	All	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN	> 1.8 to < 3.5 x ULN	≥ 3.5 x ULN
Chemistry	Glucose, High	mg/dL	Male/Female	All	110 to 125	> 125 to 250	> 250 to 500	≥ 500
Chemistry	Glucose, High	mmol/L	Male/Female	All	6.11 to < 6.95	6.95 to < 13.89	13.89 to < 27.75	≥ 27.75
Chemistry	Glucose, Low	mg/dL	Male/Female	≥ 1 month of age	55 to 64	40 to < 55	30 to < 40	< 30
Chemistry	Glucose, Low	mmol/L	Male/Female	≥ 1 month of age	3.05 to <3.55	2.22 to < 3.05	1.67 to < 2.22	< 1.67
Chemistry	Cholesterol, High	mg/dL	Male/Female	All	200 to < 240	240 to < 300	≥ 300	NA
Chemistry	Cholesterol, High	mmol/L	Male/Female	All	5.18 to < 6.19	6.19 to < 7.77	≥ 7.77	NA
Chemistry	Inorganic Phosphorus, Low	mg/dL	Male/Female	> 14 years of age	2.0 to < LLN	1.4 to < 2.0	1.0 to < 1.4	< 1.0
Chemistry	Inorganic Phosphorus, Low	mmol/L	Male/Female	> 14 years of age	0.65 to < LLN	0.45 to < 0.65	0.32 to < 0.45	< 0.32
Chemistry	Inorganic Phosphorus, Low	mg/dL	Male/Female	<1 to 14 years of age	3.0 to < 3.5	2.5 to < 3.0	1.5 to < 2.5	< 1.5
Chemistry	Inorganic Phosphorus, Low	mmol/L	Male/Female	<1 to 14 years of age	0.97 to < 1.13	0.81 to < 0.97	0.48 to < 0.81	< 0.48
Chemistry	Magnesium, Low	mEq/L	Male/Female	All	1.2 to < 1.4	0.9 to < 1.2	0.6 to < 0.9	< 0.6
Chemistry	Magnesium, Low	mmol/L	Male/Female	All	0.60 to < 0.70	0.45 to < 0.60	0.30 to < 0.45	< 0.30
Chemistry	Potassium, High	mEq/L	Male/Female	All	5.6 to < 6.0	6.0 to < 6.5	6.5 to < 7.0	≥ 7.0
Chemistry	Potassium, High	mmol/L	Male/Female	All	5.6 to < 6.0	6.0 to < 6.5	6.5 to < 7.0	≥ 7.0
Chemistry	Potassium, Low	mEq/L	Male/Female	All	3.0 to < 3.4	2.5 to < 3.0	2.0 to < 2.5	< 2.0
Chemistry	Potassium, Low	mmol/L	Male/Female	All	3.0 to < 3.4	2.5 to < 3.0	2.0 to < 2.5	< 2.0
Chemistry	Sodium, High	mEq/L	Male/Female	All	146 to < 150	150 to < 154	154 to < 160	≥ 160

							Clinically Significant	
LAB GROUP	**TEST**	**UNITS**	**SEX**	**AGE Group**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Chemistry	Sodium, High	mmol/L	Male/Female	All	146 to < 150	150 to < 154	154 to < 160	≥ 160
Chemistry	Sodium, Low	mEq/L	Male/Female	All	130 to < 135	125 to < 130	121 to < 125	≤ 120
Chemistry	Sodium, Low	mmol/L	Male/Female	All	130 to < 135	125 to < 130	121 to < 125	≤ 120
Chemistry	Triglycerides, High	mg/dL	Male/Female	All	150 to 300	>300 to 500	>500 to < 1,000	> 1,000
Chemistry	Triglycerides, High	mmol/L	Male/Female	All	1.71 to 3.42	>3.42 to 5.7	>5.7 to 11.4	> 11.4
Chemistry	Uric Acid, High	mg/dL	Male/Female	All	7.5 to < 10.0	10.0 to < 12.0	12.0 to < 15.0	≥ 15.0
Chemistry	Uric Acid, High	mmol/L	Male/Female	All	0.45 to < 0.59	0.59 to < 0.71	0.71 to < 0.89	≥ 0.89
Chemistry	Activated Partial Thromboplastin Time, High		Male/Female	All	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Chemistry	Prothrombin Time, High		Male/Female	All	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
Chemistry	Partial Thromboplastin Time, High		Male/Female	All	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Hematology	Absolute CD4+ Count, Low	cell/mm^3	Male/Female	> 5 years of age (not HIV infected)	300 to < 400	200 to < 300	100 to < 200	< 100
Hematology	Absolute CD4+ Count, Low	cells/L	Male/Female	> 5 years of age (not HIV infected)	300 to < 400	200 to < 300	100 to < 200	< 100
Hematology	Absolute Lymphocytes, Low	cell/mm^3	Male/Female	> 5 years of age (not HIV infected)	600 to < 650	500 to < 600	350 to < 500	< 350
Hematology	Absolute Lymphocytes, Low	cells/L	Male/Female	> 5 years of age (not HIV infected)	0.600 x 10^9 to < 0.650 x 10^9	0.500 x 10^9 to < 0.600 x 10^9	0.350 x 10^9 to < 0.500 x 10^9	< 0.350 x 10^9
Hematology	Absolute Neutrophil Count, Low	cell/mm^3	Male/Female	> 7 days of age	800 to 1,000	600 to 799	400 to 599	<400
Hematology	Absolute Neutrophil Count, Low	cells/L	Male/Female	> 7 days of age	0.800 x 10^9 to 1.000 x 10^9	0.600 x 10^9 to 0.799 x 10^9	0.400 x 10^9 to < 0.599 x 10^9	< 0.400 x 10^9
Hematology	Hemoglobin, Low	g/dL	Male	≥ 13 years of age	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
Hematology	Hemoglobin, Low	mmol/L	Male	≥ 13 years of age	6.19 to 6.76	5.57 to < 6.19	4.34 to < 5.57	< 4.34
Hematology	Hemoglobin, Low	g/dL	Female	≥ 13 years of age	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
Hematology	Hemoglobin, Low	mmol/L	Female	≥ 13 years of age	5.88 to 6.48	5.25 to < 5.88	4.03 to < 5.25	< 4.03
Hematology	Hemoglobin, Low	g/dL	Male/Female	57 days of age to < 13 years of age	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
Hematology	Hemoglobin, Low	mmol/L	Male/Female	57 days of age to < 13 years of age	5.88 to 6.48	5.25 to < 5.88	4.03 to < 5.25	< 4.03
Hematology	Platelet Count, Decreased	cells/mm^3	Male/Female	All	100,000 to < 125,000	50,000 to < 100,000	25,000 to < 50,000	< 25,000

							Clinically Significant	
LAB GROUP	**TEST**	**UNITS**	**SEX**	**AGE Group**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hematology	Platelet Count, Decreased	cells/L	Male/Female	All	100.000 x 10^9 to < 125.000 x 10^9	50.000 x 10^9 to < 100.000 x 10^9	25.000 x 10^9 to < 50.000 x 10^9	< 25.000 x 10^9
Hematology	White Blood Cell, Decreased	cells/mm^3	Male/Female	> 7 days of age	2,000 to 2,499	1,500 to 1,999	1,000 to 1,499	< 1,000
Hematology	White Blood Cell, Decreased	cells/L	Male/Female	> 7 days of age	2.000 x 10^9 to 2.499 x 10^9	1.500 x 10^9 to 1.999 x 10^9	1.000 x 10^9 to 1.499 x 10^9	< 1.000 x 10^9
Urinalysis	Urine Glucose		Male/Female	All	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or >500 mg	NA
Urinalysis	Urine Blood		Male/Female	All	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross OR Presence of RBC casts OR Intervention indicated	Life-threatening consequences
Urinalysis	Urine Protein		Male/Female	All	1+	2+	3+ or higher	NA

RBC = red blood cell; ULN=upper normal limit

Appendix 2 Criteria for Potentially Clinical Significant Vital Sign Abnormalities

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate[b]	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic Blood Pressure[b]	> 160 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure[b]	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Weight	-	≥ 5% increase ≥ 5% decrease

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

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Appendix 3 Definition of Grades for Vital Sign in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adeverse Events

Abnormality	AGE Group	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hypertension (with the lowest reading taken after repeat testing during a visit) Male/Female	≥ 18 years of age	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
	< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Underweight	> 5 to 19 years of age	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	ALL	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Fever (non-axillary temperatures only)		38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F

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Appendix 4 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Category **Diagnosis**	**Criterion Value**[a]	**Change Relative to Baseline**[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 0.20 second	increase of ≥ 0.05 second
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 0.12 second	increase of ≥ 0.02 second
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post trial entry
ST/T Morphological		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc	QTc > 450 msec (males and females)	
QT	> 500 msec	
Increase in QTcF	QTc > 450 msec (males and females)	
	QTc > 500 msec (males and females)	
		Increase of ≥ 30 msec and ≤ 60 msec
		Increase of > 60 msec
Increase in QTcB	QTc > 450 msec (males and females)	
	QTc > 500 msec (males and females)	
		Increase of ≥ 30 msec and ≤ 60 msec
		Increase of > 60 msec

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

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[b]No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c]No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[dd]No current diagnosis of left bundle branch block or right bundle branch block.

Appendix 5 Grading Scale for reporting Sputum Smears

The following grading scale is used for reading and reporting sputum smears:

Grading Scale for Fluorescent Stain			
What you see (200x)	**What you see (400x)**	**What to Record**	**What to Report for MAD EBA**
No AFB in one length	No AFB in one length	No AFB observed	Negative
1-4 AFB in one length	1-2 AFB in one length	Confirmation required*	Rare
5-49 AFB in one length	3-24 AFB in one length	Scanty	Rare
3-24 AFB in one field	1-6 AFB in one field	1+	Few (1+)
25-250 AFB in one field	7-60 AFB in one field	2+	Many (2+)
> 250 AFB in one field	> 60 AFB in one field	3+	TNTC (3+)

*Confirmation required by another technician or prepare another smear, stain and read. If second technician confirms result, record as Scanty.

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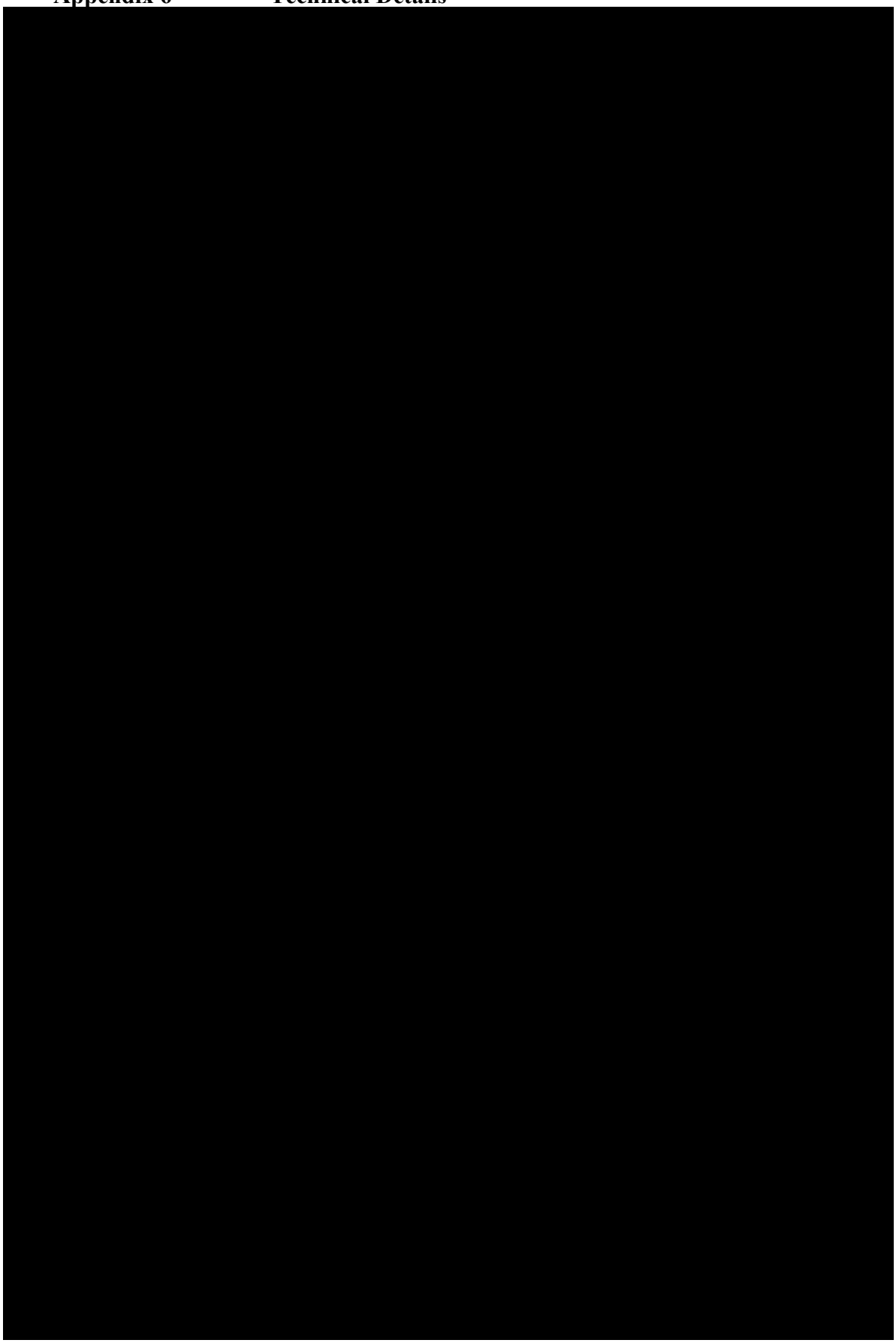
Appendix 6 Technical Details



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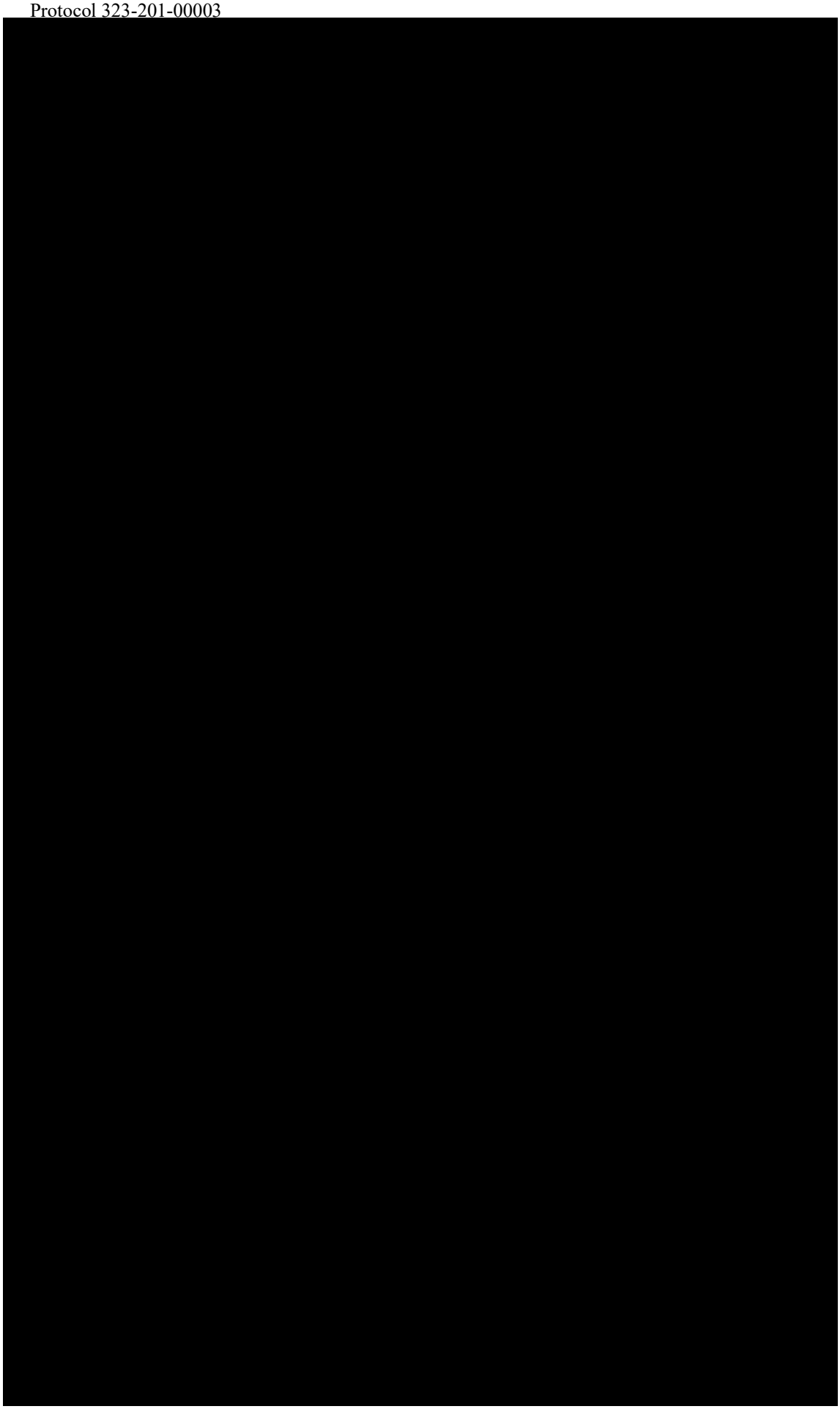

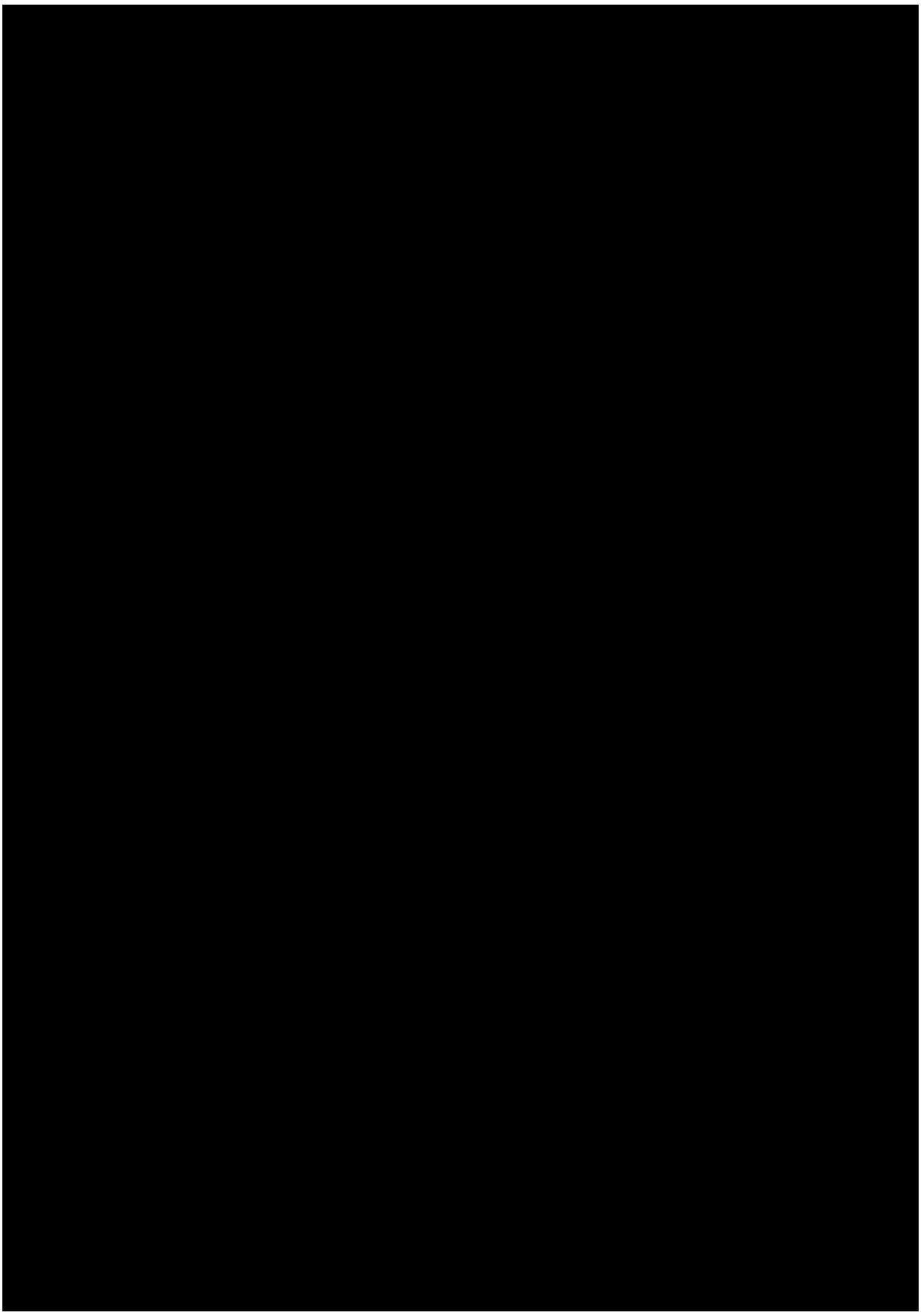

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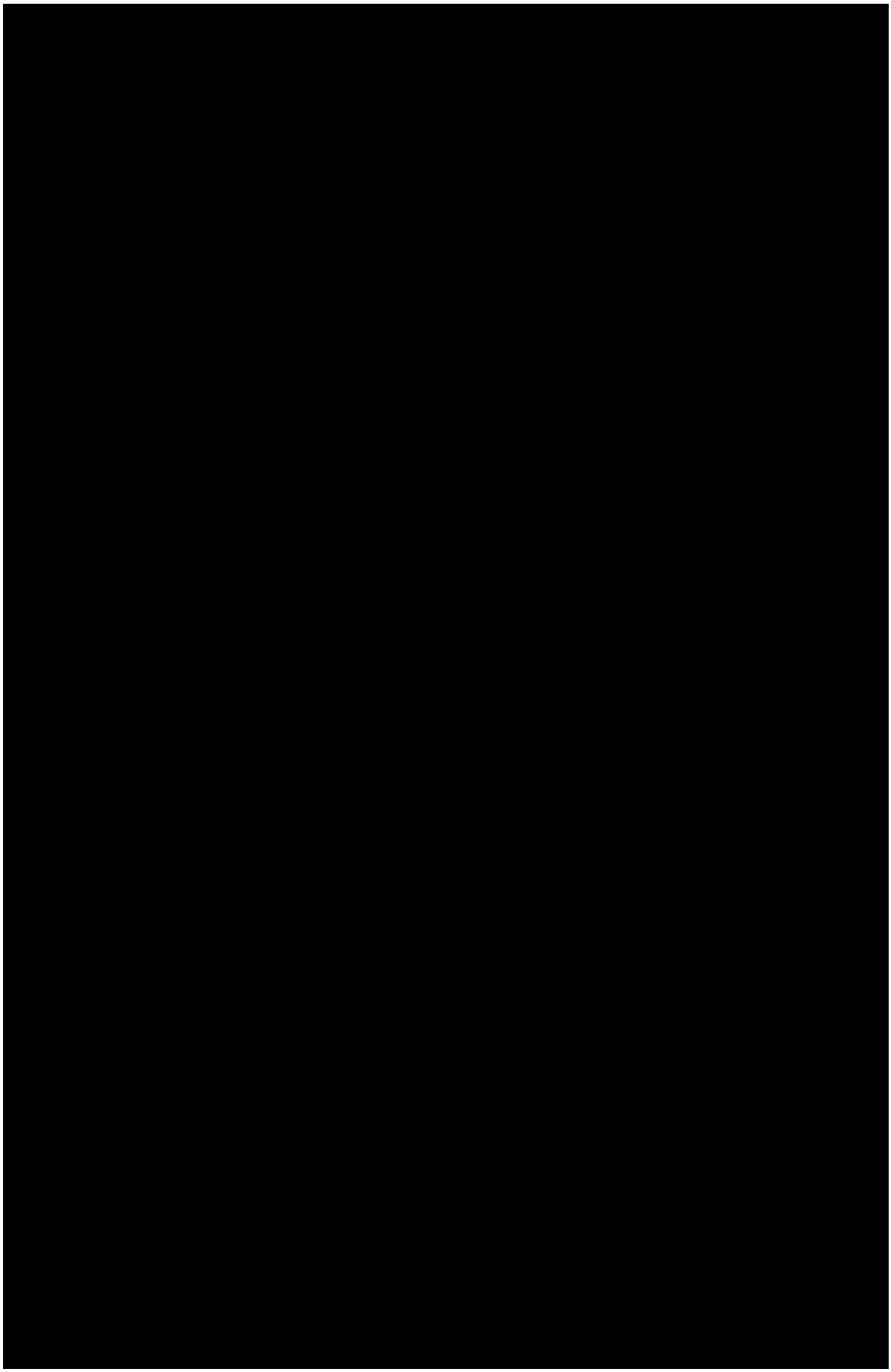
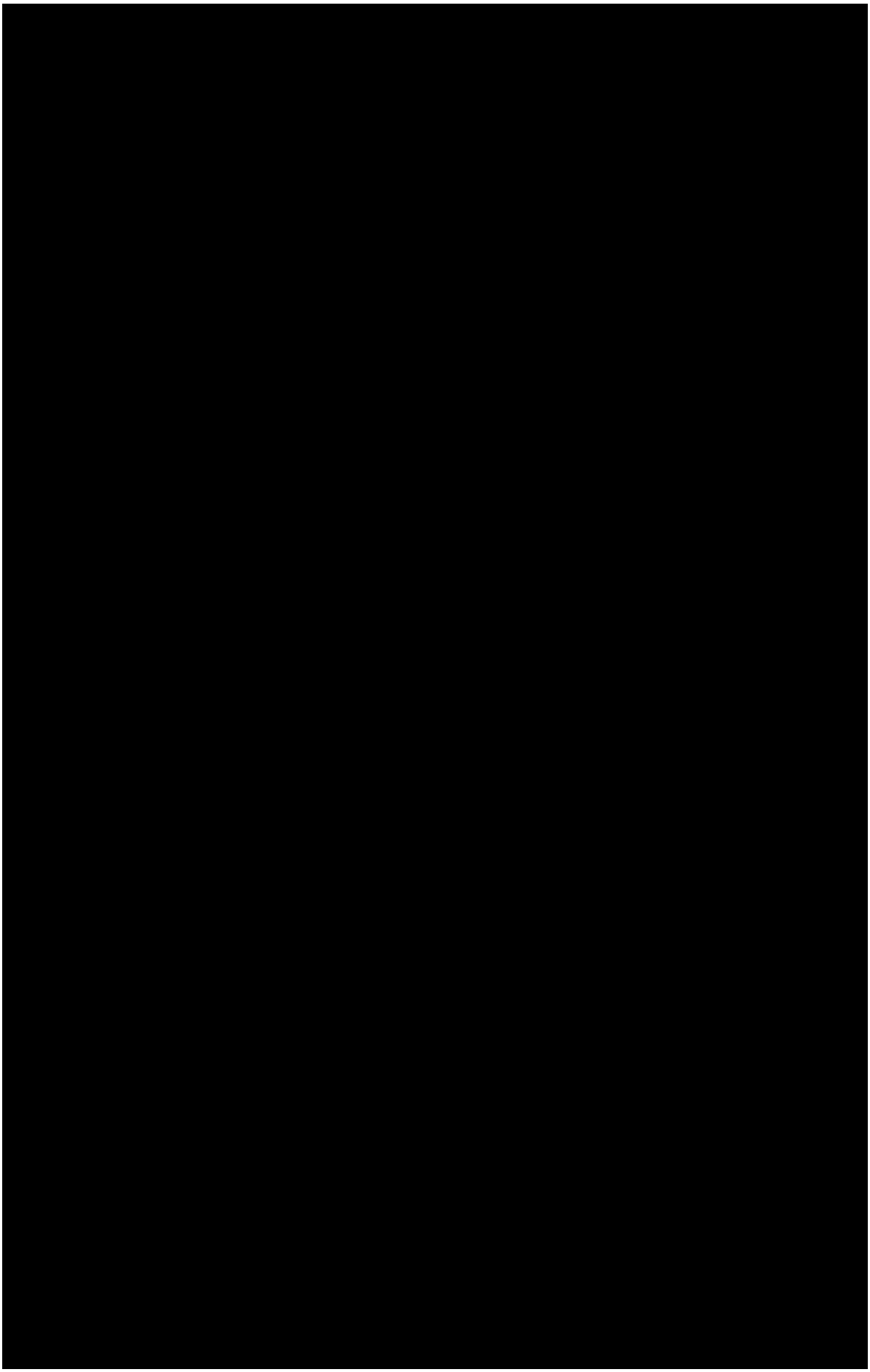
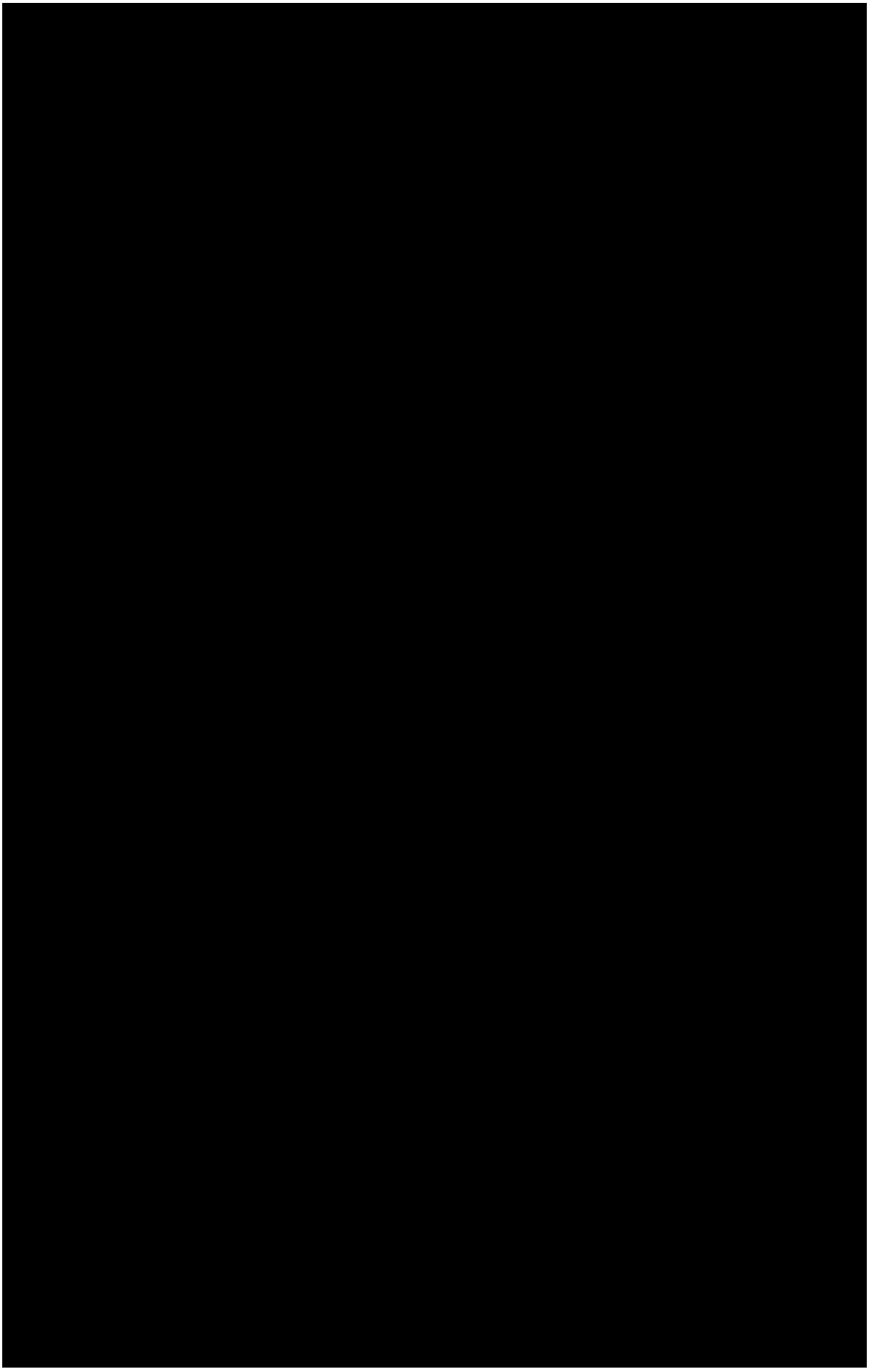
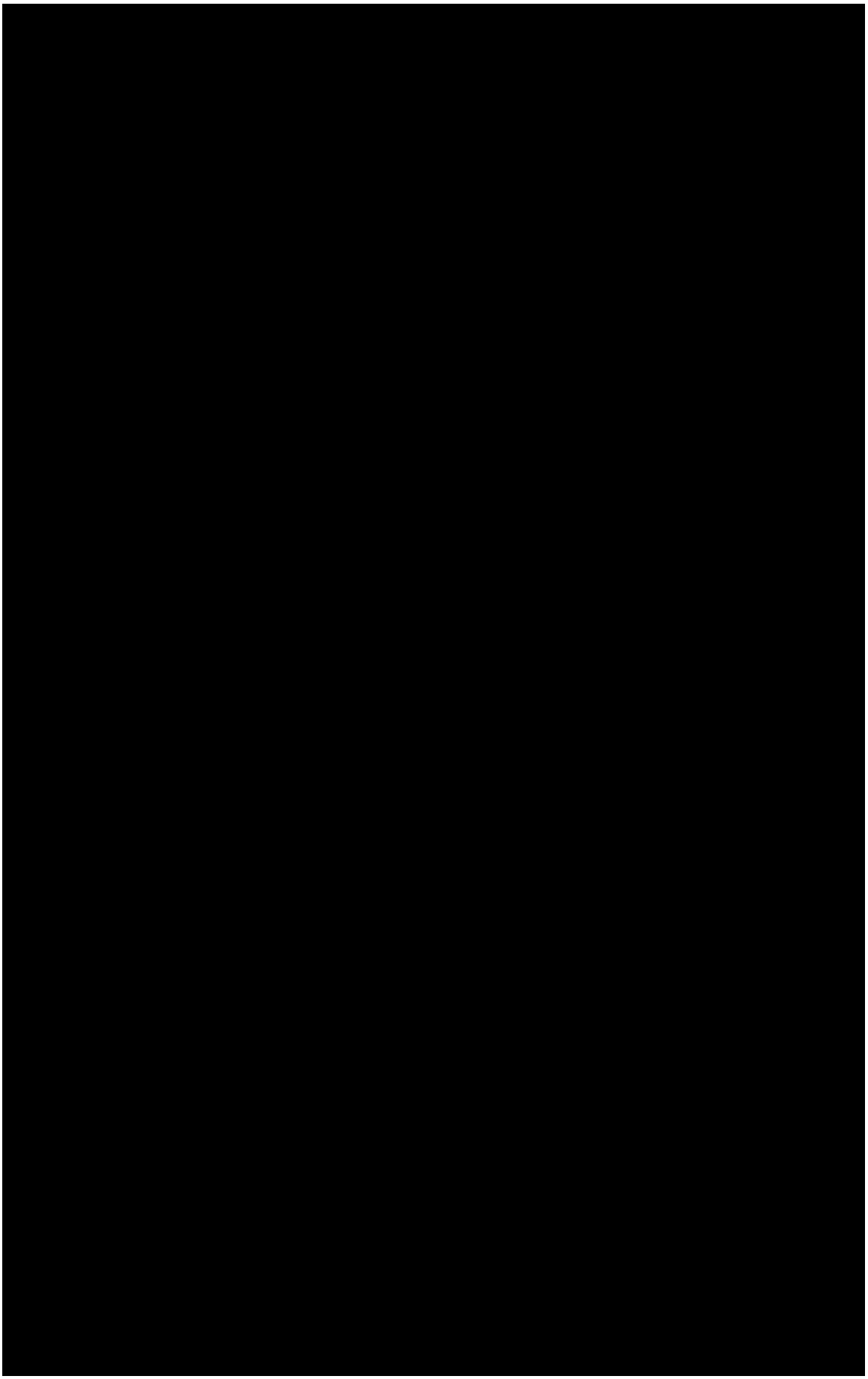
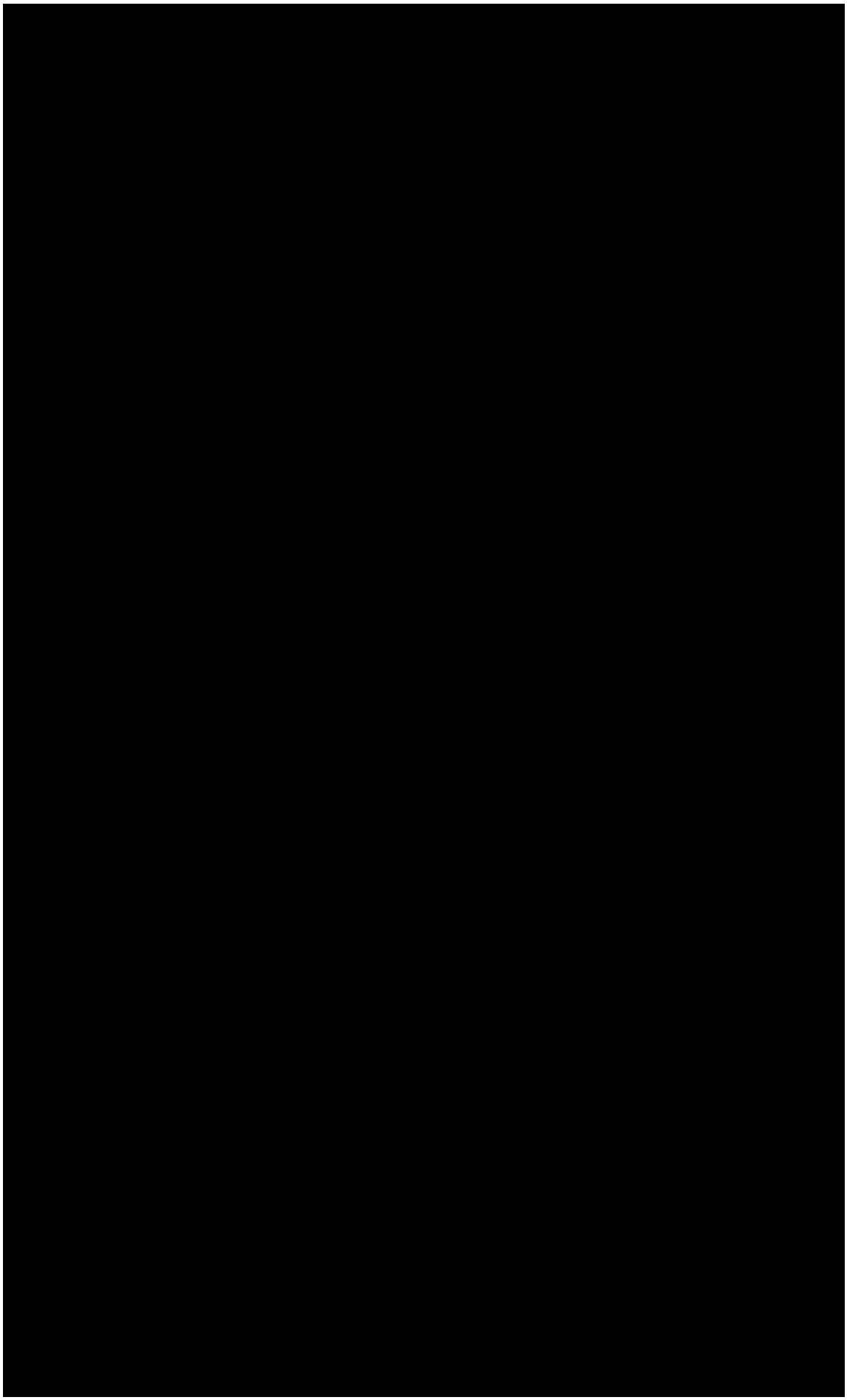
Appendix 7 List of Proposed Summary Tables

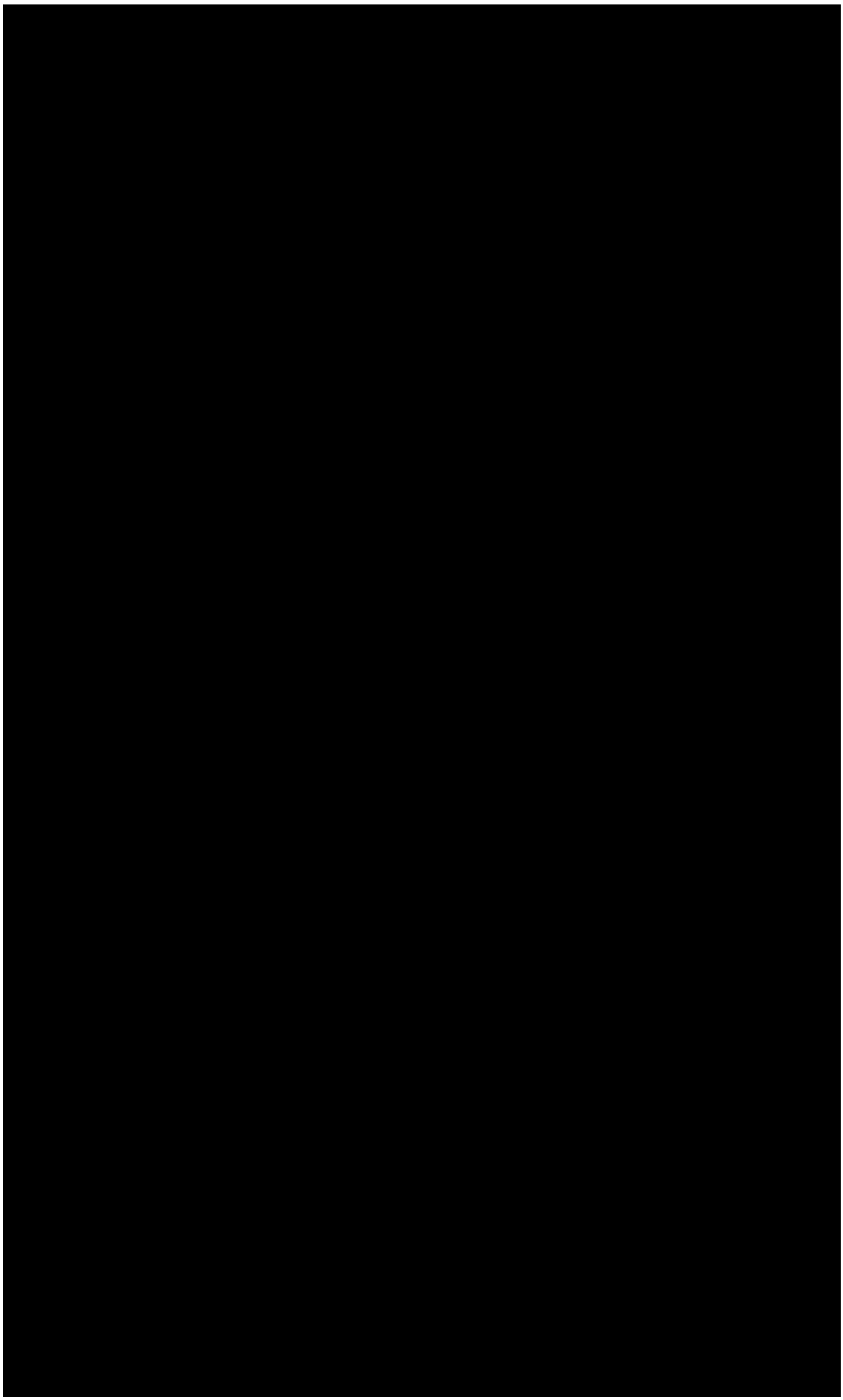


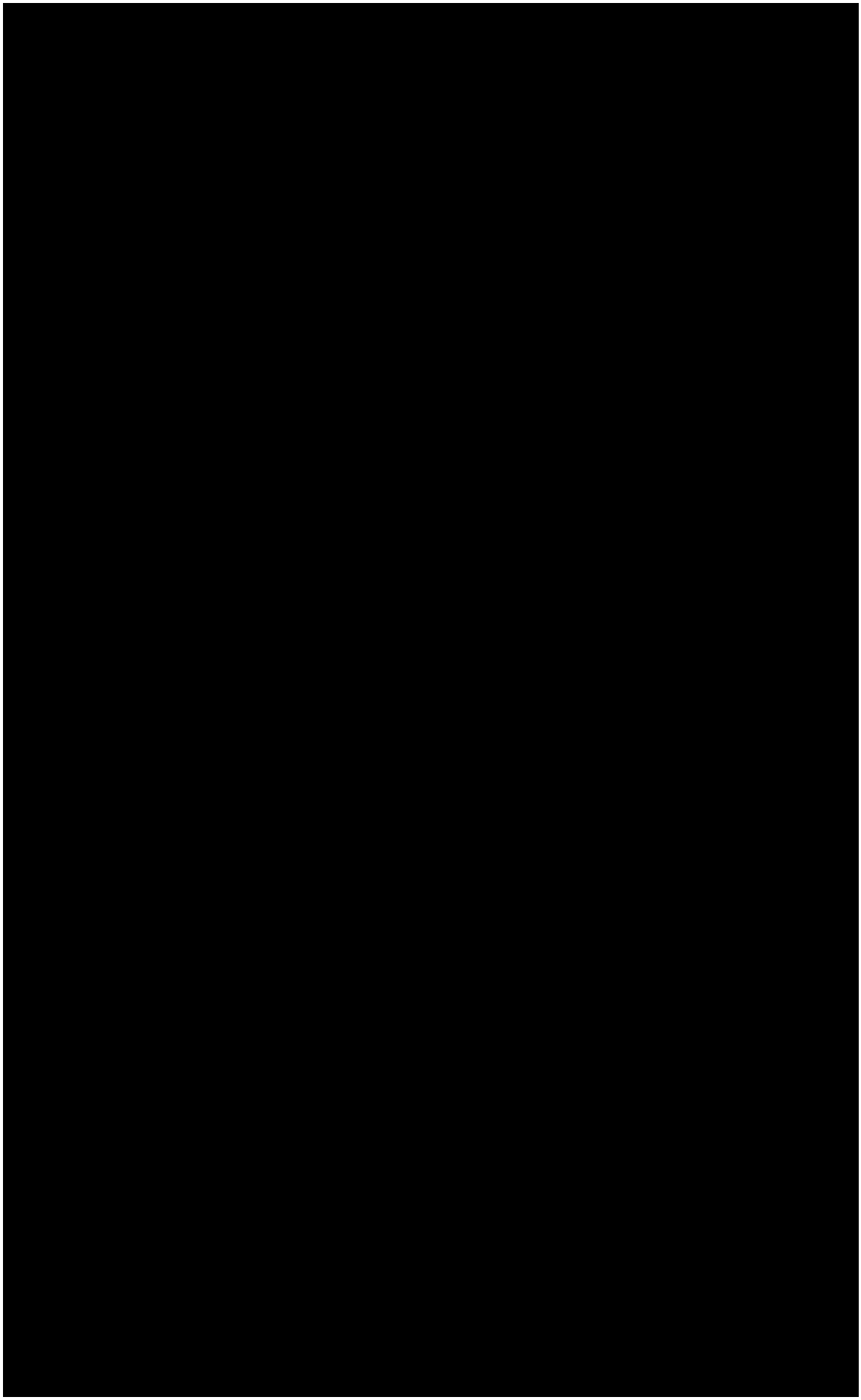












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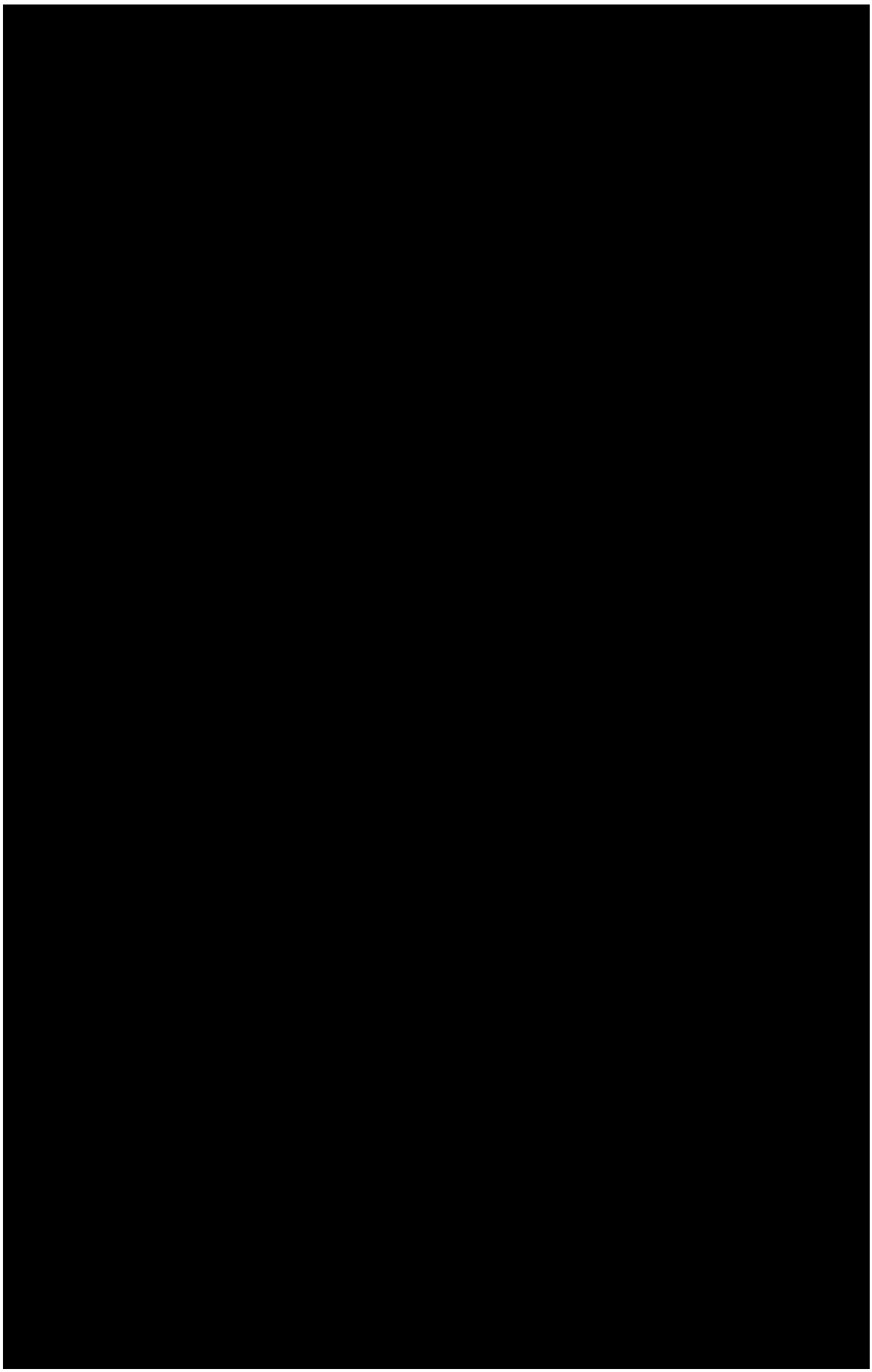

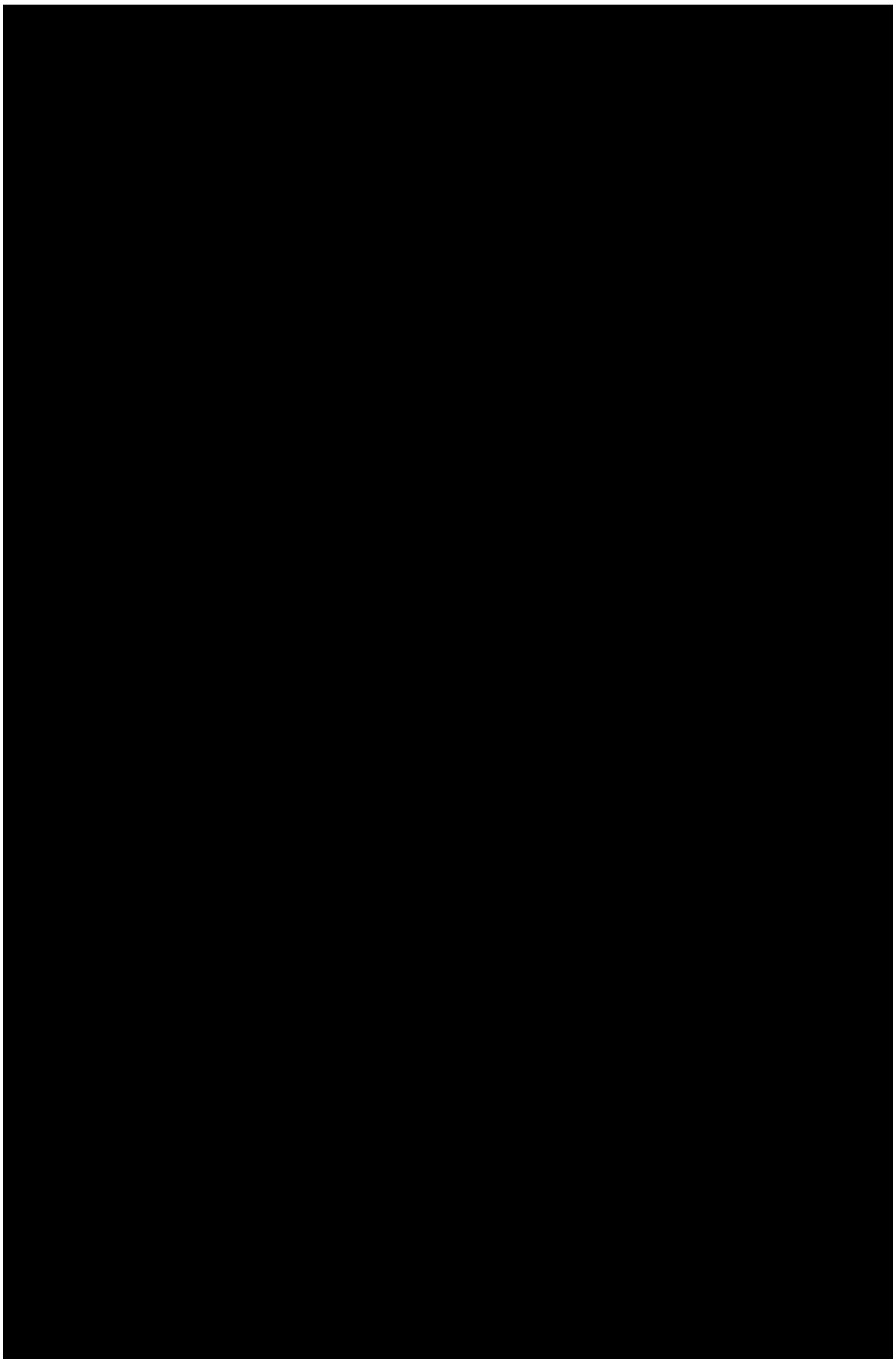

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Appendix 8 List of Proposed Subject Data Listings

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
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