Study Number: ONO-7475-01 Protocol	**Version:** 10.0 [incorporating Amendments #1–9]

CLINICAL STUDY PROTOCOL

Title:	A Phase I/II open label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary clinical efficacy of ONO-7475 in patients with acute leukemias or myelodysplastic syndromes

Version:	**10.0 [incorporating Amendments #1–9]**
Version Date:	9 February 2022
Study Number:	ONO-7475-01
Phase:	I/II

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Ono Pharmaceutical Co., Ltd.

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INVESTIGATOR SIGNATURE PAGE

I agree to conduct this study in accordance with the requirements of this document (the Clinical Study Protocol), the Study Procedures Manual and also in accordance with the following:

- The ethical principles founded in the Declaration of Helsinki
- The International Council for Harmonization harmonized tripartite guideline regarding Good Clinical Practice (E6 Consolidated Guidance, Revision 1, Jun 1996)
- US Code of Federal Regulations, Chapter 21: Parts 11, 50, 54, 312, and 314 plus Amendments

I acknowledge the confidential nature of the documentation generated as part of this study and that the Sponsor of the study (Ono Pharmaceutical Co., Ltd.) has the right to discontinue the study at any time.

_____

Investigator Name

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Affiliation

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Investigator Signature Date

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ABBREVIATIONS

AE	Adverse event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
[redacted]	[redacted]
AST	Aspartate aminotransferase
[redacted]	[redacted]
AUC	Area under the curve
BA	Bioavailability
[redacted]	[redacted]
BM	Bone marrow
CBC	Complete blood count
Cmax	Maximum observed plasma concentration
COVID-19	Coronavirus Disease 2019
CR	Complete remission
CrCl	Creatinine clearance
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DLT	Dose limiting toxicity
DoR	Duration of response
DMP	Data management plan
[redacted]	[redacted]
EA	Expansion efficacy assessment
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture system
EFS	Event-free survival
ELN	European Leukemia Net
ERG	Electroretinogram
ETDR	Early Treatment Diabetic Retinopathy
FAS	Full analysis set
FDA	Food and Drug Administration
[redacted]	[redacted]
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HNSTD	Highest non severely toxic dose
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration

ICH	International Council for Harmonization
Ig	Immunoglobulin
INR	International normalized ratio
IRB	Institutional Review Board
ITD+	internal tandem duplication positive
IWG	International Working Group
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
[redacted]	[redacted]
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	[redacted]
OBD	Optimal biological dose
[redacted]	[redacted]
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic(s)
[redacted]	[redacted]
PIA	Plasma inhibitory activity
PK	Pharmacokinetic(s)
PR	Partial remission
PT	Prothrombin time
QTcF	QT interval corrected according to Fredericia's formula
R/R	Relapsed/Refractory
RBC	Red blood cell
[redacted]	[redacted]
SA	Safety assessment
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SOP	Standard operating procedure
SRC	Study Review Committee
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAM	Tyro3, Axl and Mer
TLS	Tumor lysis syndrome
Tmax	Time to reach Cmax
TTR	Time to response
T1/2	Elimination half-life
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

IMPORTANT NOTE TO READERS

PROTOCOL SUMMARY

STUDY TITLE: A Phase I/II open label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary clinical efficacy of ONO-7475 in patients with acute leukemias or myelodysplastic syndromes.

Study Phase: I/II

Rationale

Axl and Mer belong to the Tyro3, Axl and Mer (TAM) family of receptor tyrosine kinases and play a role in regulating cell proliferation, survival, migration and cytokine production. Axl and Mer are over-expressed in various types of hematological and solid cancers, and mediate multiple oncogenic phenotypes such as survival, proliferation and epithelial-to-mesenchymal transition, which accelerate cancer metastasis and resistance[9]. In addition to the roles of Axl and Mer expressed in tumor cells, recent reports indicate that TAM kinases expressed by immune cells, such as antigen presenting cells and natural killer cells, suppress anti-tumor immunity. Therefore, Axl and Mer are unique and promising therapeutic targets in the treatment of a wide variety of malignancies.

High levels of Axl and Mer expression are detected in patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). Axl and Mer expression is detected in 57% and 85% of AML patients respectively and Axl expression represents an independent prognostic marker for AML[1].

ONO-7475 is a highly potent and selective oral inhibitor of Axl and Mer [redacted]

This first-in-human patient study aims to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of oral doses of ONO-7475 as monotherapy in R/R AML or R/R MDS and in combination with venetoclax in R/R AML.

Primary Study Objectives and Endpoints*

Part A: The primary objective of this part of the study is to assess the safety and tolerability of ONO-7475 monotherapy in patients with R/R AML or R/R MDS. The primary endpoints are incidence, nature, and severity of adverse events (AEs) and serious adverse events (SAEs) of ONO-7475, clinically significant changes in ophthalmology parameters and 12-lead electrocardiogram (ECG).

Part D: The primary objectives of this part of the study are to assess: i) safety and tolerability and ii) preliminary efficacy of the combination of ONO-7475 and venetoclax in patients with R/R AML. The primary endpoints are i) incidence, nature, and severity of AEs and SAEs related to ONO-7475, and ii) complete remission and complete remission with incomplete hematologic recovery rate.

Study Design

The study design incorporates 2 parts (A and D) and will investigate ONO-7475 in 2 distinct patient populations (see below). Part A applies a dose escalation design which will establish a dose of ONO-7475 monotherapy with an acceptable safety

* Texts relating to Parts B and C were removed from the protocol and Parts B and C will not be conducted due to the significant changes in AML treatment landscape for Part B and the re-strategic evaluation for Part C.

profile. [redacted]

Part D uses a dose escalation design [redacted] which will establish a dose of ONO-7475 plus venetoclax with an acceptable safety profile, and an expansion efficacy group analysis to assess the preliminary efficacy of ONO-7475 in combination with venetoclax [redacted].

Study Population

Part A

- R/R AML or R/R MDS
  - ONO-7475 will be administered as monotherapy

Part D

- R/R AML
  - ONO-7475 will be given in combination with venetoclax

Number of Patients

The estimated number of patients and patient study populations required for adequate data interpretation are:

Part A: up to approximately 42 patients with R/R AML or R/R MDS.

Part D: up to approximately 47 patients with R/R AML.

Table 1 Study Assessments

Safety	• Demographics • Medical and surgical history (including cancer history), cancer diagnosis • Medication history (including prior anti-leukemic therapies) • Pregnancy test • Height and weight • Echocardiogram or multigated acquisition scan • Clinical laboratory tests (chemistry and hematology) • 12-lead electrocardiogram • Ophthalmological assessments • Visual function • Eastern Cooperative Oncology Group Performance Score • Physical examination • Vital sign measurements • Concomitant medication • Adverse events
Efficacy	• Complete blood counts • [redacted] • Pharmacodynamic marker (plasma inhibitory activity)
Others	• Exploratory biomarkers

1 INTRODUCTION

1.1 Background

ONO-7475 (previously known as ONO-9330547) is a potent and reversible Axl/Mer inhibitor [redacted]

1.1.1 Disease Area and Current Medical Need

AML is a heterogeneous hematological malignancy involving the clonal expansion of myeloid blast cells in the BM and peripheral blood which may also spread to other organs such as the liver and spleen. In 2020, it is estimated that there will be 19,940 new cases of acute myeloid leukemia in the United States (US). The median age at diagnosis is 68 years, with approximately 59% patients over 65 years, and approximately 33% over 75 years[21].

After more than 30 years of no new drugs being approved to treat AML, the last few years have seen multiple drugs (e.g., venetoclax and HMAs or low dose cytarabine or glasdegib and low dose cytarabine) approved by the US Food and Drug Administration (FDA) and other agencies, especially for patients with newly-diagnosed AML who are ineligible for intensive chemotherapy. However, those AML patients who fail to achieve CR and become R/R still have limited treatment options. Most therapies for patients with R/R AML show neither a significant clinical response nor prolongation of survival. Specifically, less aggressive therapy—such as HMA—in R/R AML patients who are ineligible for intensive chemotherapy showed approximately 20% CR rate and survival was less than a year[1]. Therefore, patients with R/R AML have, in general, a very poor prognosis and there is a high unmet medical need for improved treatments in this patient population.

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological malignancies involving stem cells. MDS is characterized by dysplastic and ineffective blood cell production and the risk of progression to AML. Current estimates of the incidence of MDS in the US are approximately 10,000 cases each year[15]. MDS is uncommon before the age of 50 and commonly diagnosed in elderly people in their 70s. Patients are treated according to several underlying options at

the time of diagnosis of MDS; this includes risk stratification using tools such as the revised International Prognostic Scoring System[5].

With the exception of allogeneic hematopoietic stem cell transplantation (HSCT), which is only an option for a small group of patients who are relatively fit and can tolerate it, there are no options for patients who are R/R following treatment with HMA. Accordingly, there is a high unmet medical need in patients with R/R MDS who have failed standard therapy and for whom HSCT is not an option.

1.1.2 Name and Description of the Investigational Drugs

1.1.2.1 ONO-7475

ONO-7475 is a highly potent and selective oral Axl/Mer dual inhibitor. [redacted]

1.1.2.2 Venetoclax

Venetoclax will be provided by the Sponsor for in-study patient treatment in Part D of the study. It will be provided as VENCLEXTA®. VENCLEXTA is manufactured by AbbVie Inc and marketed by AbbVie Inc (North Chicago, IL, US) and Genentech USA Inc (South San Francisco, CA, US).

Venetoclax is a 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl} sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide). The empirical formula is $C_{45}H_{50}ClN_7O_7S$.

1.1.3 Non-clinical Studies

[redacted]

1.1.3.1 Non-clinical Pharmacology

[redacted]

[redacted]

[redacted]

1.1.3.2 Preclinical Pharmacokinetics

[redacted]

1.1.3.3 Toxicology and Safety Pharmacology

[redacted]

[redacted]

[redacted]

[redacted]

1.1.4 Clinical Experience with ONO-7475

Three clinical trials (ONO-7475-01, ONO-7475-02, and ONO-7475-03) are currently ongoing. ONO-7475-01 is the first-in-human trial in patients with acute leukemias or MDS. ONO-7475-02 study is a Phase I clinical trial being conducted in patients with advanced or metastatic solid tumors, and is currently ongoing in Japan only. ONO-7475-03 study is a Phase I clinical trial being conducted in patients with epidermal growth factor receptor-mutated non-small cell lung cancer, and is currently ongoing in Japan only. The preliminary clinical information for these studies is described in the ONO-7475 IB[25].

1.1.5 Clinical Experience with Venetoclax (VENCLEXTA®)

In 2016, the US FDA first granted accelerated approval of VENCLEXTA for the treatment of patients with chronic lymphocytic leukemia with 17p deletion, who have received at least 1 prior therapy. In 2018, VENCLEXTA was approved under accelerated approval (in combination with either azacitidine, or decitabine, or low-dose cytarabine) to treat adults with newly-diagnosed AML who are aged 75 years or older, or who have other medical comorbidities that prevent the use of intensive induction chemotherapy. In 2019, the US FDA approved VENCLEXTA for adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.

1.1.5.1 Clinical Efficacy in Study M14-358

The efficacy and safety of VENCLEXTA was studied in a non-randomized, open label clinical trial of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Sixty-seven patients who received the azacitidine combination and 13 who received decitabine combination were aged 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy. CR and CR with partial hematologic recovery (CRh) in patients who received the VENCLEXTA plus azacitidine combination were 37% and 24%, respectively. CR and CRh in patients who received the VENCLEXTA plus decitabine combination were 54% and 7.7%, respectively. The median follow-up was 7.9 months (range: 0.4 to 36 months) for VENCLEXTA in combination with azacitidine. The median follow-up was 11 months (range: 0.7 to 21 months) for VENCLEXTA in combination with decitabine.

1.1.5.2 Clinical Efficacy in Study M14-387

The efficacy and safety of VENCLEXTA was studied in a non-randomized, open label clinical trial of VENCLEXTA in combination with low dose cytarabine (N=82) in patients with newly-diagnosed AML, including patients with previous exposure to an HMA for an antecedent hematologic disorder. Sixty-one patients aged 75 years or older had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2–3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, creatinine clearance ≥30 to <45 mL/min, or another comorbidity. CR and CRh in patients who received VENCLEXTA in combination with low-dose cytarabine were both 21%. The median follow-up was 6.5 months (range: 0.3 to 34 months).

1.2 Rationale

1.2.1 Study Rationale

This first-in-patient study aims to determine the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of oral doses of ONO-7475 given as monotherapy in patients with AML and MDS and in combination with venetoclax in patients with AML.

The rationale for investigating ONO-7475 in AML and MDS is based on preclinical data, the nature of the disease, and the significant unmet need in these indications.

The rationale for investigating the combination of ONO-7475 with venetoclax in AML is based on preclinical data showing efficacy of ONO-7475 plus venetoclax in mouse AML disease models and the significant unmet need in R/R AML.

1.2.2 Study Design Rationale

This is the first-in-human patient clinical trial for ONO-7475 and is an open label study in 2 parts (Parts A and D). Part A will apply a dose escalation design [redacted]

The primary objective of Part A (patients with R/R AML or R/R MDS) is to characterize the safety and DLTs of ONO-7475 for the first time in humans [redacted].

The objective of Part D is to characterize the safety, tolerability, and preliminary efficacy of ONO-7475 in combination with venetoclax in patients with R/R AML. Preclinical studies have shown ONO-7475 has positive synergistic effects with venetoclax, suggesting ONO-7475 plus venetoclax may be a promising approach in R/R AML. Part D will initially assess the safety and tolerability of ONO-7475 in combination with venetoclax. Assuming no safety concerns are raised then an efficacy assessment will be initiated.

[redacted]

Since Part D is the first study in which ONO-7475 has been used in combination with venetoclax, the safety and tolerability of ONO-7475 plus venetoclax will be evaluated in [redacted] evaluable patients after which the study will be expanded for the preliminary efficacy assessment of the ONO-7475/venetoclax combination regimen.

Part D comprises 2 groups for the purpose of analysis: the safety assessment (SA) group and the expansion efficacy assessment (EA) group. The SA group will apply a dose escalation design [redacted] for the assessment of safety and tolerability and, subsequently, the EA group will be used for the assessment of preliminary efficacy [redacted]

1.2.3 Dose Rationale

1.2.3.1 Starting Dose in Part A

[redacted]

[redacted]

[redacted]

1.2.3.2 Starting Dose in Part D

ONO-7475

A dose of ONO-7475 6 mg once daily will be used in Part D [redacted]

[redacted]

Venetoclax

The recommended dose of venetoclax is 400 mg orally taken once a day where no concomitant medication is taken in the maintenance period. Dose adjustment of venetoclax (70 to 200 mg once daily) is required where concomitant medication [redacted]

Further details are provided in Table 3.

Table 3 Venetoclax Dosing

[redacted]

1.3 Risk/Benefit Assessment

ONO-7475

Overall, the risk/benefit ratio of ONO-7475 with respect to Part A of the current proposed first-in-human trial is considered to be positive.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Venetoclax

Potential Risks

The potential risks for venetoclax use are as outlined in the prescribing information: "VENCLEXTA. Initial U.S. Approval: 2016[22].

During ramp-up dosing of venetoclax for the first 3 days in Cycle 1, it is recommended that prophylactic measures should be provided to minimize the risk of tumor lysis syndrome (TLS) and continuous blood monitoring should be performed as it is described in the Venetoclax FDA label (see Section 6.2).

Although venetoclax can cause pancytopenia in some patients, there is no evidence to suggest that the addition of ONO-7475 will exacerbate this, based on non-clinical safety profile and emergent data from Part A.

Potential Benefits of ONO-7475 Plus Venetoclax Combination

Venetoclax in combination with HMA or low-dose cytarabine has demonstrated clinical benefit in studies of AML patients (see Section 1.1.5.1 and Section 1.1.5.2).

The potential benefit from the combination of ONO-7475 with venetoclax based on preclinical data justifies testing the combination in the R/R AML population for whom very few treatment options exist. [redacted]

[redacted]

Study Considerations Relating to the Coronavirus Disease 2019 (COVID-19)

In view of the ongoing COVID-19 pandemic, testing of patients in Part D for COVID-19 will be undertaken. This should be symptom-directed and positive results will be handled according to local site/institution procedures. Patients who test positive for COVID-19 (i.e., have active infection) will be ineligible for enrolment and excluded from the study. This is considered a reasonable precaution given the fact that R/R AML patients are often immuno-compromised.

1.4 Study Conduct

This study will be conducted in accordance with the requirements of this document (the Clinical Study Protocol), and also in accordance with the following:

- The ethical principles founded in the Declaration of Helsinki
- The International Council for Harmonization (ICH) harmonised tripartite guideline regarding Good Clinical Practice (GCP; E6 Consolidated Guidance, Revision 1 June 1996)
- US Code of Federal Regulations, Chapter 21: Parts 11, 50, 54, 312 & 314 plus Amendments
- Local laws and regulations

Part D of the study will not commence until a safe dose of ONO-7475 as a single agent has been established in Part A, and the data from Part A have been evaluated by the applicable regulatory authority. Part D will only proceed after approvals from the applicable regulatory authority and Institutional Review Board(s) (IRB[s]) are in place for these parts of the study.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 4 below outlines the primary, secondary, and exploratory objectives of the study and their associated endpoints.

Table 4 Objectives and Endpoints for all study parts

Part A – Monotherapy Dose Escalation	
Primary Objective	**Primary Endpoints**
To assess the safety and tolerability of ONO-7475 monotherapy in patients with R/R AML or R/R MDS	• Incidence, nature, and severity of AEs and serious AEs (SAEs) • Clinically significant changes in ophthalmology parameter examinations and 12-lead electrocardiogram (ECG)

Secondary Objectives	Secondary Endpoints
To select an optimal dose of ONO-7475 for further clinical evaluation	Maximum tolerated dose (MTD) and/or recommended pharmacological dose based on clinical response or pharmacodynamics (PD) markers
To assess the pharmacokinetics (PK) of ONO-7475 in in patients with R/R AML and R/R MDS	PK parameters: maximum observed plasma concentration (Cmax), time to reach Cmax (Tmax), area under the plasma concentration-time curves (AUC) on Days 1 and 28, elimination half-life (T1/2) plasma concentration prior to next dose
To evaluate food effect on the PK of ONO-7475	The PK of the food effect on ONO-7475 (Cmax, Tmax, AUC, T1/2, and plasma concentration prior to next dose)
To assess the PD activity of ONO-7475 in patients with R/R AML and R/R MDS	PD biomarkers of response: plasma inhibitory activity (PIA) assay (pAxl/pMer inhibition)
To assess the preliminary clinical efficacy of ONO-7475 in patients with R/R AML and R/R MDS	• Overall response rate (ORR), duration of response (DoR), event-free survival (EFS) • Complete remission (CR) without minimal residual disease (MRD)
Part D – Combination with Venetoclax	
Primary Objectives	**Primary Endpoints**
<u>SA group:</u> To assess the safety and tolerability of ONO-7475 in combination with venetoclax <u>EA group:</u> To assess the preliminary efficacy of ONO-7475 in combination with venetoclax	<u>SA group</u>: Incidence, nature, and severity of AEs and SAEs <u>EA group</u>: CR/CR with partial hematologic recovery (CRh) rate
Secondary Objectives	**Secondary Endpoints**
<u>Both groups:</u> • To assess the PK of ONO-7475 in combination with venetoclax in patients with R/R AML • To assess the PK of venetoclax alone or in combination with ONO-7475 in patients with R/R AML <u>SA group:</u>	<u>Both groups:</u> PK parameters (Cmax, AUC, Tmax, T1/2 for ONO-7475 and venetoclax) <u>SA group:</u> Recommended Phase 2 dose (RP2D) <u>EA group:</u>

• To select a dose for further clinical evaluation EA group: To assess the safety of ONO-7475 in combination with venetoclax	• Incidence, nature, and severity of AEs and SAEs • ORR • Transfusion independence rate • DoR • EFS • CR • CRh • CR/CRh without MRD • Overall survival (OS)
Exploratory Objectives	**Exploratory Endpoints**
Both groups: • To assess PD effect of ONO-7475 by PIA [redacted]	Both groups: • Inhibition rate of phosphorylated Axl and Mer [redacted]

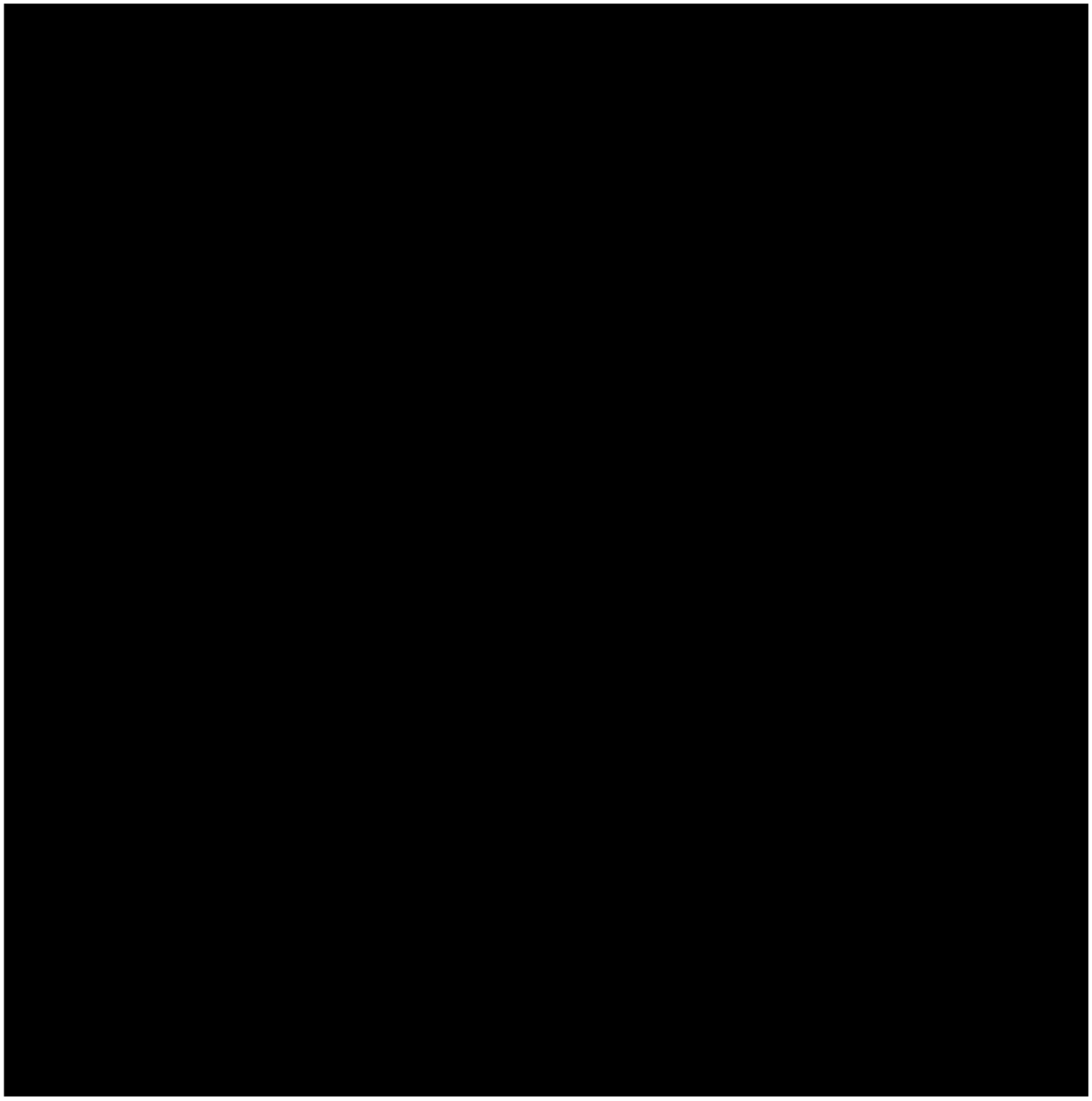
EA=expansion efficacy assessment; SA=safety assessment.

The following exploratory objective will be reported in the Clinical Study Report (CSR):

- To assess the PD effect of ONO-7475 by plasma inhibitory activity assay [redacted]

3 STUDY DESIGN

3.1 Overview of Study Design



3.1.1 Description of Study Design

This is a Phase I/II, multi-center, open label study to evaluate the safety, tolerability, PK, PD, and preliminary clinical efficacy of ONO-7475 in patients with acute leukemias and MDS. Patients with R/R AML or R/R MDS will be recruited.

The study design incorporates 2 parts (Parts A and D). Part A applies a dose escalation design [redacted] Part D is divided into 2 groups for the purpose of analysis: the SA group and the EA group. For the SA group a dose escalation design will be used to assess the safety and tolerability of ONO-7475 in combination with venetoclax, and, subsequently, the EA group will be used for the assessment of efficacy [redacted].

In Part D, a dose of ONO-7475 6 mg once daily will be initiated in the SA group and the ONO-7475 dose level will be escalated to 10 mg if tolerated. [redacted]

Part A

Part A is a dose escalation in R/R AML or R/R MDS patients. Up to 42 patients ([redacted] cohorts and up to [redacted] patients per cohort) will be entered into Part A.

The first cohort in Part A will commence at 3 mg/day of ONO-7475. [redacted]

[redacted]

The SRC, as governed by a charter that will predefine decision making, will then make a recommendation as to whether the next cohort should commence and, if so, what dose of ONO-7475 the patients will receive.

Part A will also include an investigation of the effect of food on the PK of ONO-7475 (see Section 6.1.1)

Once the MTD has been potentially achieved or sufficient PD data have been obtained, the SRC will then review all available data including safety, preliminary efficacy, and PK/PD from all patients in Part A to determine and recommend a clinically optimal biological dose (OBD) for Part D.

Once OBD has been identified, Part D can commence.

Part D

Part D of the study comprises 2 groups; the SA group and the EA group, as follows:

1) Safety Assessment (SA) Group

The purpose of SA group is to assess the safety and tolerability of the ONO-7475 combination regimen. For this group a dose escalation design will be applied [redacted] with two cohorts, 6 mg and 10 mg.

The first cohort will commence at 6 mg/day of ONO-7475 plus venetoclax. If ONO-7475 6 mg plus venetoclax is shown to be both safe and well tolerated, a dose of 10 mg of ONO-7475 plus venetoclax will be assessed in the second cohort. It should be noted that the venetoclax dose will be adjusted according to a pre-defined schedule based on what concomitant medication (if any) is used (Table 3).

[redacted]

[redacted]

[redacted]

2) Expansion Efficacy Assessment (EA) Group

Once an ONO-7475 plus venetoclax regimen in the SA group is confirmed to be safe and well tolerated based on data from the SA group, the study will proceed towards the EA group analyses to assess the preliminary efficacy of the combination regimen.

All patients in the SA and EA groups will be dosed with the combination regimen until one of the following events: disease progression, unacceptable toxicity, patient's withdrawal, or Investigator's decision to discontinue the combination regimen. However, if the investigator considers that the patient has no alternative therapy available and that they may still obtain some benefit by continuing treatment, this will be discussed on a case-by-case basis between the investigator and the Sponsor's Medical Officer.

3.1.2 Dose Escalation

3.1.2.1 Part A

The initial monotherapy dose escalation phase (Part A) will start with a dose of 3 mg ONO-7475 once daily. Dose escalation will proceed in increments not exceeding [redacted]. Depending on emerging PK, PD, and safety data, the posology of ONO-7475 (e.g., intermittent dosing or twice daily) may be modified. Example dose levels are shown in Table 5. The exact dose increase and number of dose levels will be based upon the review of safety and, where available, PK, PD, and efficacy data, and dose escalation will only occur after discussion and agreement between the Sponsor and members of the SRC who may recommend alternative doses to those in Table 5 based on their review. ONO-7475 will be administered in a fasted state ([redacted]) in all cohorts, except as outlined in Section 6.1.1.

Table 5 Proposed Dose-Escalation Plan*

Dose Level	Dose of ONO-7475
Level 1	3 mg
Level 2	6 mg
Level 3	10 mg
[redacted]	

*May be modified based on the emerging safety/tolerability profile

[redacted]

[redacted]

A SRC will be convened to review draft safety, PK, and PD data on an ongoing basis (see Section 11.6). At the end of the dose escalation stage for Part A of the study, the SRC will recommend a dose level of ONO-7475 (MTD or OBD) to evaluate in the subsequent Part D of the study or expansion cohorts in the current part of the study, as applicable, based on available data including safety, preliminary efficacy, PK and PD. The roles, responsibilities and procedures of the SRC will be documented in a written SRC Charter. As stated above, dose escalation will proceed in increments not exceeding [redacted], until significant ONO-7475-related toxicity is observed, at which time the maximum allowed increase (if any) is to be reviewed by the SRC. A pre-specified plan for altering dose increases will be included in the SRC charter.

The SRC will meet at the predefined time points for study decision making and will also monitor the safety of patients throughout the study and may make recommendations at any time if there are concerns about the safety of the patients in the study.

3.1.2.2 SA group in Part D

The SA group in Part D will constitute two cohorts (i.e., ONO-7475 6 mg plus venetoclax or ONO-7475 10 mg plus venetoclax). The first cohort, will start with ONO-7475 6 mg plus venetoclax. The dosing schedule of venetoclax will be followed as per Table 3.

[redacted]

3.1.3 Dose Adjustments during Study

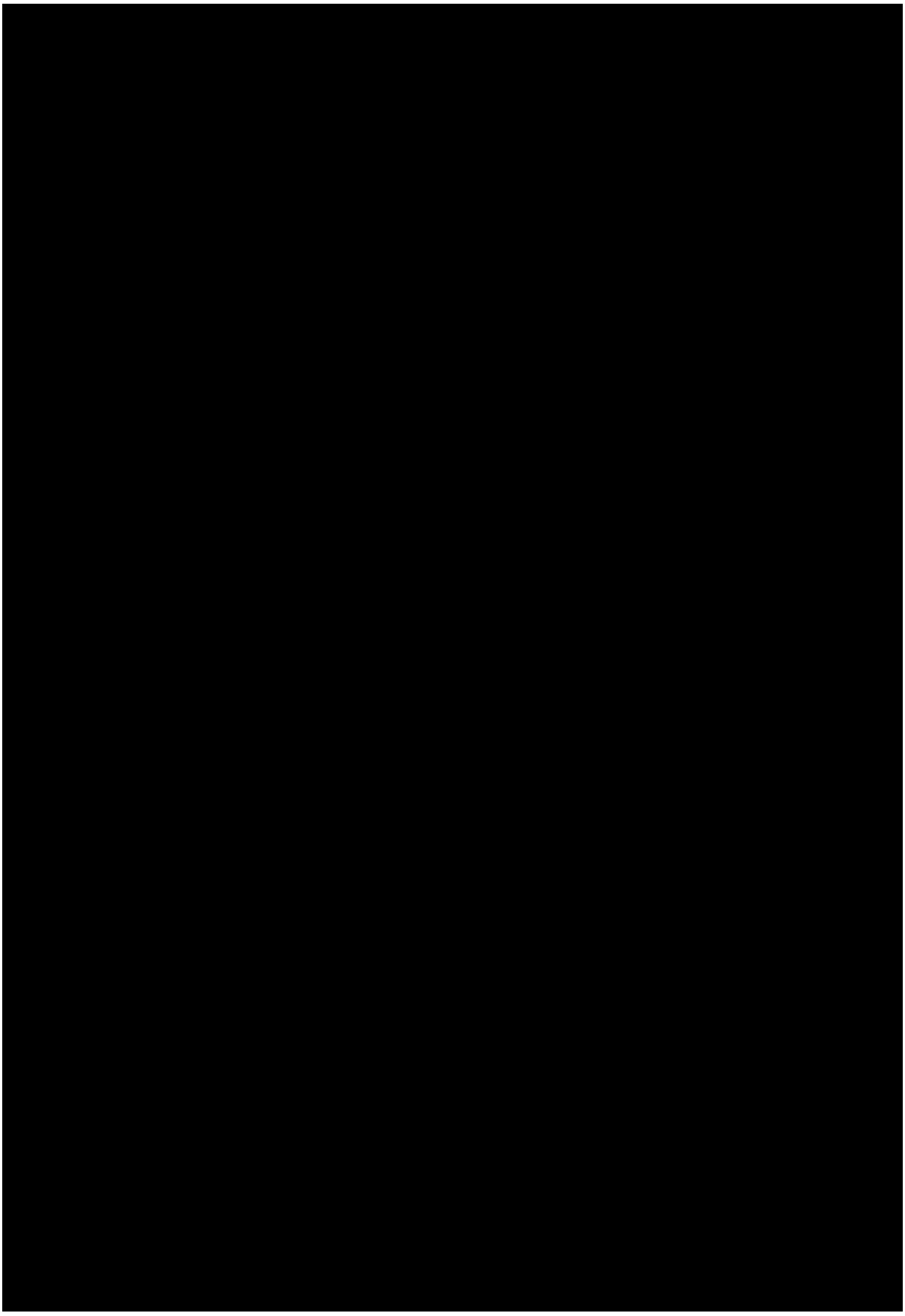
3.1.3.1 Dose Adjustments for ONO-7475 for Part A

[redacted]

3.1.3.2 Dose Adjustments for ONO-7475 for Part D

[redacted]

[redacted]



[redacted]

[redacted]

3.1.3.3 Dose Adjustments for Treatment Emergent Adverse Events for Part A and Part D

[redacted]

[redacted]

[redacted]

3.1.3.4 Dose Adjustment for Venetoclax

In the ramp-up period, the dose of venetoclax should be adjusted according to the concomitant medication used by the patient, as outlined in Table 3.

The following dose modification rules in Table 7 and Table 8 should be followed in the event of each toxicity related to venetoclax during the study.

Table 7 Venetoclax Dose Modification for Toxicities

Tumor Lysis Syndrome

Event	Occurrence	Action
Blood chemistry changes or symptoms suggestive of tumor lysis syndrome (TLS)	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 8).
		For any events of clinical TLS, resume at a reduced dose following resolution.
Non-Hematologic Toxicities		
Event	**Occurrence**	**Action**
Grade 3 or Grade 4 nonhematologic toxicities	First occurrence	Interrupt venetoclax. For the event of infection, monitor patients closely for signs and symptoms of infection and treat promptly. Venetoclax may be resumed at the same dose once the toxicity has resolved to Grade 1 or baseline level. No dose modification is required.
	Second and subsequent occurrences	Interrupt venetoclax. For the event of infection, monitor patients closely for signs and symptoms of infection and treat promptly. Follow dose reduction guidelines in Table 8 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the Investigator.
Hematologic Toxicities		
Event	**Occurrence**	**Action**
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia	Occurrence prior to achieving remission	Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated. [redacted]
	First occurrence after achieving remission and lasting at least 7 days	Monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. [redacted]

	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	[redacted] Monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. [redacted]

Table 8 Venetoclax Dose Reduction for Toxicity

Dose at Interruption (mg)	Restart Dose (mg)
400	300
300	200
200	100
100	50
50	20
20	10

3.2 Dose-Limiting Toxicities

3.2.1 Part A

[redacted]

[redacted]

3.2.2 Part D

[redacted]

[redacted]

3.3 Dose-Limiting Toxicity Evaluability Criteria

3.3.1 Part A

[redacted]

[redacted]

3.3.2 Part D

[redacted]

s the patient's DLT evaluability with the SRC Chair and/or members, as required.

3.4 Stopping Rules

3.4.1 Study Stopping Rules

The study may be stopped by the Sponsor for the following reasons:

[redacted]

3.4.2 Individual Stopping Rules

The reasons for protocol-specified patient withdrawal are listed below:

[redacted]

[redacted]

3.5 Blinding and Randomization

This study is an open label, non-randomized study.

3.6 Duration of Patient Participation

The duration of participation for each patient will depend on the progression of their disease and how well they tolerate ONO-7475 administration. All patients may continue in the trial and will continue to receive study drug(s) during and after completion of the study, as long as they are gaining benefit from trial treatment and do not meet stopping criteria. The estimated combined duration of study participation and post-study survival follow-up for each part based on median survival times is [redacted] (Part A) and [redacted] (Part D), though these may differ significantly in individual cases. The patient end of study reason is the reason for discontinuing treatment.

All scheduled study visits are outlined in the assessment tables in Sections 13.1 and Section 13.3.

4 STUDY POPULATION

4.1 Number of Patients

The estimated number of patients and patient study populations are outlined in Table 11:

Table 11 Estimated Number of Patients

Study Part	Population	Therapy	Phase	Approximate Number of Patients
A	AML (R/R) or MDS (R/R)	ONO-7475 (mono)	Dose Escalation	21–42
D	AML (R/R)	ONO-7475 plus venetoclax	Safety/Tolerability Expansion Efficacy	47
Total Number of Patients				Minimum: 68 Maximum: 89

AML=acute myeloid leukemia; MDS-myelodysplastic syndromes; R/R=relapsed or refractory

4.2 Patient Population

The study population will include:

- Patients with R/R AML or R/R MDS (Part A)
- Patients with R/R AML (Part D)

4.3 Eligibility Criteria

Protocol waivers are not permitted. Therefore, no patient will be enrolled in this study unless they meet all of the inclusion criteria and none of the exclusion criteria stated below.

4.3.1 Inclusion Criteria

General Inclusion Criteria:

1. Patients aged ≥18 years at time of screening.

2. Written informed consent by the patient (or their legal representative) prior to admission to this study. In addition, any locally required authorization (Health Insurance Portability and Accountability Act in the US), must be obtained from the patient prior to performing any protocol-related procedures, including screening evaluations.
3. Adequate renal and hepatic function defined as:
    a. Total bilirubin within 1.5 x upper limit of normal (ULN), except those with Gilberts syndrome for whom this must be ≤3 x ULN
    b. AST and ALT ≤2.5 x ULN
    c. Calculated creatinine clearance ≥45 mL/min
    d. Serum albumin ≥2.5 g/dL

For any patient with laboratory values outside the ranges outlined above that are considered due to the patient's underlying disease (AML or MDS), the patient may be enrolled into the study following consultation between the Investigator and the Sponsor's Medical Officer, if the patient is likely to benefit from receiving ONO-7475 (based on the Investigator's assessment).

4. ECOG performance status 0–2 as assessed during the screening period and then again anytime during the 2-day period immediately preceding the start of dosing in Parts A and D.
5. Life expectancy of at least 3 months.
6. Sexually active female patients of childbearing potential and sexually active male patients must agree to use an effective method of birth control (e.g., barrier methods with spermicides, oral or parenteral contraceptives and/or intrauterine devices) during the entire duration of the study and for 4 months after final administration of study drug. Note that sterility in female patients must be confirmed in the patients' medical records and be defined as any of the following: surgical hysterectomy with bilateral oophorectomy, bilateral tubular ligation, natural menopause with last menses >1 year ago, radiation-induced oophorectomy with last menses >1 year ago, chemotherapy-induced menopause with last menses >1 year ago.

Disease-specific Inclusion Criteria for Relapsed/ Refractory AML or MDS (Part A):

1. Diagnosis of AML or MDS according to World Health Organization (WHO) criteria 2016[12].
2. Either criterion is met:
    a. Patients with R/R AML with at least 5% blasts by BM biopsy or aspirate, or at least 1% blasts in peripheral blood, not likely to benefit from standard salvage chemotherapy

b. Patients with R/R MDS who are either not eligible for (or unlikely to benefit from) other forms of therapy, including HSCT, according to the treating Physician/Investigator

3. All patients must have received at least 1 previous line of therapy

Disease-specific Inclusion Criteria for R/R AML (Part D):

1. Diagnosis of AML according to WHO criteria (2016)[12].
2. Patients with R/R AML who have no standard-of-care options known to provide clinical benefit in patients with R/R AML
    a. Refractory AML: Patients who have not achieved complete remission after two cycles of induction chemotherapy (i.e., anthracycline containing regimen), four cycles of hypomethylating agents, or two cycles of other AML therapy
    b. Relapsed AML: Patients who have ≥5% BM blasts in BM, or reappearance of blasts in the peripheral blood not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aplasia) or (re)appearance of extramedullary disease after CR of prior AML therapy.
3. Patients must have measured BM aspirate blast counts at Screening. Where the aspirate is hypo cellular or inaspirable a biopsy would be considered.
4. Patients who were refractory to or relapsed after their 1st line treatment for AML must have received 2 or less additional lines of intensive / aggressive chemotherapy, which also includes a venetoclax-based regimen, as per the latest National Comprehensive Cancer Network (NCCN) Guidelines.

4.3.2 Exclusion Criteria

1 Patients with active central nervous system leukemia.

2 QT interval corrected according to Fredericia's formula (QTcF) prolongation defined as a QTcF interval >470 msec or other significant ECG abnormalities including second degree (type II) or third degree atrioventricular block or bradycardia (ventricular rate <50 beats/min).

3 Clinically significant liver disease, including active viral or other hepatitis, current alcohol abuse, or severe cirrhosis.

4 Human immunodeficiency virus (HIV), active hepatitis B (HBV) or C (HCV) infection.

5 Retinal disease (e.g., retinitis pigmentosa including Mertk mutations), retinal hemorrhage or any disorder which may inhibit follow up for retinal toxicity.

6 Serious intercurrent medical or psychiatric illness that will prevent participation or compliance with study procedures, including serious active infection (including COVID-19).

7 Acute promyelocytic leukemia (the French-American-British M3 classification).

8 Patients not recovered to Grade 1 or stabilized from the effects (excluding alopecia) of any prior therapy for their malignancies.

9 Concurrent treatment with other investigational drugs.

10 Daily requirement of ≥10 mg/day of prednisone or equivalent dose of other corticosteroids.

11 Prior HSCT within 12 weeks of the first dose of study treatment or ongoing immunosuppressive therapy for graft-versus-host disease.

12 Participation in another clinical trial with any investigational drug within 14 days or with any licensed drug within five half-lives, prior to the first ONO–7475 dosing (for Part A) or prior to the first venetoclax dosing (for Part D).

13 Prior AML or MDS therapy (non-experimental) within 14 days or 5 half–lives, whichever is longer, prior to the first dose of ONO-7475 (for Part A) or prior to the first venetoclax dosing (for Part D) (except those permitted in Section 7.1) and no residual toxicity from the prior therapy hindering of the ONO-7475 dosing (for Part A) or ONO-7475 plus venetoclax dosing (for Part D).

14 Prior radiotherapy within 21 days of screening, with the exception of localized palliative radiotherapy.

15 Patients undergoing current treatments for other cancers.

16 Pregnant or lactating women.

17 Proliferative disease (white blood cell [WBC] counts >30 x 10^9/L) confirmed prior to the first dose of ONO-7475 (for Part A) or WBC >25 x 10^9/L in Part D.

18 Active malignancy, other than AML (Parts A and D) or MDS (Part A), requiring systemic therapy except for those patients who have been diagnosed with either prostate or breast cancer and who have received a stable dose of hormone therapy for a minimum of 6 months prior to entering this study.

19 Known hypersensitivity to venetoclax (Part D only).

20 Calculated creatinine clearance <45 mL/min

4.4 Lifestyle and/or Contraception

Sexually active female patients of childbearing potential and sexually active male patients must agree to use an effective method of birth control (e.g., barrier methods with spermicides, oral or parenteral contraceptives and/or intrauterine devices) during the entire duration of the study and for [redacted] after final administration of study drug.

5 STUDY ASSESSMENTS AND PROCEDURES

The schedule of study events during each period of the study is presented in Sections 13.1 and Section 13.3.

In the event that an unexpected and extenuating situation which impacts on study conduct develops (e.g., a public health emergency such as a pandemic disease), certain protocol deviations (e.g., administering the study drug or adhering to protocol-mandated visits and laboratory/diagnostic testing) may be unavoidable. In this situation, the Investigator must inform the Sponsor that the patient may not meet pre-specified protocol requirements.

In the above situation, the Sponsor should evaluate whether alternative methods for performing safety assessments (e.g., phone contact, virtual visit, and alternative location for assessment, including local labs or imaging centers) could be implemented and if they would be sufficient to assure the safety of patients. The Sponsor will determine if a protocol amendment is required to implement the alternative methods.

Furthermore, the Sponsor will determine if in-person visits are necessary to fully assure the safety of patients enrolled in the trial (for example to carry out procedures to assess patient safety or to ensure safe use of the study drugs); in making the decision to continue administration of the study drugs, the Sponsor and the Investigator should discuss and consider whether the safety of trial participants can be assured with the implementation of the altered monitoring approach.

5.1 Protocol Flexibility

The following flexibilities will be allowed in this protocol:

- Where an enrolled patient is unable to attend the site due to an extenuating circumstance(s) such as a public health emergency and associated restrictions the following may occur at the discretion of the Investigator after consultation with the Sponsor's Medical Officer:
    - The visit may be scheduled outside the protocol-defined window
    - Procedures may be performed, where possible, at the patient's home or remotely via telephone or video call

Further details will be provided in the Study Reference Manual.

5.2 Medical History and Baseline Characteristics

The following demographic parameters will be recorded as in Section 13.1 and Section 13.3. The collection of some of this information may be restricted depending on local/country data guidelines:

- Date of birth
- Sex
- Race and ethnicity

Medical history including AML/MDS diagnosis and all previous therapies e.g., HSCT will also be recorded.

All other medical/surgical/medication history will be recorded as in Section 13.1 and Section 13.3 and will be assessed as related to the eligibility criteria listed in Section 4.3.1 and Section 4.3.2.

5.3 Screening Evaluations

[redacted]

[redacted]

5.4 Visit Schedule

For full list of assessments at each visit please see Section 13.1 and Section 13.3.

5.5 Clinical Response Efficacy Assessments

[redacted]

[redacted]

5.6 Pharmacokinetic Procedures

Blood samples (3 mL) will be taken for bioanalytical quantification of ONO-7475 levels in the plasma in Parts A and D. In Part D, blood samples (3 mL) will be taken separately for analysis of venetoclax.

[redacted]

[redacted]

5.7 Biomarkers and Pharmacodynamics Procedures

5.7.1 Pharmacodynamic Marker

PD effect will be assessed using a PIA assay for Axl/Mer inhibition. [redacted]

[redacted]

[redacted]

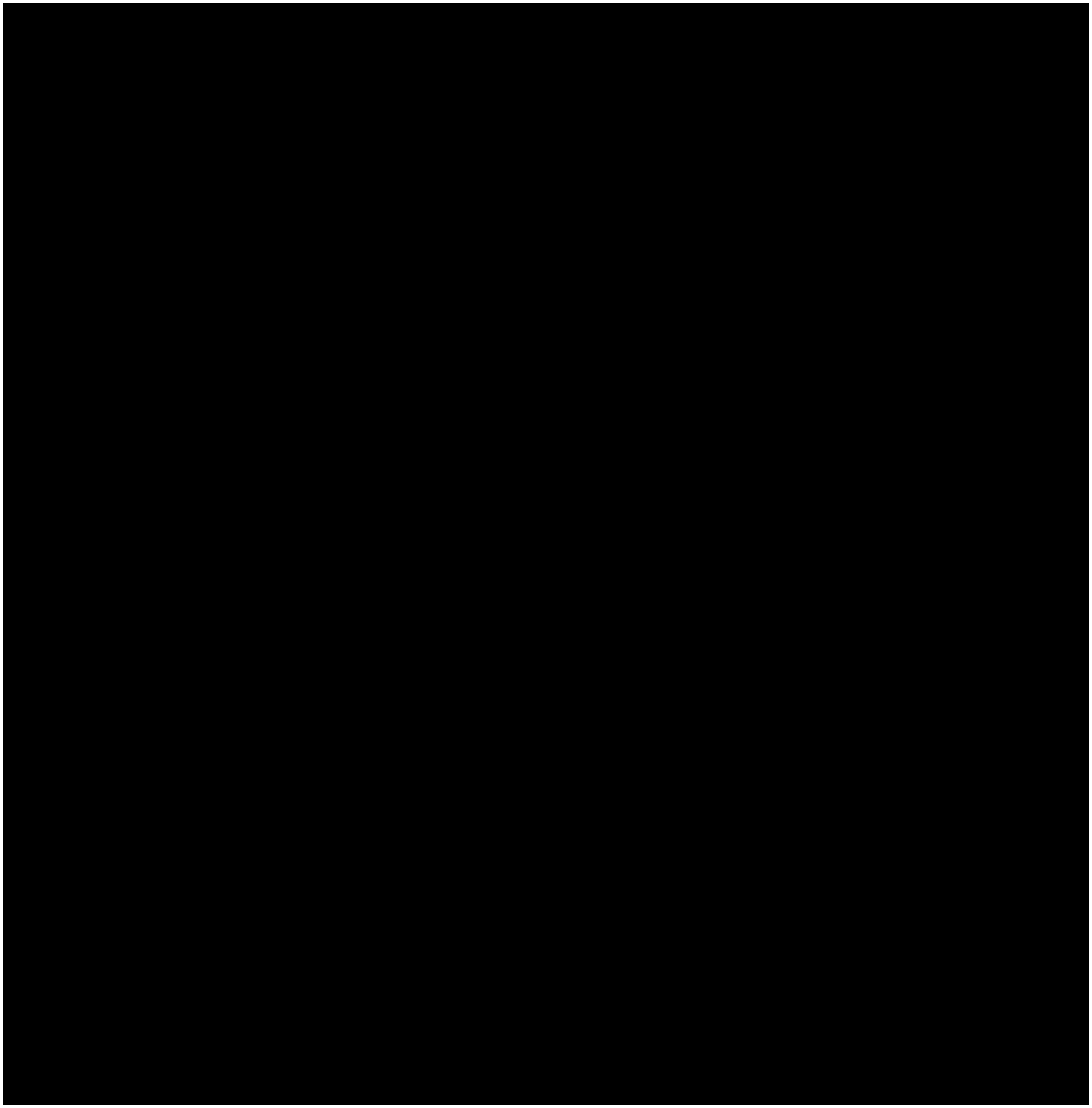
[redacted]

[redacted]

5.7.2 Exploratory Biomarkers

[redacted]

[redacted]



[redacted]

5.8 [redacted]

[redacted]

5.9 Safety Procedures

Safety will be assessed by AEs, classified according to the NCI CTCAE version 4.03, clinical laboratory tests (clinical chemistry and hematology), vital signs, physical examination (including a brief neurological exam), and 12-lead ECG. Ophthalmology safety tests are also included in Table 20 and Table 21 and described in Section 5.9.5 (for a full schedule of assessments, please refer to Section 13.1 and Section 13.3).

[redacted]

5.9.1 Electrocardiogram

Twelve-lead ECGs will be recorded at times outlined in the Time and Events tables (Sections 13.1 and 13.3). [redacted]

In Part A, all ECGs should be captured in triplicate (3 unique ECGs), with all 3 ECGs being captured within a 5-minute window. In Part D, the ECGs at Screening and Baseline (Day 1) will be performed in triplicate. At all other times, only a single ECG will be captured. If the quality of the single ECG means that parameters cannot be reliably calculated or the ECG cannot otherwise be assessed, the ECG should be repeated. Each ECG will also be printed and should be stored in the subject's source file.

Full 12-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTcF (heart rate–corrected) intervals.

The ECG will be repeated if a QTcF value exceeds 500 msec or >60 msec from baseline or if judged by the Investigator to be clinically appropriate. Additional 12-lead ECGs will be performed if judged by the Investigator to be clinically appropriate.

5.9.2 Multigated Acquisition Scan/Echo

A MUGA or echo scan of the heart will be done at Screening to assess ventricular ejection fraction then subsequently, if clinically indicated according to the Investigator's discretion and the site's standard of care.

5.9.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, respiration rate, body temperature, and pulse rate) will be measured, at times outlined in the Time and Events tables (Sections 13.1 and 13.3), after the patient has rested supine on a bed for at least 5 minutes.

5.9.4 Laboratory Assessments

The full list of clinical laboratory tests to be performed is presented in Section 13.5.

5.9.5 Ophthalmology Assessments

The schedule for ophthalmological assessments is outlined in Sections 13.1 and 13.3.

[redacted]

[redacted]

[redacted]

5.9.6 Pregnancy of Female Partners of Male Patients

Male patients will be instructed that if their partner becomes pregnant during the study and up to [redacted] after the last dose of study drug, this should be reported to the Investigator.

If a male patient's female partner becomes pregnant, the pregnancy must be reported to the Sponsor (or designated service provider) as soon as possible. Consent should be obtained from the pregnant partner in order to collect further information.

All pregnancies will be followed until delivery or the end of pregnancy (i.e., delivery, still birth, miscarriage), provided consent is obtained. The mother and child exposed *in utero* will also be followed for [redacted] after the birth, provided consent is obtained.

5.10 Total Blood Volume

[redacted]

5.11 [redacted]

[redacted]

[redacted]

6 INVESTIGATIONAL PRODUCTS

6.1 Dosage and Administration of ONO-7475

ONO-7475 will initially be dosed once daily. Posology may be modified based on emerging safety PK and PD data (see Sections 3.1.2 and 3.1.3).

ONO-7475 will be administered as an oral tablet or as a combination of multiple oral tablets [redacted] ONO-7475, which are packed in bottles.

[redacted]

[redacted]

6.1.1 Assessment of the Effect of Food on the Pharmacokinetics of ONO-7475 (Part A)

In this part of the study, the effect of food on the PK of ONO-7475 will be evaluated.

[redacted]

6.2 Dosage and Administration of Venetoclax

In Part D only: venetoclax will be administered orally with food and water. The dose will be made up of tablet(s) containing 10, 50 and/or 100 mg venetoclax which are packed in bottles or blisters.

The dose of venetoclax must be titrated for the first 3 days of dosing in Cycle 1 (ramp-up period) according to Table 3 to minimize the risk of tumor lysis syndrome prior to dosing with the maintenance dose. During the ramp-up period, prophylactic measures including adequate hydration and anti-hypouricemic agents should be considered according to the site's standard procedures. Patient's blood chemistry parameters will be monitored (e.g., potassium, uric acid, phosphorus, calcium and creatinine) at pre-dose, 6–8 hours after each new dose during ramp-up period (i.e., Day 1, 2, 3 and 4 in Cycle 1) and 24 hours after reaching final dose (i.e., Day 5 in Cycle 1) (see Section 5.9, Section 13.3, and Section 13.4). Hospitalization during ramp-up period is recommended if appropriate.

6.3 Treatment Assignment

Patients will be assigned to treatment groups for each dose cohort and will be assigned ONO-7475 treatment kits via the interactive web response system. The

same process will apply for those patients who have their dose increased (or decreased).

6.4 Packaging and Labelling

All packaging and labels will be prepared in accordance with 21 Code of Federal Regulations 312.6 – Labelling of an investigational new drug and any local regulatory requirements.

6.5 Preparation of Investigational Drugs

ONO-7475

No further preparation of ONO-7475 tablets is needed.

Venetoclax

No further preparation of venetoclax tablets is needed.

6.6 Handling and Storage

ONO-7475 should be stored [redacted] and a temperature log will be maintained during the conduct of the study. All study drugs must be stored in a secure location and may only be dispensed by the Investigator or by a member of staff who is authorized by the Investigator, or by a pharmacist, as appropriate.

Venetoclax should be stored as per the approved label of VENCLEXTA[22].

6.7 Product Accountability and Assessment of Compliance

In accordance with GCP, all supplies of ONO-7475 and venetoclax will be accounted for by the investigational site.

The dispensing and return of the study drug will be carefully recorded on appropriate drug accountability forms and an accurate accounting will be available for verification and assessment of compliance by the clinical research associate at each monitoring visit.

Investigational product accountability records will include:

- Details of receipt
- Storage
- Administration, and
- Return or destruction

The unit of accountability for the study is 1 tablet. At the end of the study, following full accountability and reconciliation, the Sponsor will provide instruction for all

unused study drugs to be destroyed. A certificate of destruction will be supplied to the Sponsor.

6.8 Treatment of Investigational Product Overdose

ONO-7475

At this stage in development, no specific treatment for overdose has been identified and the physician is advised that there is no specific antidote. Supportive measures to maintain the patient's vital functions should be implemented and patient should be carefully monitored. Any event of overdose should be reported as a SAE by the Investigator (or designee) to the Sponsor immediately, in accordance with Section 9.2.2.

Venetoclax

In the event of overdose, the patient should be monitored (including relevant blood counts) and should receive supportive treatment, as necessary. There is no known specific antidote for venetoclax overdose.

7 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

7.1 Permitted Medications and Supportive Therapies

[redacted]

[redacted]

7.2 Prohibited Medications

[redacted]

7.3 Medications to be Used with Caution

[redacted]

[redacted]

As per the prescribing information for VENCLEXTA[22], the safety and efficacy of immunization with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. The Investigator should advise patients that vaccinations may be less effective.

8 PATIENT COMPLETION AND WITHDRAWAL

8.1 Patient Completion

Any patients who are continuing to receive study drug at the time of final data cut-off (i.e., those who have not previously withdrawn) will be deemed as having completed the study.

If a patient withdraws from the study during the treatment period, every attempt should be made for the patient to attend the safety follow-up visit, which will represent the end of the patient's participation in the study, and to provide information of survival status. If the patient does not agree to have the safety follow-up, only survival data will be collected. The last clinic visit will be considered the final study visit for the patient (i.e., the patient completion/withdrawal date). If a patient refuses a safety follow-up visit after withdrawing from the study, the last contact date with the patient will define the patient completion/withdrawal date.

8.2 Study Completion

The study will be regarded as completed, once the last patient has attended their last study visit. The study may be terminated by the Sponsor at any stage. If the study is halted, the reasons for doing so will be provided to the Investigator and the patients. The regulatory authorities will also be notified according to local regulations. For those patients who are already enrolled into the trial, their treatment regimen will be provided until disease progression, or until patient withdrawal due to development of an unacceptable toxicity or patient withdrawal of consent.

8.3 Patient Withdrawal

8.3.1 Patient Withdrawal from Study

In accordance with the Declaration of Helsinki, a patient has the right to withdraw from the study at any time without giving a reason.

The reasons for protocol-specified patient withdrawal are as follows: withdrawal by patient (informed consent withdrawn or patient requests discontinuation from the study); Investigator decision; DLT or progressive disease.

In cases where a female patient becomes pregnant, the decision of whether or not to withdraw the patient from investigational product will be taken locally at site level and handled on a case-by-case basis.

[redacted]

8.4 Screen and Baseline Failures

Data for all study visits will be recorded on the eCRF for patients who receive study drug treatment. Only minimal data (i.e., demography and reasons for screen failure) will be recorded on the eCRF for patients who fail inclusion/exclusion criteria and/or do not receive study drug. Further data, such as AEs, will not be collected from patients once they are considered screen failures or have decided to withdraw prior to receiving study drug.

9 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

9.1.1 Adverse Event Severity

Each AE must be rated in intensity according to NCI CTCAE criteria version 4.03.

The NCI CTCAE, version 4.03, grades refer to the severity of AEs. The NCI CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the general guideline presented below:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3 Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

9.1.2 Adverse Event Relationship to Investigational Product(s)

The Investigator must classify the relationship of the AE to ONO-7475 (both Parts) and venetoclax (Part D only).

The possible relationships for Part A are:

Not related/ unlikely related	The temporal sequence between the AE and drug administration is such that the drug is not likely to have had any reasonable association with the observed event; or underlying disease, other drugs or chemicals provide plausible explanations.
Possibly related	The AE follows a reasonable time relationship from drug administration; and The AE could also be explained by concurrent disease or other drugs or chemicals. *Note: Information on drug withdrawal may be lacking or unclear.*
Probably related	The AE follows a reasonable time relationship from drug administration; The AE is unlikely to be attributed to concurrent disease or other drugs or chemicals; and Follows a clinically reasonable response upon withdrawal (dechallenge); Note: rechallenge positive data are not required to fulfill this definition.
Definitely related	The AE follows a reasonable time relationship from drug administration (i.e., occurs in a plausible time relationship to drug administration); The AE cannot be explained by concurrent disease or other drugs or chemicals;

The AE abates or follows a clinically reasonable response upon withdrawal (dechallenge positive);

and

The AE is confirmed by reappearance of the reaction on repeat exposure (rechallenge positive).

The possible relationships for Part D are:

Not related	The temporal sequence between the AE and drug administration is such that the drug is not likely to have had any reasonable association with the observed event; or underlying disease, other drugs or chemicals provide plausible explanations.
Related	The AE follows a reasonable time relationship from drug administration (i.e. occurs in a plausible time relationship to drug administration); The AE cannot be explained by concurrent disease or other drugs or chemicals; The AE abates or follows a clinically reasonable response upon withdrawal (dechallenge positive); or The AE is confirmed by reappearance of the reaction on repeat exposure (rechallenge positive).

9.1.3 Adverse Event Reporting

The Investigator, or authorized designee, should regularly ask the patients how they are feeling to encourage AE reporting. The person approaching the patients should use a non-leading question such as “How are you feeling?”.

All observed or volunteered AEs, regardless of suspected causal relationship to study drug, will be recorded on the AE page(s) of the eCRF.

In addition, abnormal objective test findings (e.g., ECG changes, abnormal laboratory test results) that result in a change in the study drug dosage or in discontinuation of the drug, or require intervention or diagnostic evaluation to assess the risk to the patient, should be recorded as AEs. Clinically significant changes in physical examination findings and objective test findings should also be recorded as AEs.

Adverse events will be collected from the time informed consent is given until the patient has completed the study.

Any AEs that are ongoing at the time the patient completes the study will be followed by the Investigator until the AEs are resolved, the patient's condition is stable or persistent, the patient's death, or until the patient is lost to follow-up. Any pregnancies reported after completion of the study must also be reported as per Section 9.2.5.

9.2 Serious Adverse Events

9.2.1 Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically important

Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not reach the above definition but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are referred to as "important medical events" and should also be considered serious. Examples of such events are the emergence of any secondary cancers unrelated to AML or MDS, intensive treatment in an accident and emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.2.2 Serious Adverse Event Reporting by the Investigator or Designee

All SAEs, regardless of suspected relationship to study drug, must be reported by the Investigator or their authorized designee to designated service provider immediately, and in no case later than 24 hours, following knowledge of the SAE.

All SAEs are documented in the SAE form and reported electronically through the designated service provider's electronic data capture (EDC) system.

If the event meets serious criteria and it is not possible to access the EDC system, the Investigator or their authorized designee should contact the designated service provider, either by e-mail or telephone, and fax the completed paper SAE form to the designated service provider within 24 hours of awareness. The SAE

information must be entered into the EDC system within 24 hours of the system becoming available.

Safety Contact Information

The initial report of an SAE must not be delayed by the investigational site beyond 24 hours in order to collect additional information. Any medical information relevant to the reported SAE which becomes available to the investigational site staff following the initial SAE report should be reported to designated service provider as part of a follow-up SAE report. The reporting procedure should be referred to the outlined above for initial reporting of SAEs. Medical records transmitted as part of the SAE report must not disclose study patients' personal data, such as patient name, any contact information, name of patients' relatives, etc. The study patient is to be identified by the unique study-specific subject number only.

As for AEs, SAEs will be collected from the time informed consent is given until the follow-up visit, or until voluntary withdrawal of a clinical study patients' consent (refer to Section 8.3). SAEs that occur after the SAE reporting period and that are considered related to study drug will be reported to the Sponsor, if the Investigator becomes aware of them.

Unless they withdraw consent for further follow-up, patients who discontinue study therapy will be followed for acquisition of safety information through 30 days after the last dose of study treatment (or initiation of new anti-cancer therapy, whichever occurs first), and for collection of information regarding survival.

9.2.3 Serious Adverse Event Processing and Reporting by the Study Sponsor or Designee

All SAEs will be processed by the study Sponsor or contracted designee according to study-specific SAE processing guidelines.

The Sponsor, or contracted designee, will be responsible for submitting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug to the applicable regulatory authorities according to ICH guidelines and applicable regulations. In addition, the Sponsor, or designee, will be responsible for the submission of safety letters to the central IRB and to the Investigator of all SUSARs involving the active study drug according to applicable regulations. For clinical sites

that use a local IRB, it is the responsibility of the Investigator to promptly notify the local IRB of all SUSARs involving risk to human patients.

These reports should be submitted within 7 calendar days of the Sponsor being notified of the event for fatal or life-threatening events, or 15 calendar days for all other events.

9.2.4 Reference Safety Information

The Sponsor or designee is responsible for determining the expectedness of the reported event(s) as per the applicable Reference Safety Information. The Reference Safety Information is contained in the IB for ONO-7475[25] and in the approved Product Labelling for venetoclax (VENCLEXTA)[22].

9.2.5 Reporting of Pregnancy

Information on pregnancy of a study patient (or partner) will be collected until the follow-up visit or until voluntary withdrawal of a clinical study patient's or partner's consent.

If the patient or female partner of a male patient participating in the study becomes pregnant during the study or within 90 days of discontinuing study drug, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the "Exposure *In Utero"* form to the Investigator for completion. Provided consent is obtained, the designated service provider will follow up on the outcome of all pregnancies until delivery or the end of pregnancy (i.e., delivery, still birth, miscarriage, termination), and also on the health status of the newborn. This also applies to pregnancies reported to the designated service provider after the required reporting period.

9.2.6 Adverse Events of Special Interest

ONO-7475

Adverse events of special interest have yet to be defined for ONO-7475.

Venetoclax

Adverse events of special interest for venetoclax when taken in combination with ONO-7475 have yet to be defined.

9.2.7 Events Not To Be Reported as Serious Adverse Events

The following events do not qualify as SAEs as defined in Section 9.2.1.

Any planned hospitalizations or hospitalizations purely for diagnostic purposes (as required by the protocol) do not qualify as AEs or SAEs and do not require reporting.

A brief stay in an outpatient clinic or emergency room which does not involve formal admission or overnight stay does not qualify as a SAE and does not require reporting (medical judgement should be applied to assess if the reported event term would nevertheless qualify as medically important event as per Section 9.2.1).

Admission to a nursing home due to purely social reasons and in the absence of deterioration in the patient's general health status is captured in the source data but does not qualify as AE or SAE and does not require immediate reporting.

9.3 Progression of Underlying Malignancy

Progression or relapse of the malignancy will not be reported as an SAE, however unexpected clinical signs or symptoms that do not fit the expected pattern of AML or MDS disease progression must be reported, even if they are eventually attributable to disease progression or relapse.

If there is any uncertainty on the part of the Investigator and/or Sponsor about an AE being attributable only to the disease under study, it should be reported as an AE or SAE.

[redacted]

10 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1 Study Design Considerations

10.1.1 Sample Size Assumptions and Design Considerations

Part A

[redacted]

Approximately 42 patients across approximately [redacted] cohorts will be enrolled for dose escalation in Part A. This is based on the assumption that it may take up to [redacted] cohorts ([redacted]) to determine an efficacious dose of ONO-7475 monotherapy in R/R AML or R/R MDS.

Part D

[redacted] DLT evaluable (for definition of evaluability see Section 3.3.2) are required for the SA analysis [redacted]. Analysis of the safety, tolerability, PK and PD data will occur once there are [redacted] DLT evaluable patients.

The EA of the study has 2 stages following Simon's 2-stage design. The null hypothesis is that the CR/CRh rate associated with the combination therapy is ≤20% versus the alternative hypothesis that the CR/CRh rate is ≥40%. Under the minimax design criterion, a total sample size of 41 is required to test the above hypotheses with a 1-sided significance level of 0.023 and 80.26% power. The number of EA evaluable patients will include SA group patients who met EA evaluable criterion (i.e., patients who had at least 1 dose of ONO-7475 and/or venetoclax at the same planned dose level, 6 mg or 10 mg).

[redacted]

[redacted]

10.2 Data Analysis Considerations

10.2.1 Analysis Populations

The SAF will be based on all patients who have been enrolled into the study and who have received at least 1 dose of ONO-7475 for Part A or who have received at least 1 dose of venetoclax and/or ONO-7475 for Part D. The patients in the SAF will be grouped by the initial dose level of ONO-7475 actually received. The SAF will be used for all safety analyses by default.

Since it is feasible patients may receive study drug at different dose levels for varied lengths of time, 2 alternative groupings are defined for the SAF: one is by the highest dose received and the other is by dose received for the longest duration (in the case that 2 or more dose levels are administered for the same duration, the highest dose level will be selected). These will be used only for supportive safety analyses.

The Full Analysis Set (FAS) will be the primary analysis set used for assessment of efficacy and will be based on all patients who have been enrolled into the study and who have received at least 1 dose of ONO-7475 for Part A or who have received at least 1 dose of venetoclax and/or ONO-7475 for Part D. The patients in the FAS will be grouped by the dose level as assigned at the study entry. The FAS will be used for all demographic and baseline summaries and all efficacy

analyses. For Part A, the efficacy summaries will focus on the subset of the FAS who are diagnosed with AML. For Part D, patients in the FAS may be replaced if the efficacy analysis is compromised by extenuating circumstances (for example, a pandemic in which patient site visits are not possible and therefore clinical response cannot be evaluated).

The Response Evaluable Analysis Set for Part D will be based on all patients who received at least 1 dose of venetoclax and/or ONO-7475 and whose response has been determined by the **Revised Recommendations of the IWG for Response Criteria, in Acute Myeloid Leukemia** (Section 13.8). Patients in the Response Evaluable Analysis Set will be grouped by the dose level as assigned at the study entry.

The PK Analysis Set will include patients who are administered ONO-7475 for Part A or ONO-7475 or venetoclax for Part D, and from whom results of plasma concentrations are obtained for at least 1 sampling point. Patients in the PK analysis set will be grouped based on the dose level received during the PK sample collection period. If necessary, there will be 2 PK Analysis Sets in Part D; 1 for ONO-7475 and 1 for venetoclax.

The PD Analysis Set will include patients who have received at least 1 dose of ONO-7475 for Part A or ONO-7475 or venetoclax for Part D, and from whom results of PD collection assays are obtained for at least 1 sampling point which is suitable for analysis. Patients in the PD analysis set will be grouped based on the initial dose they actually received.

Detailed definitions of the analysis sets will be provided in the Statistical Analysis Plan (SAP).

10.2.2 Key Elements of Analysis Plan

All data will be presented in the most appropriate manner allowing for type and distribution.

Where appropriate, summaries will be made for each dose level.

Details of summaries and analyses of the data, including where patients may have changed their ONO-7475 dose level, will be provided in the SAP.

Continuous variables will be summarized using mean, standard deviation, median, minimum and maximum, and categorical variables will be summarized using frequencies and percentages.

Baseline and demographic characteristics (e.g., age, sex etc.) will be summarized as continuous or categorical variables, as appropriate.

Statistical analysis, including the PK analysis for after database lock, will be described in the SAP.

10.2.2.1 Efficacy analyses

The CR/CRh rate in Part D is defined as the proportion of patients who have a best overall response in AML of CR or CRh.

ORR is defined as the proportion of patients who achieve responder status, i.e, having a best overall response in AML and MDS including:

[AML]

- CR
- CRh (Part D only)
- CRi (note for Part D this will constitute CRi patients who did not meet the requirements for CRh)
- Morphologic leukemia-free state
- PR

[MDS]

- CR
- Marrow CR
- PR

Patients who do not have sufficient baseline or on-study efficacy status information to be adequately assessed for response status (i.e., those with best overall response of not evaluable) or received anti-leukemic therapy other than the study treatment prior to becoming a responder (per the definition above) will be considered as non-responders. Patients with a best overall response of treatment failure (Parts A and D patients with AML), failure or stable disease (Part A patients with MDS), progression (per the definition given below), or missing response assessments, will be considered non-responders.

Best Overall Response is defined as the best response assessment assigned to a patient at any time-point during the study up to and including progression, prior to the patient's study completion and prior to initiation of any other anti-leukemic therapy.

Time to Response (TTR) is defined as the duration in months from the date of first study treatment to the date of first documentation of responder status (per definition above). TTR is not defined for patients who do not achieve a best overall response of PR or better.

DoR is defined as duration in months from the date of first documentation of responder status (per definition above) to the date of disease progression or death due to any cause, whichever is earlier. DoR is not defined for patients who do not achieve a best overall response of PR or better.

If the specified event does not occur, the DoR will be censored at the date of last adequate efficacy assessment. If there is no adequate assessment available after the first documentation of responder status (per definition above), the DoR will be censored at the date when responder status is first recorded.

The date of definitive progression will be the time point at which progression is first identified. Progression is defined as disease recurrence for AML in Parts A and D, relapse after CR or PR and disease progression in MDS (per IWG criteria for MDS).

An adequate tumor assessment is defined as one with an outcome other than “Not Evaluable”.

EFS is defined as the duration in months from the date of first study treatment to treatment failure (for AML patients in Parts A and D), failure (for MDS patients in Part A), progression (per definition above), or patient death from any cause.

If the specified event does not occur, the EFS will be censored at the date of last adequate efficacy assessment. If there is no adequate assessment available, the EFS will be censored at the date of first study treatment.

OS is defined as duration in months from the date of first study treatment to death from any cause. OS will be censored at the date last known to be alive for patients who are still alive.

The primary efficacy variables will be listed and summarized using descriptive statistics based on the FAS for each part of the study.

The CR/CRh rate (for Part D only) and ORR will be calculated using the FAS. The 2-sided 95% exact confidence intervals of the CR/CRh rate and ORR will be estimated using the Clopper-Pearson method.

The rate of CR/CRh without MRD will be provided for patients in Part D.

The rates of CR and CRh will also be provided separately for patients in Part D.

TTR will be summarized descriptively as a continuous variable for those patients who achieve PR or better.

DoR will be characterized using the Kaplan-Meier method for patients who achieve PR or better (in Part A) and CR/CRh (in Part D). Medians, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum will be provided along with the 95% confidence intervals for the median. Kaplan-Meier curves will be provided.

OS and EFS will be analyzed for all patients in a similar manner to DoR.

For Part A, the efficacy endpoint summaries will focus on AML patients only.

In addition, the CR/CRh rate analysis will be repeated using the Response Evaluable Analysis Set as a supportive analysis for Part D and the ORR analysis will be repeated using the Response Evaluable Analysis Set as a supportive analysis for Part D.

If necessary (for example in the case of a pandemic disease whereby there is an inordinate amount of missing data), the amount of missing efficacy data may be reviewed and appropriate multiple imputation methods may be applied for analytical purposes.

[redacted]

Full details of all planned analyses will be provided in the SAP.

10.2.2.2 Pharmacokinetic and Pharmacodynamic Analyses

Plasma concentrations of ONO-7475 and venetoclax (Part D only) will be used to calculate relevant PK parameters. Calculated PK parameters will include: Cmax, Tmax, AUC, T1/2. Details will be provided in the SAP.

For assessment of the effect of food on the PK of ONO-7475 Cmax and AUC[redacted] will be calculated in Part A.

The plasma concentration versus time data obtained in this study may be combined with the PD data (PIA assay) obtained. This data will be used to develop a quantitative PK/PD model and support dose selection.

As needed, the concentration versus time data obtained in this study may be combined with PK data from future studies conducted as part of the clinical development program. This data will be used to develop a population PK/PD model using a non-linear mixed-effects modelling approach. This model will be used to evaluate the effects of various covariates on the PK and PD of ONO-7475.

10.2.2.3 Biomarker Analyses

Parameters such as mean, standard deviation, median, minimum and maximum will be calculated for PD (PIA assay) data. The PIA data will be reported in the CSR.

As needed, exploratory data analyses will be conducted for the other biomarker data. These analyses will be detailed in a separate analysis plan and the results reported separately from the CSR.

10.2.2.4 Safety Analyses

The SAF will be used for all safety analyses by default.

Safety will be evaluated by monitoring all AEs and SAEs.

All AEs will be tabulated and graded according to NCI CTCAE version 4.03 for each patient cohort. Verbatim descriptions of AEs reported during the study period will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and body systems.

Treatment-emergent AEs are defined as:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug (or initiation of new anti-cancer therapy, whichever occurs first)

All treatment-emergent AEs will be summarized in frequency tables.

For any AE summary showing the AEs by NCI CTCAE grade, the highest grade will be used for those AEs that occurred more than once in an individual patient during the study.

The DLTs will be summarized in frequency tables and also listed.

Laboratory safety assessments will include regular, routine monitoring of hematology and blood chemistry, and urinalysis.

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided and will include data collected up to the last dose of study drug plus 30 days for patients who have permanently discontinued study drug.

Laboratory NCI CTCAE grades at baseline and worst post baseline will be summarized in shift tables.

Body weight and vital signs and their change from baseline will be summarized.

Descriptive statistics will be used to summarize ECOG performance status.

A summary of ECG parameters will be provided for each scheduled time point and categorical summaries of maximum observed and change from baseline values will be presented for QTcF.

Prior and concomitant medications will be summarized.

Full details will be provided in the SAP.

10.2.3 Interim Analysis (Part D only)

All interim analyses will be assessed by the SRC for Part D as described in Section 11.7 (further details are given in the SRC Charter) with the purpose of providing recommendations to the Sponsor.

10.2.3.1 Safety Assessment Group Analysis

The SA group analysis will be performed when each cohort has the required number of DLT evaluable patients. The analysis will include all patients in the SAF and will include safety and PK data. No formal efficacy testing or analysis will be performed at this point.

10.2.3.2 [redacted]

[redacted]

[redacted]

[redacted]

10.2.4 Reporting Deviations from the Statistical Analysis Plan

The SAP will be approved prior to the database lock on Part A for Part A analysis. For Part D, the SAP will be reviewed and updated based on the emerging data from Part A accordingly but updates will be approved prior to database lock for Part D. Any deviations from the SAP will be described in the CSR.

11 STUDY ADMINISTRATION

11.1 Regulatory and Ethical Considerations

11.1.1 Regulatory Authorities

Approval from the Regulatory Authorities will be obtained prior to study-specific screening of the first patient, according to applicable national and international regulations and guidelines.

11.1.2 Institutional Review Board

Before initiating the trial, the Investigator must have written and dated approval from the IRB for the trial protocol, the written informed consent form, consent form updates, and any other written information to be provided to the patients. As part of the Investigator's written application to the IRB, the Investigator must provide the IRB with a current copy of the IB. If the IB is updated during the trial, the Investigator must supply a copy of the updated IB to the IRB.

The Investigator is required to obtain approval from the IRB if changes to the protocol, written informed consent form, written information to be provided to the patients and/or other documents are classed as substantial amendments.

The Investigator is required to report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the trial.

If required by local regulations the Investigator should submit written summaries of the trial status to the IRB on an annual basis and upon completion of the trial, the Investigator should complete and send the End of Trial Notification form.

11.1.3 Protocol Adherence

The protocol must be read thoroughly and the instructions followed exactly. Any deviations should be agreed by both the Sponsor and the Investigator and where appropriate, written protocol amendments will be made to reflect the changes agreed upon. Where a deviation is necessary for the well-being of a patient, the ONO Medical Officer must be informed of the action as soon as possible and amendments submitted to IRB.

A protocol amendment requires IRB and regulatory approval if it constitutes a substantial amendment.

In the event that an unexpected and extended situation which impacts on study conduct develops (e.g., a public health emergency such as a pandemic disease), certain protocol deviations may be unavoidable. In this circumstance, any protocol deviations must be recorded along with the specific reason for the deviation as per usual practice but additional information must be recorded regarding the root cause of the issue (e.g., pandemic disease) and the Sponsor will consider if

alternative study procedures are required to ensure the patient's safety. Where the Investigator determines a deviation is necessary to maintain patient safety, the Sponsor/Clinical Research Associate or the Medical Monitor must be informed of the action as soon as possible and it must be appropriately documented.

11.1.4 Patient Information and Consent

The Investigator, or person designated by the Investigator, must obtain written informed consent prior to the patient undertaking any study-related activity. The Investigator or an authorized designee must explain the nature of the study and the treatment in such a manner that the patient is aware of his/her rights and responsibilities, as well as potential benefits and risks. The Investigator is also responsible for answering any questions the patient may have throughout the study and for sharing any new information that may be relevant to the patient's willingness to continue his/her participation in the trial in a timely manner.

Patients must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent must be recorded. Once all of their questions have been answered and the patient has voluntarily agreed to participate in the study, patients will be asked to sign and date the informed consent form.

Each patient's original consent form, signed and dated by the patient and by the person who conducted the informed consent discussion, will be retained by the Investigator and a copy will be given to the patient for their records. In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirements and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

11.1.5 Indemnity and Compensation

In the event that it can be demonstrated that a patient suffers any significant deterioration in health or well-being or any harmful susceptibility or toxicity as a direct result of their participation in this study, [redacted] will agree to abide by the applicable local guidelines with regard to compensation payable to the patient. The amount of compensation will be calculated by reference to the level of damages commonly awarded in laws of the state in the US for similar injuries at the time when such injury occurred. The Investigator and their employer have insurance cover for the malpractice and/or negligence of their employees and agents.

11.2 Reporting of Urgent Safety Measures

Urgent safety measures may be implemented to protect patients against any immediate hazard to their health and safety. The Investigator must notify the Sponsor immediately (<24 hours) to discuss the hazard and any actions taken or to be taken (if time permits prior to implementation). The Sponsor is required to

inform the appropriate competent authorities, Investigators and IRBs immediately and in any event no later than 3 calendar days of any urgent safety measures implemented during the study.

11.3 Study Monitoring

Study monitoring will be performed by a Service Provider (Medpace). Monitoring procedures will be followed in order to comply with GCP guidelines and applicable SOPs.

The purposes of trial monitoring are to verify that:

- The rights and well-being of patients are protected
- The reported trial data are accurate, complete and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements

Study data recorded on source documents will be made available to the study monitors for source document verification. The site monitors will perform source document verification in compliance with GCP and the respective SOPs.

11.3.1 Access to Source Data

The Investigator(s), as outlined in GCP, must provide direct access to source data for study-related monitoring, audits, ethics review, and regulatory inspection(s).

11.3.2 Quality Control and Quality Assurance

The Sponsor, or its designee, may audit the study at any time during or after its completion as part of their Quality Assurance program. The Investigator must provide access to source data, eCRFs, and study files for Sponsor-accredited auditors or Regulatory Authority or IRB inspectors. If the Investigator is notified of a scheduled Regulatory Authority inspection, they must notify the Sponsor immediately (within 24 hours of notice). The same applies to unannounced audits and inspections.

11.3.3 Data Handling and Record Keeping

The Investigator is responsible for filing and archiving appropriate essential documents as outlined in the ICH-GCP Section 8.

All data derived from the study will remain the property of the Sponsor. The study CSR will be compiled by order of the Sponsor. Records of patients, source documents, eCRFs and drug inventory records, pertaining to the study must be retained according to GCP and the current national and international regulations.

Paper files should be kept in a rodent-proof, fire-proof and water-proof environment.

If the Investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the Investigator records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor and documented in writing.

Essential documents must be stored securely for a minimum period, depending on the country-specific requirements.

11.4 Provision of Study Results and Information to Investigators

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

The Investigators will be provided with an electronic copy of the eCRF data for their patients after completion of the study.

On finalization of the CSR, a copy will be provided to the Investigator(s).

11.5 Data Management

Data management for all study data will be conducted by Medpace designated staff.

An EDC system [redacted] will be used to collect data for this study. Trained Investigator site staff will enter the data required by the protocol into the EDC system by completing an eCRF from source documents (e.g., medical records and study-specific data capture tools as needed). All information in the eCRFs must be traceable to these source documents. Data management processes will be described in a Data Management Plan (DMP). The DMP will be reviewed and approved by the Sponsor and made final prior to study start.

The EDC system will keep track of all data entry, alterations, and query resolution in an audit trail. The audit trail will form an integral part of the application and will be archived alongside the data.

Automatic validation programs within the EDC system will check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated site staff. The system will keep track of all data entry, alteration, and query resolution via an audit trail. The Investigator must certify that the data entered are complete and accurate by provision of an electronic signature for each eCRF. If any changes are made to the eCRF after a form has been locked and electronically signed, the Investigator will be required to repeat the electronic signature process to authorize agreement with any new information or changes.

After database lock, the Investigator will receive copies of the patient data for archiving at the investigational site. The data will also be extracted and provided to the Sponsor.

The majority of the data will firstly be recorded onto source documents and the Investigator will be required to complete an Investigator source agreement at the site initiation visit where the source, location, and type of source will be agreed with the Investigator and documented. Other data will be handled and processed as follows:

- Medical history and AEs will be coded using the MedDRA terminology
- Concomitant medications will be coded using WHO Drug dictionary. Concomitant (non-drug) therapies will be coded using MedDRA (same as medical history and AEs)
- Safety laboratory samples will be processed locally and the results entered into the eCRF
- PK and biomarker samples will be processed centrally and the results sent electronically to Medpace
- Ophthalmological assessments will be done locally and the results entered into the imaging eCRF. [redacted]

Further coding details and data management processes will be described in the DMP.

11.6 Study Review Committee for Part A

The SRC will be organized and comprised according to the SRC Charter and will include a coordinating Investigator (or designee) who will act as SRC Chair, selected Principal Investigators (or designees), and Sponsor representative(s). Additional external experts may be requested by the SRC, as permitted in the SRC Charter. The organization, roles, responsibilities, procedures, documentation, communication, and reporting of the SRC will be contained in a written SRC Charter to ensure appropriate responsibility and accountability is assigned.

The SRC will meet at the predefined time points for study decision making. It will also monitor the safety of patients throughout the study and may make recommendations at any time if there are concerns about the safety of the patients in the study.

11.7 Study Review Committee for Part D

The study will use an SRC to assess ongoing safety analyses and to review safety and efficacy data for the interim analysis as described in Section 10.2.3. The SRC will be organized and comprised according to the SRC Charter and will not include

any members employed by the Sponsor or the main contract research organization.

The organization, roles, responsibilities, procedures, documentation, communication, and reporting of the SRC will be contained in a written SRC Charter, to ensure appropriate responsibility and accountability is assigned. The SRC will meet at the predefined time points described in the SRC Charter for review of the safety data from the study. Additionally, the SRC will review the safety data for the SA group analysis and the efficacy and safety data [redacted].

[redacted]

Final decisions regarding conduct of the study remain the responsibility of the Sponsor and must be submitted to the authorities along with an amendment to the protocol, if applicable. The Sponsor or SRC may call additional meetings at any time if there is concern about the safety of patients in the study.

Full details of the SRC procedures and processes can be found in the SRC Charter.

11.8 Publications

Following completion of the study, a CSR (synopsis), written in accordance with ICH Guideline E3, will be submitted to the Regulatory Authorities and IRB in accordance with local regulations.

The Investigator may be involved in a cooperative publication in conjunction with other investigators participating in the study and the Sponsor, prior to publication or oral presentations on an individual basis, as detailed in the Clinical Trial Agreement. The development of any cooperative publication will follow the International Committee of Medical Journal Editors recommendations[14].

12 REFERENCES

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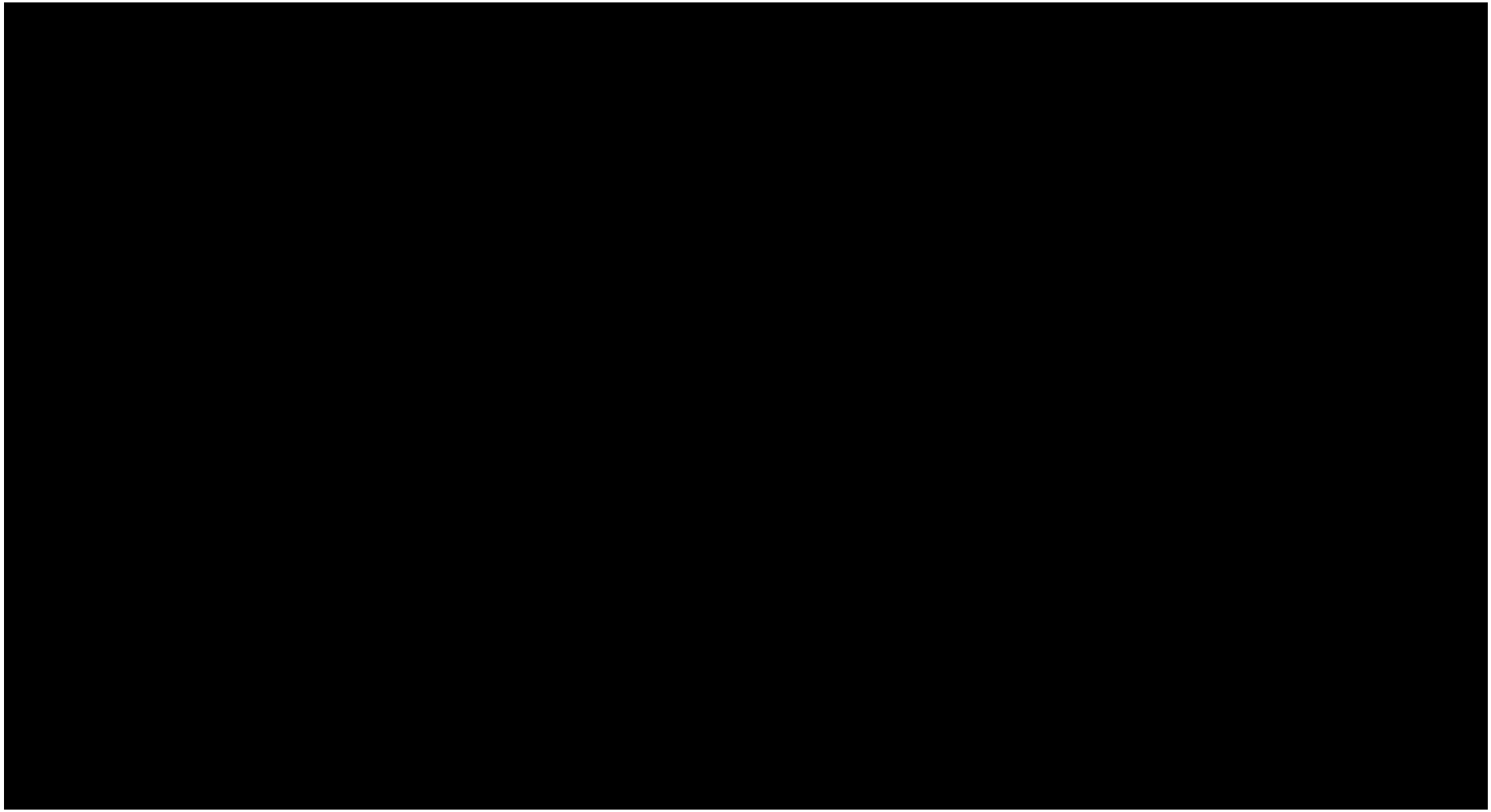
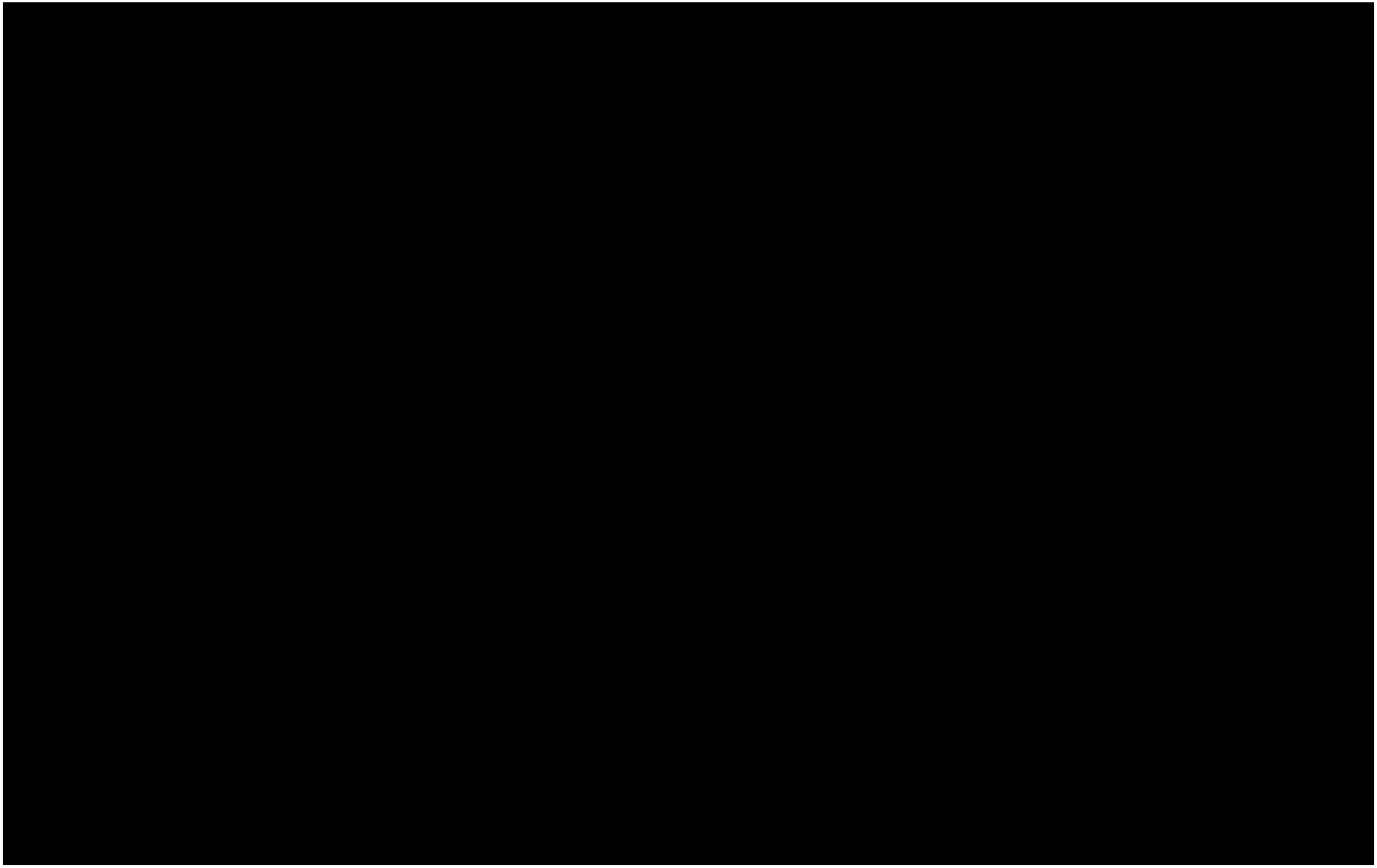
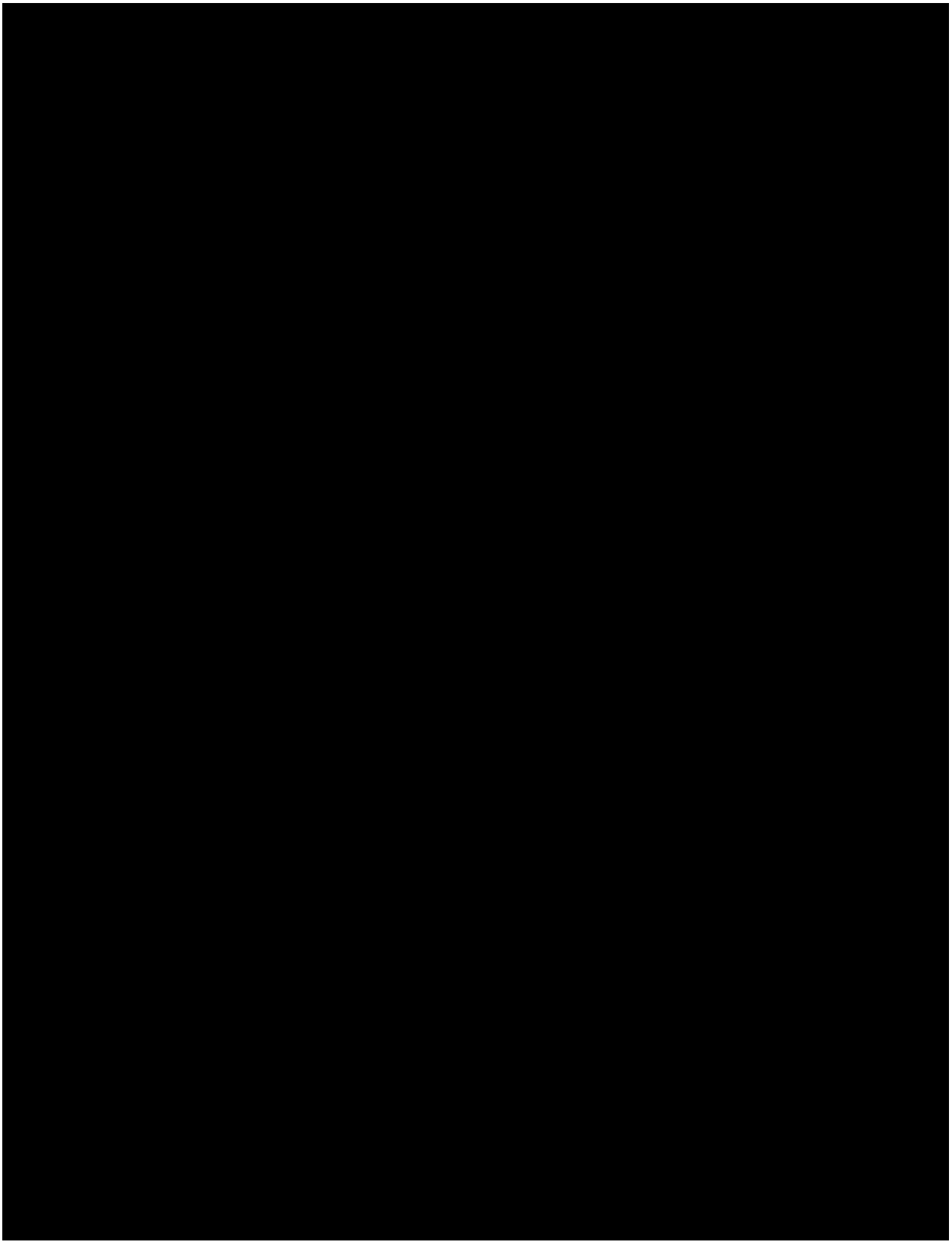
13 APPENDICES

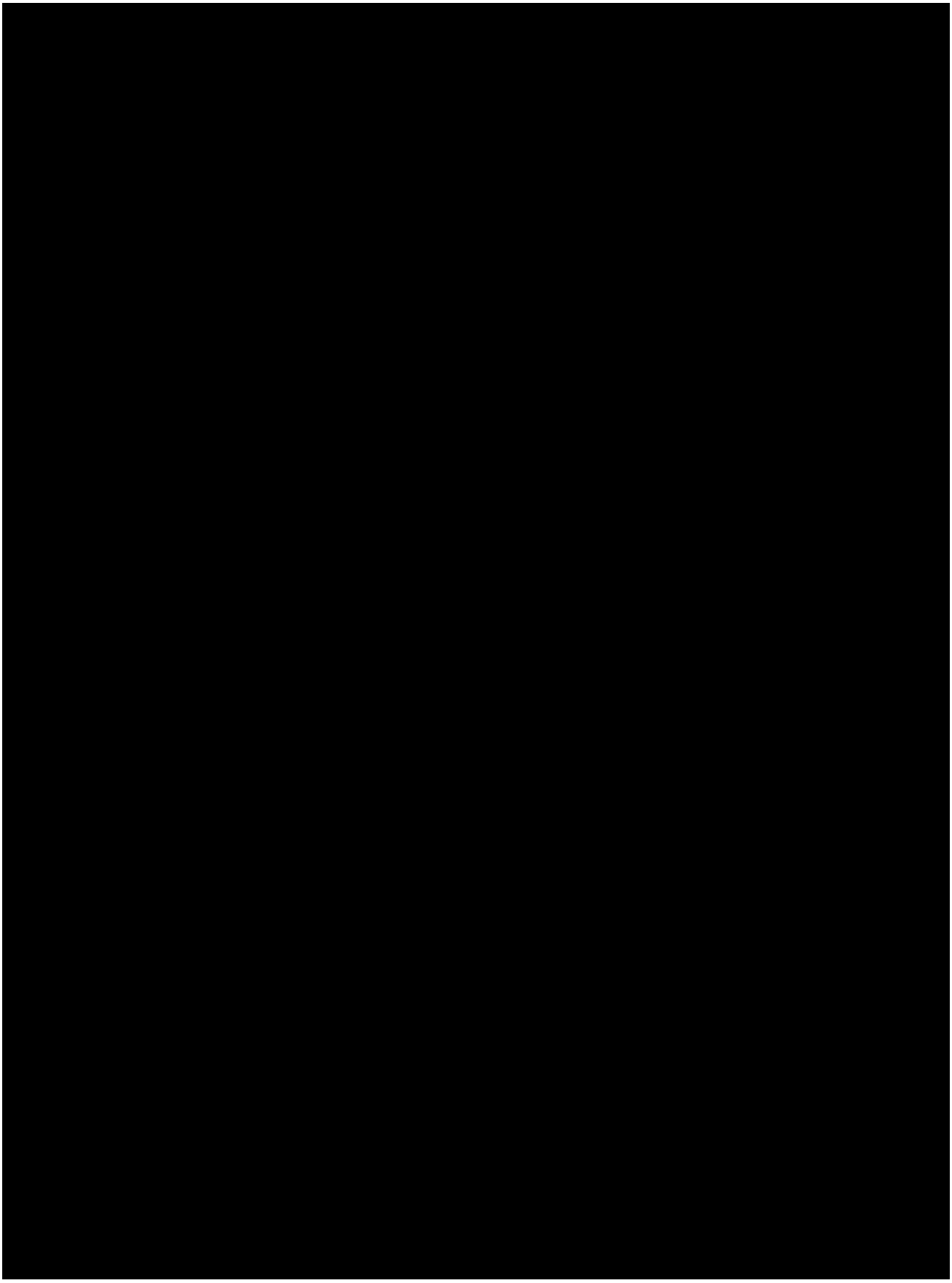
13.1 Appendix 1 Time and Events Table (Part A)

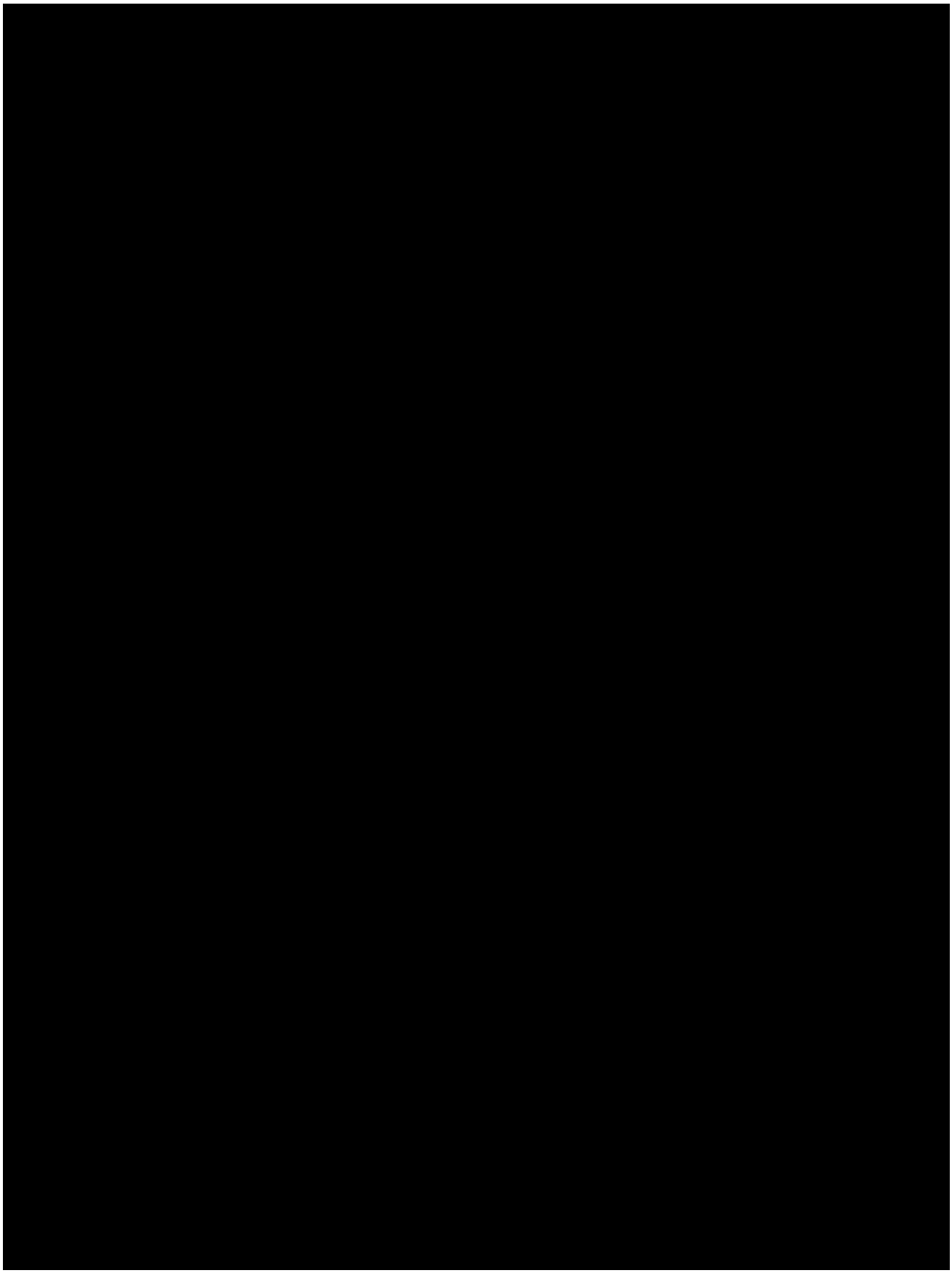


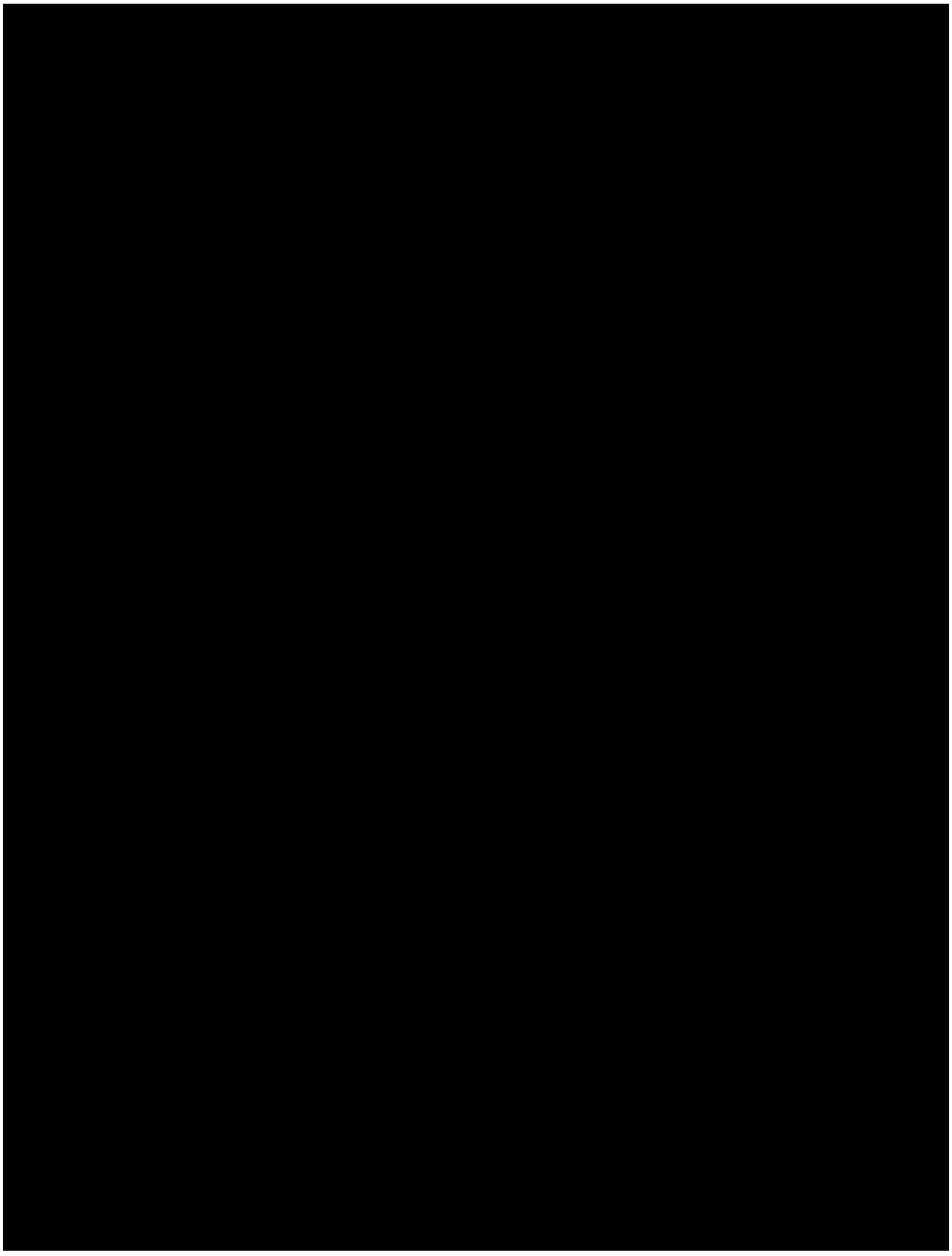


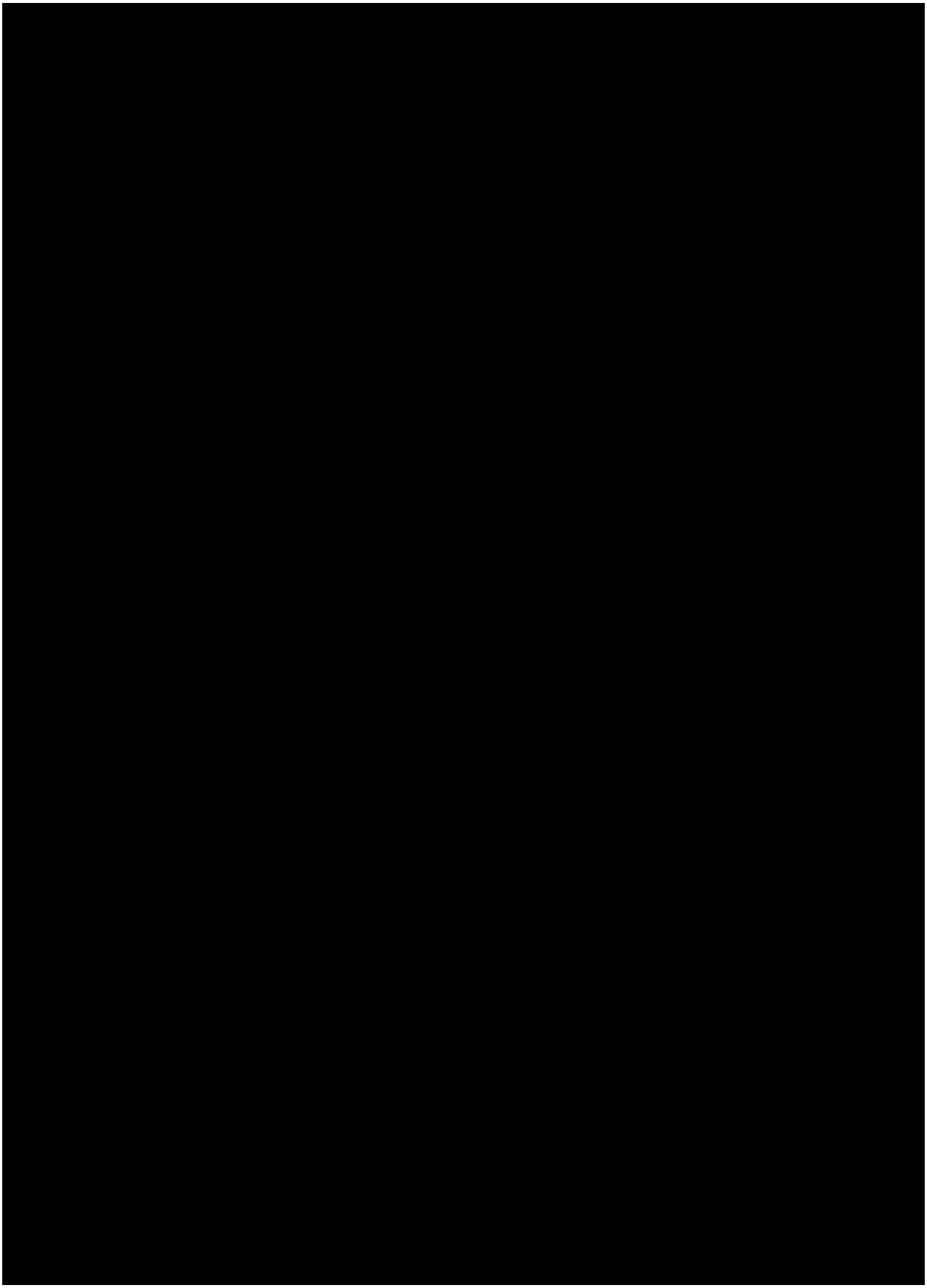
13.2 Appendix 2 Visit Schedule (Part A)











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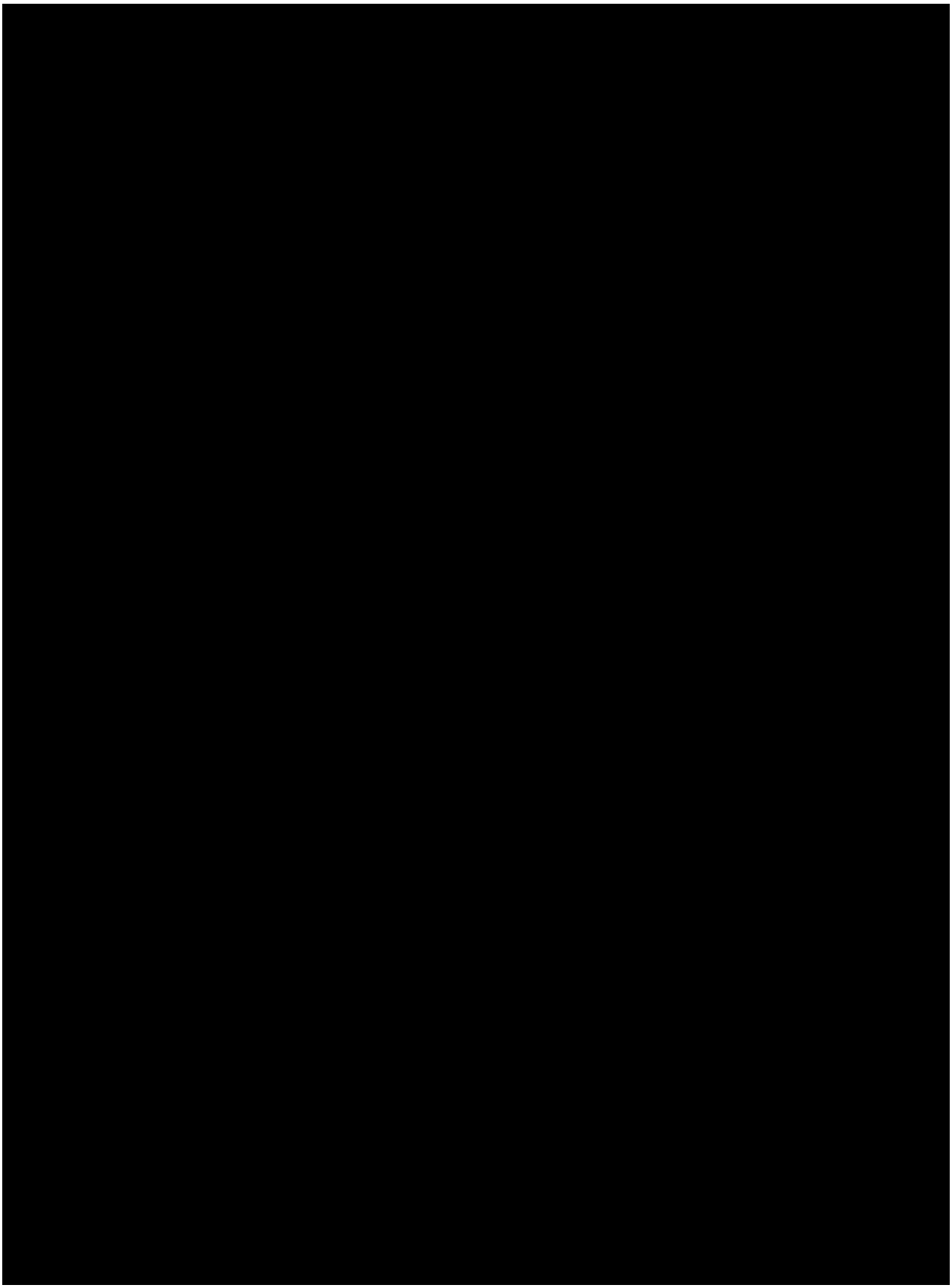
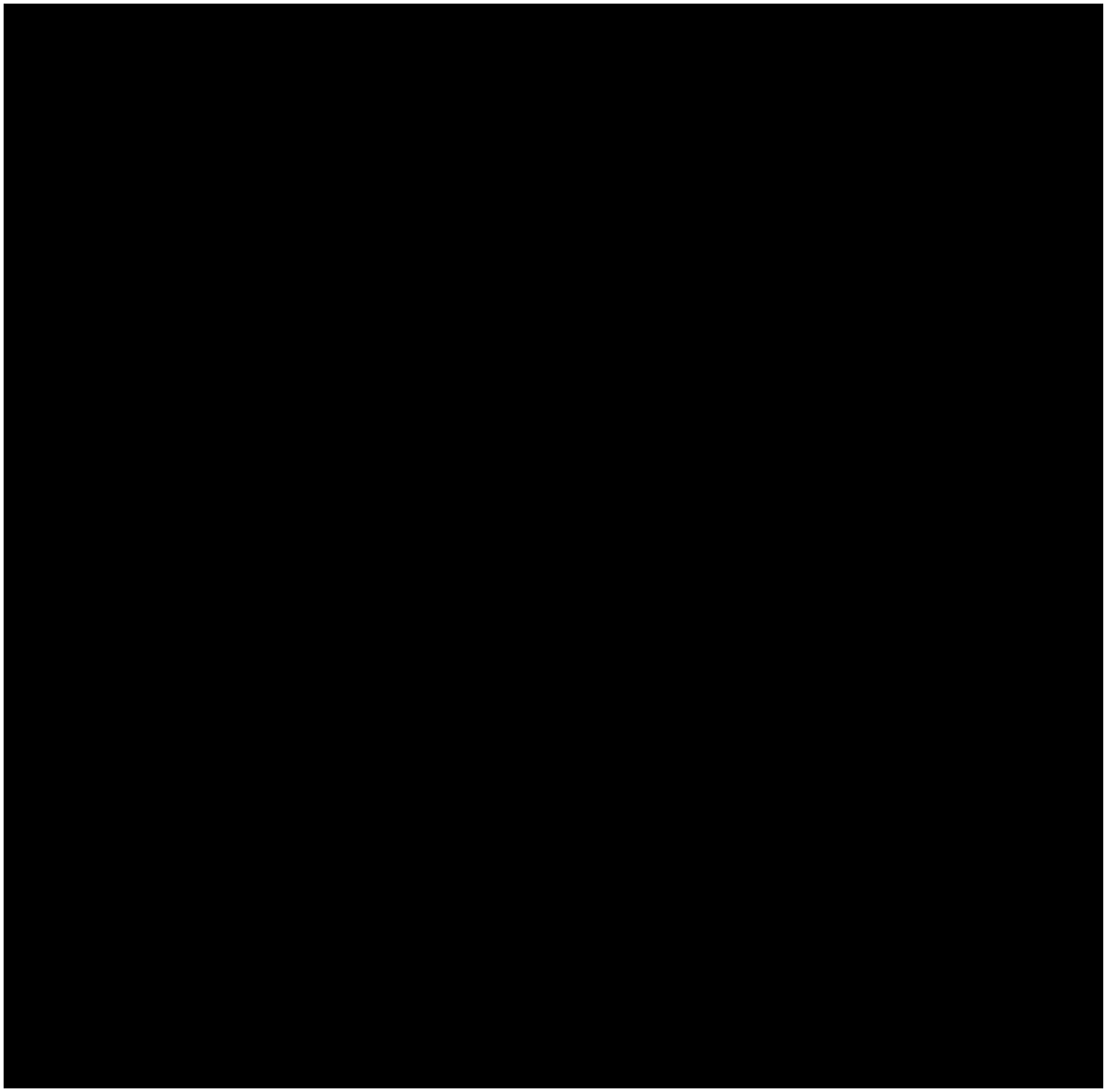
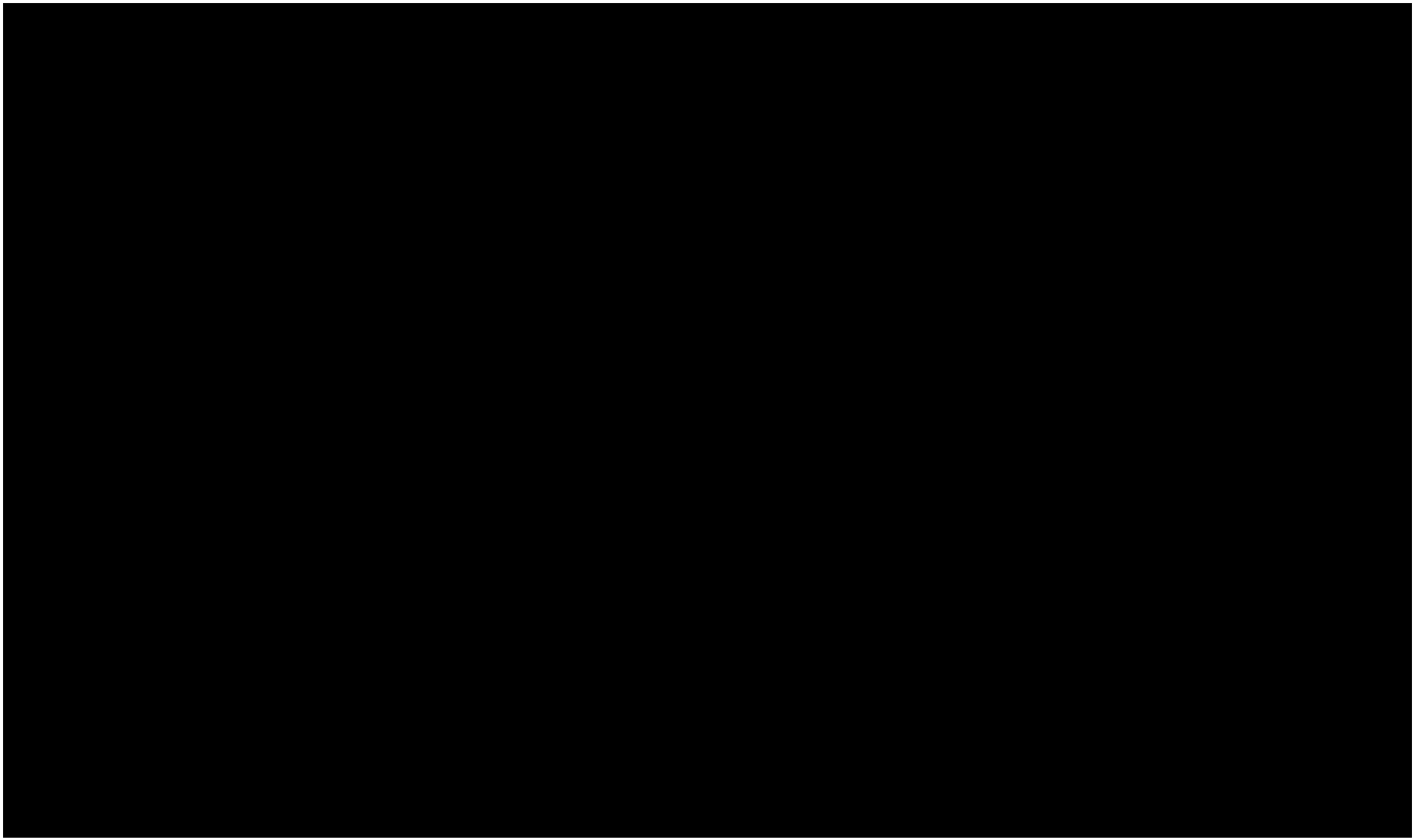
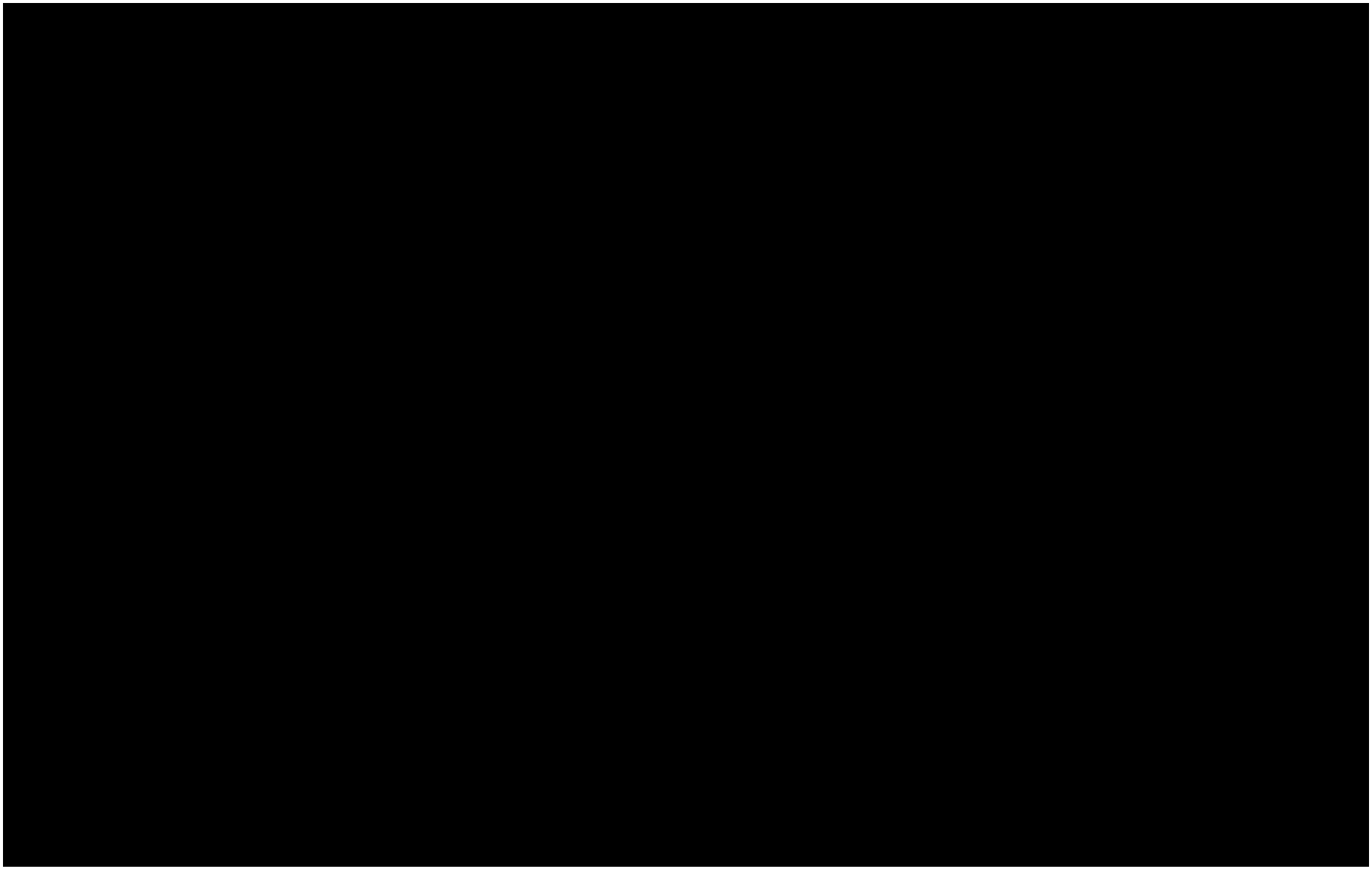




13.3 Appendix 3 Time and Events Table (Part D)





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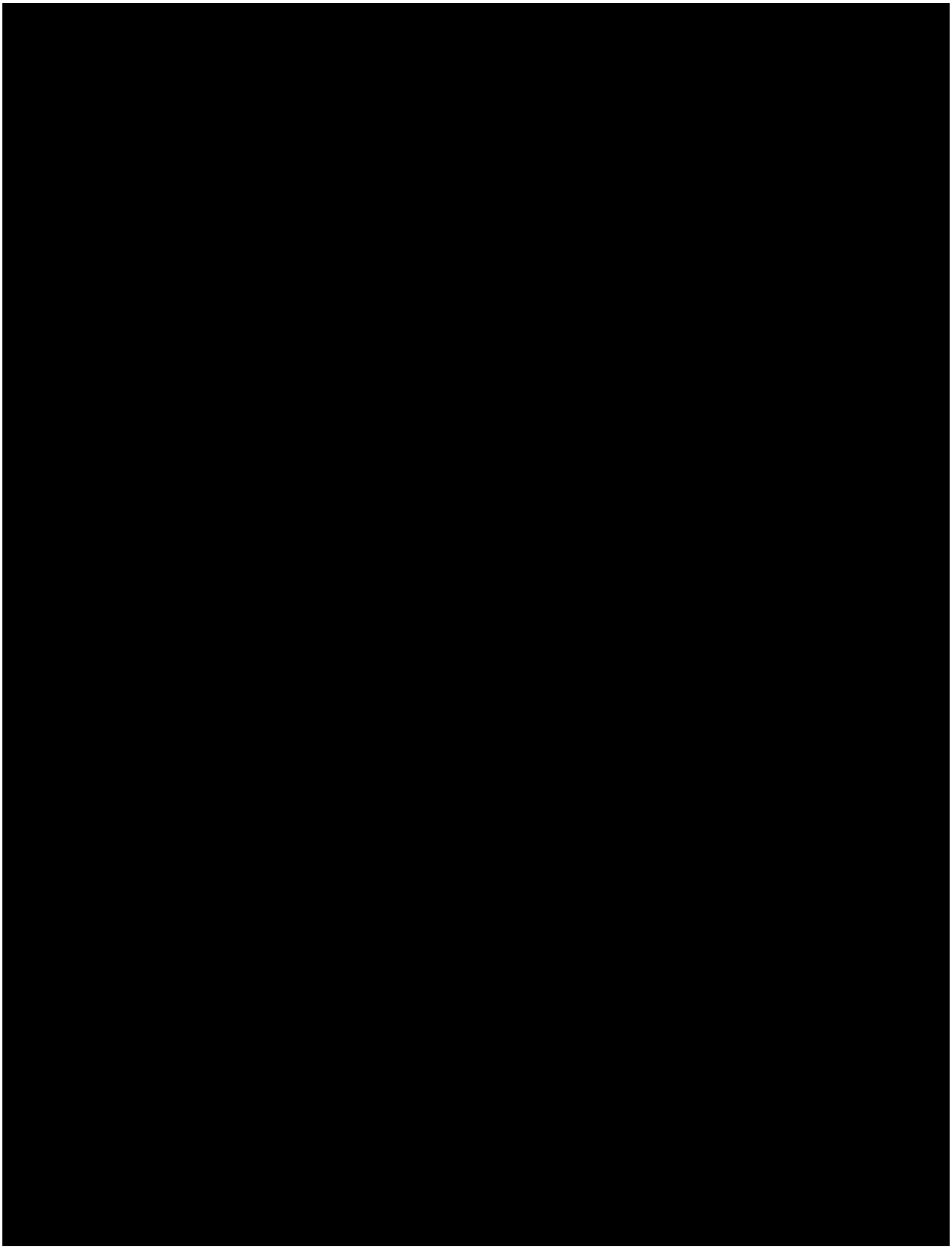
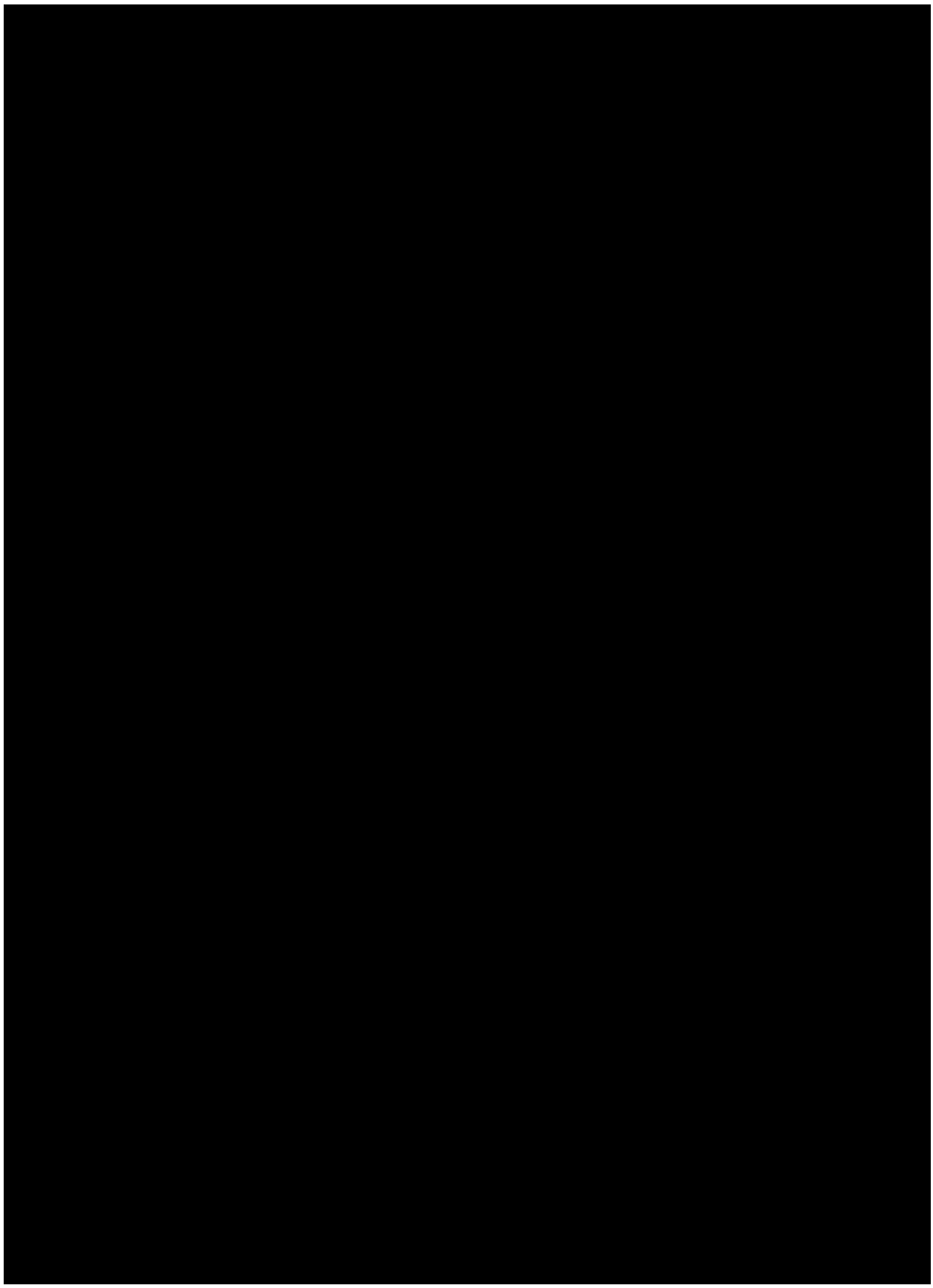
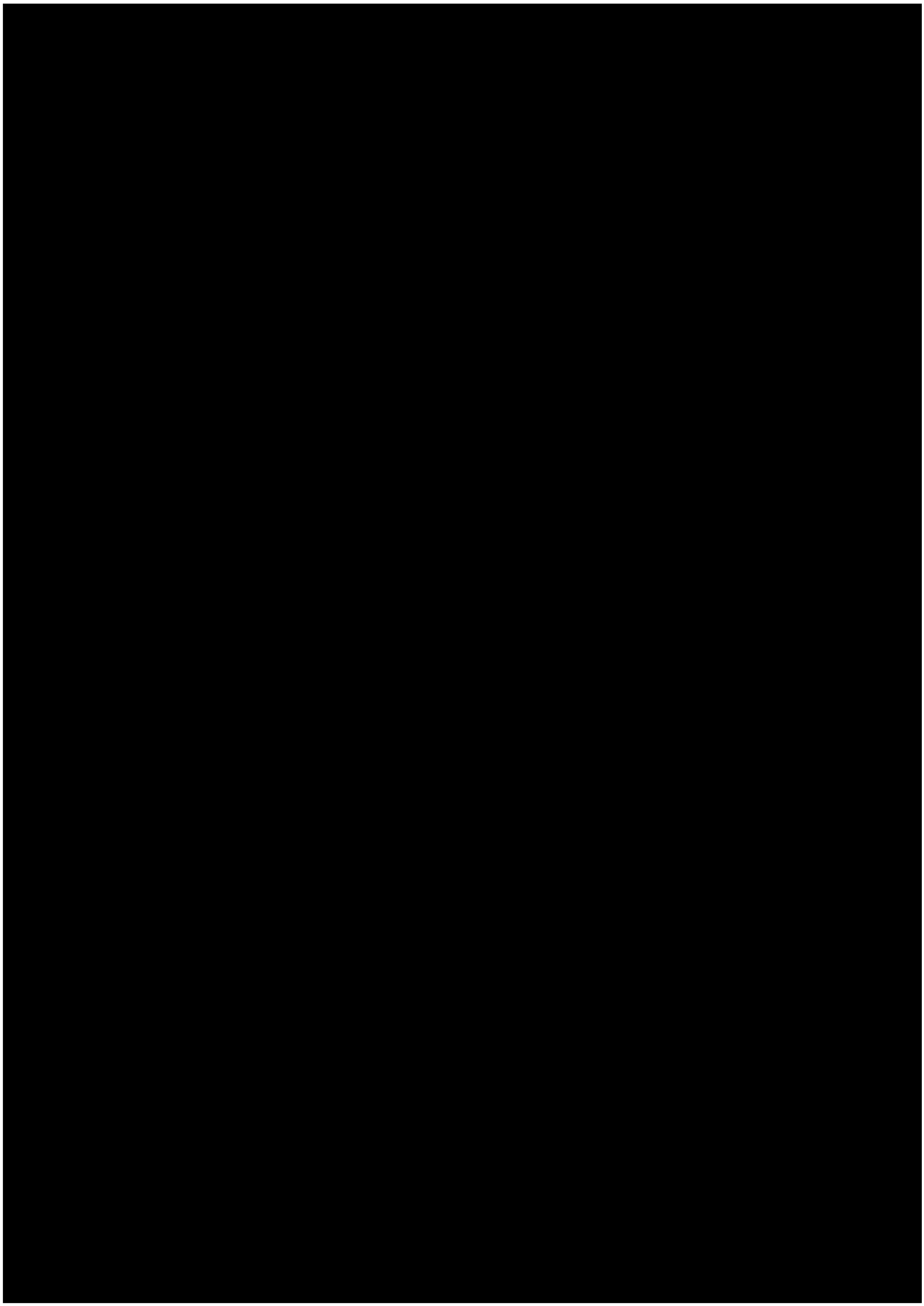
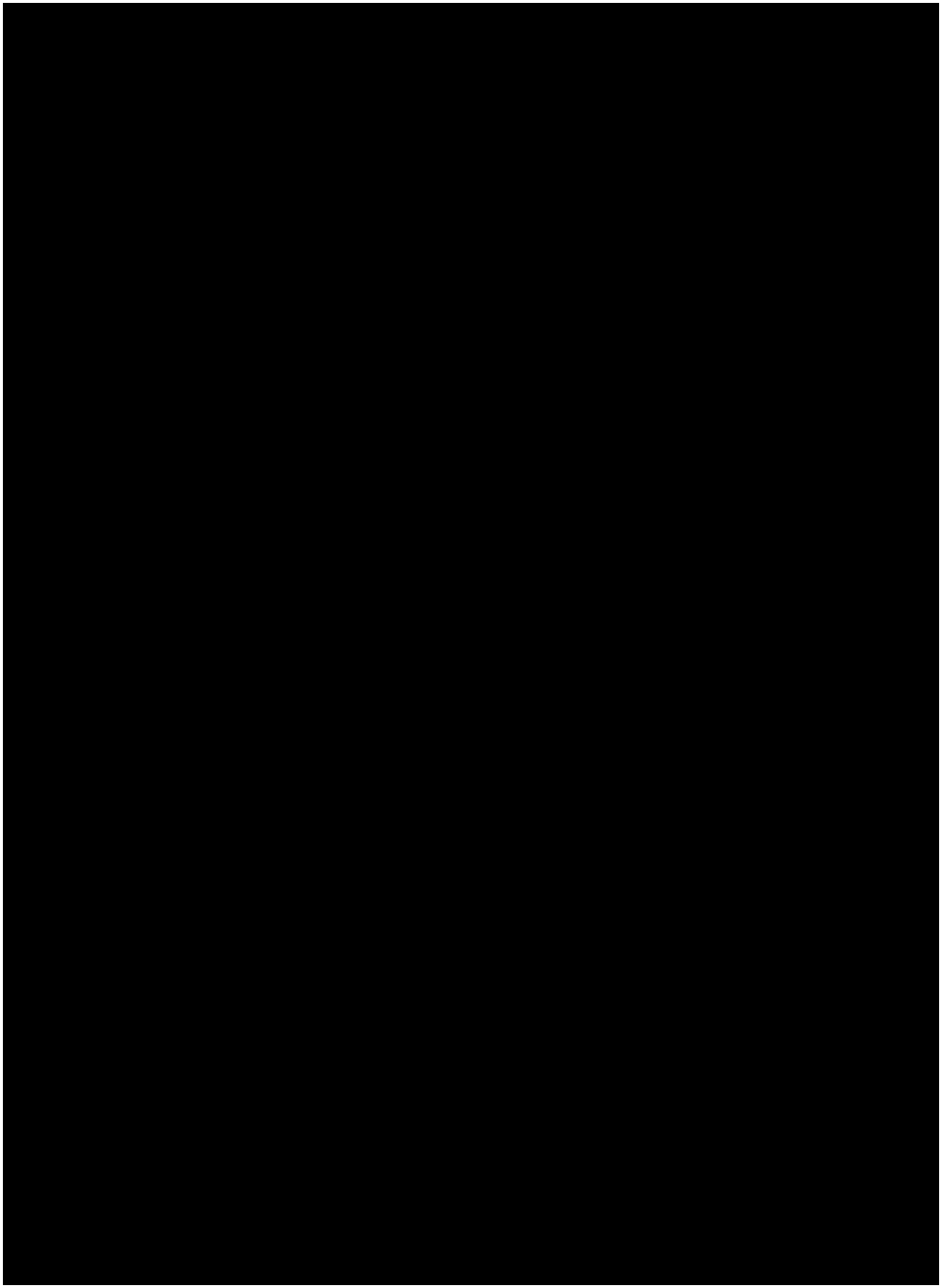
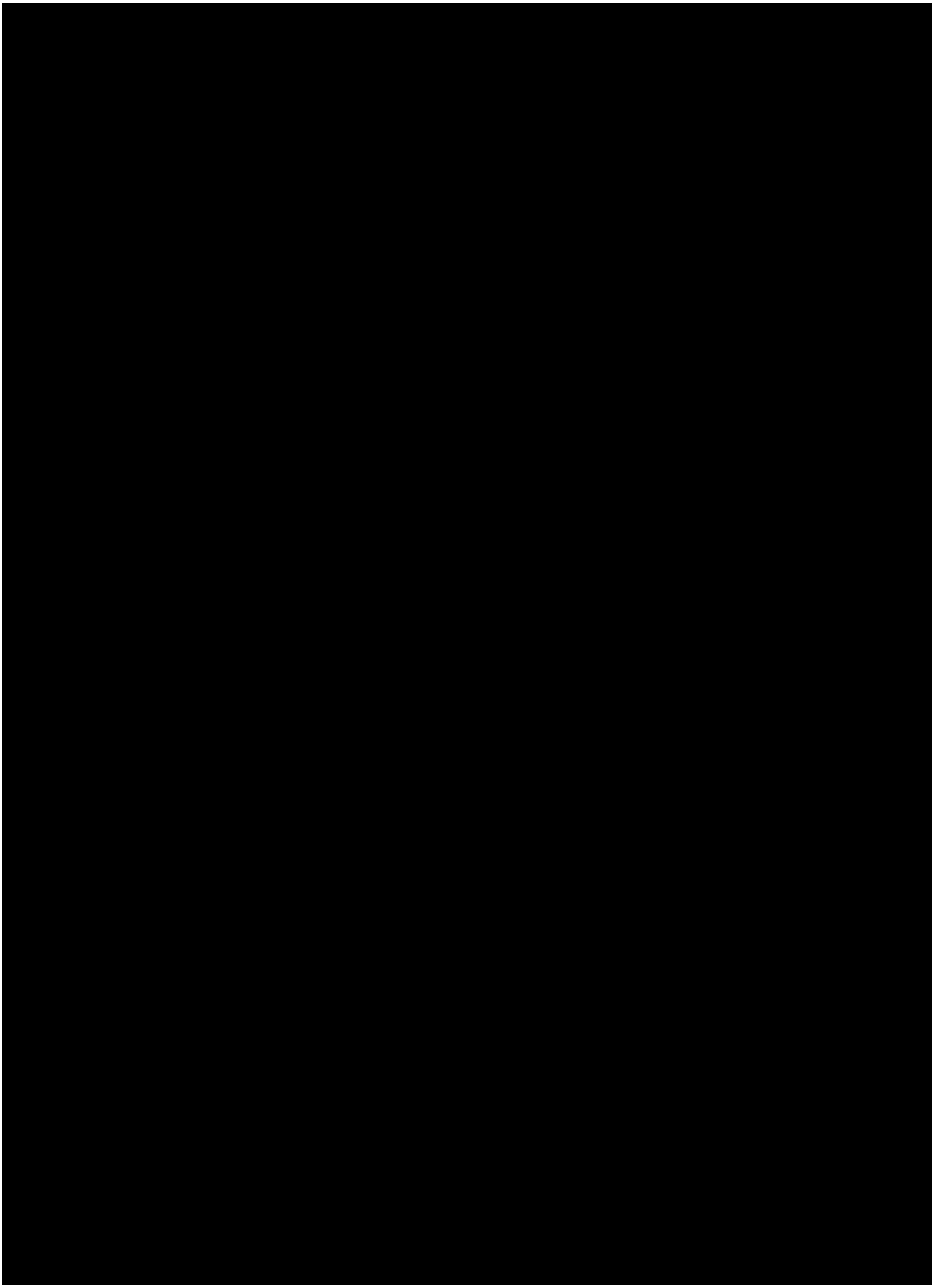
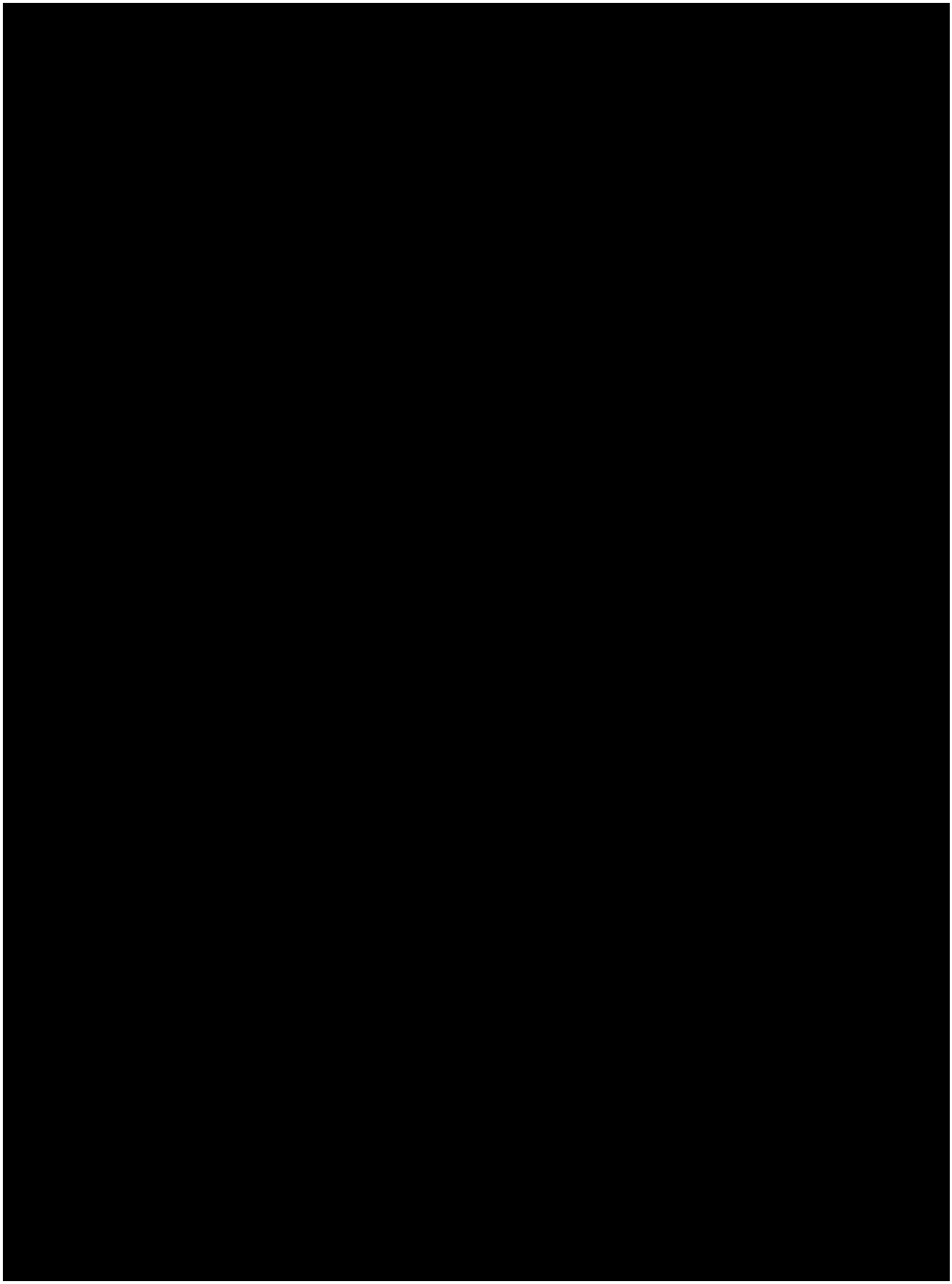








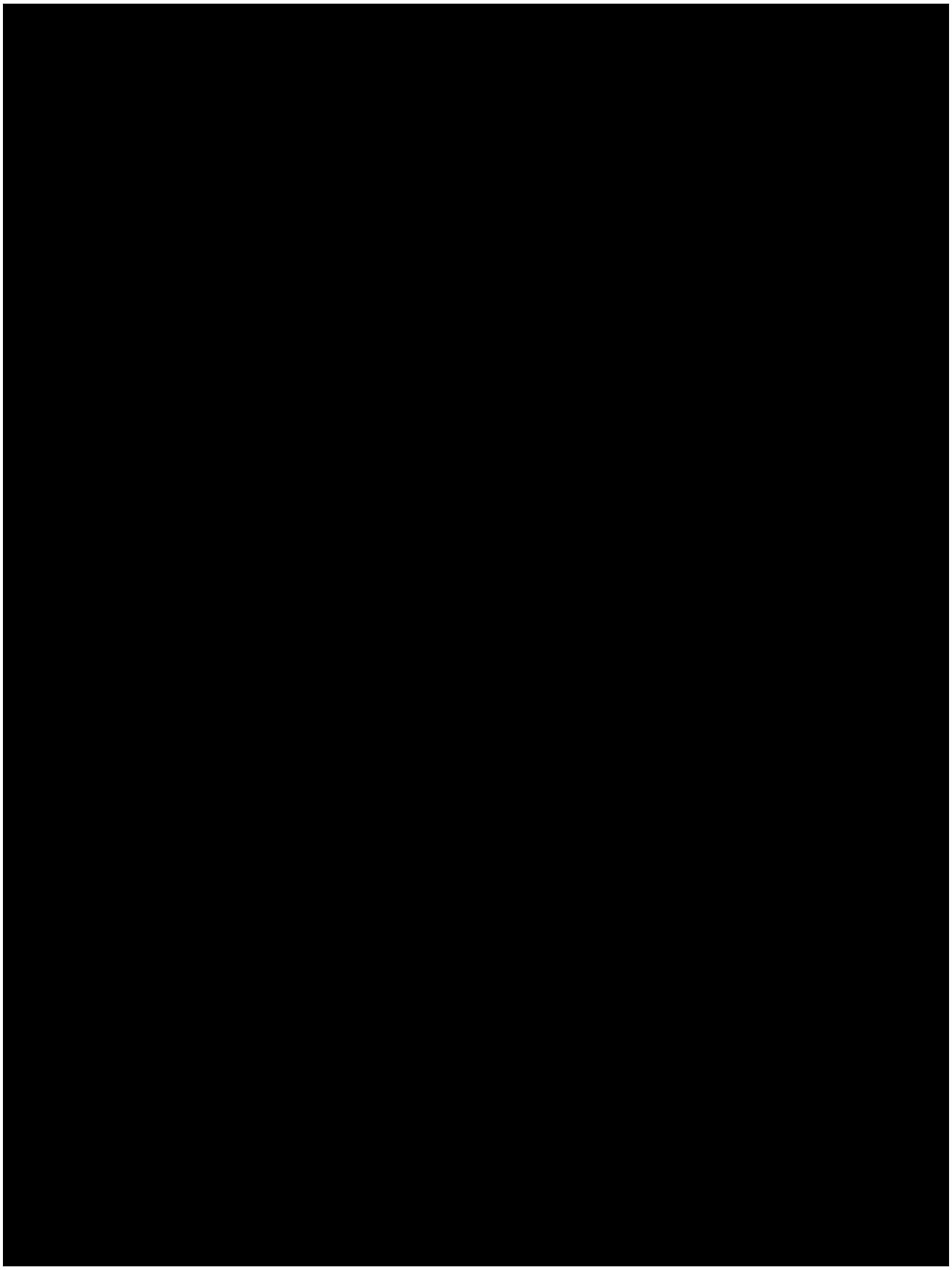


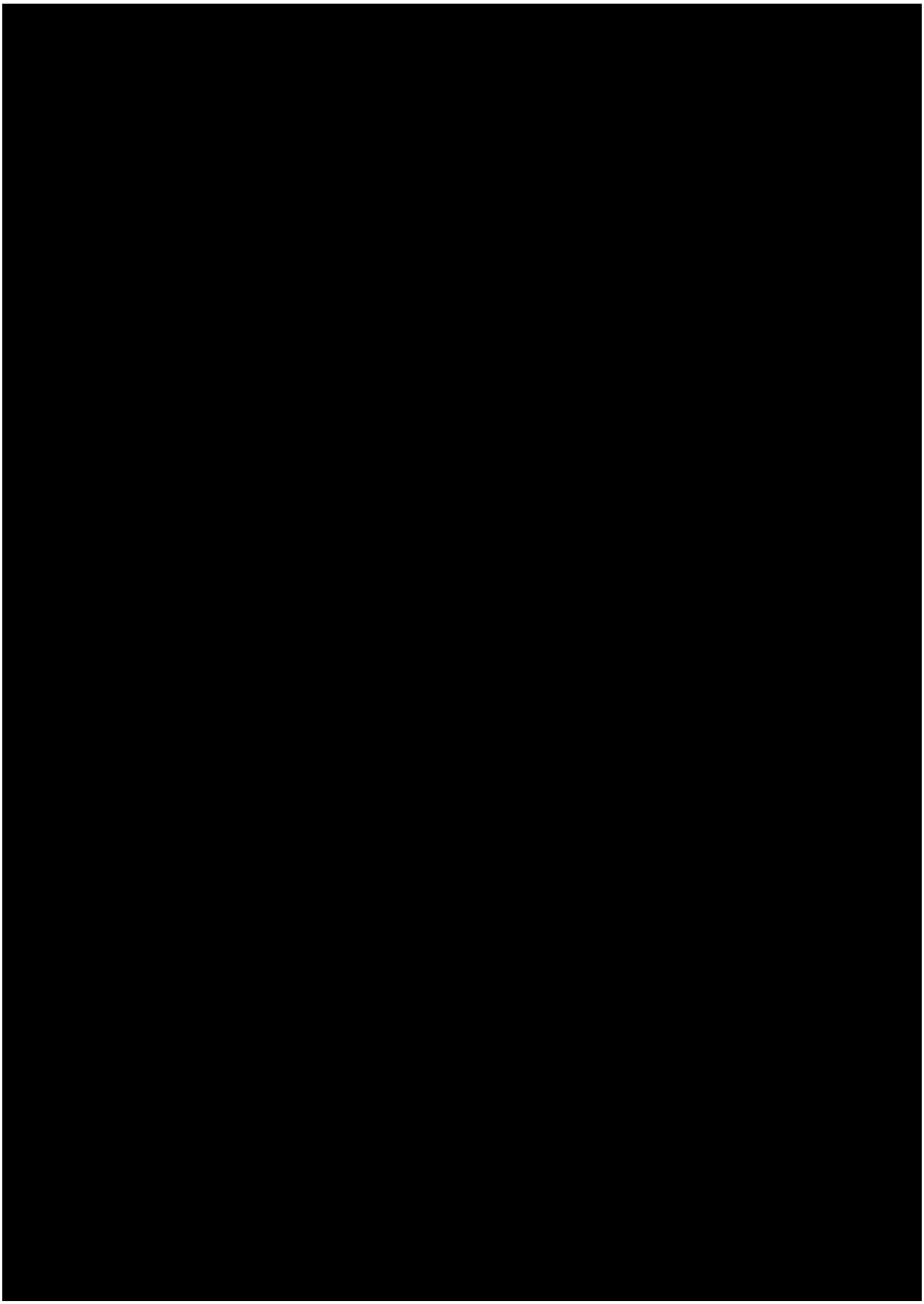


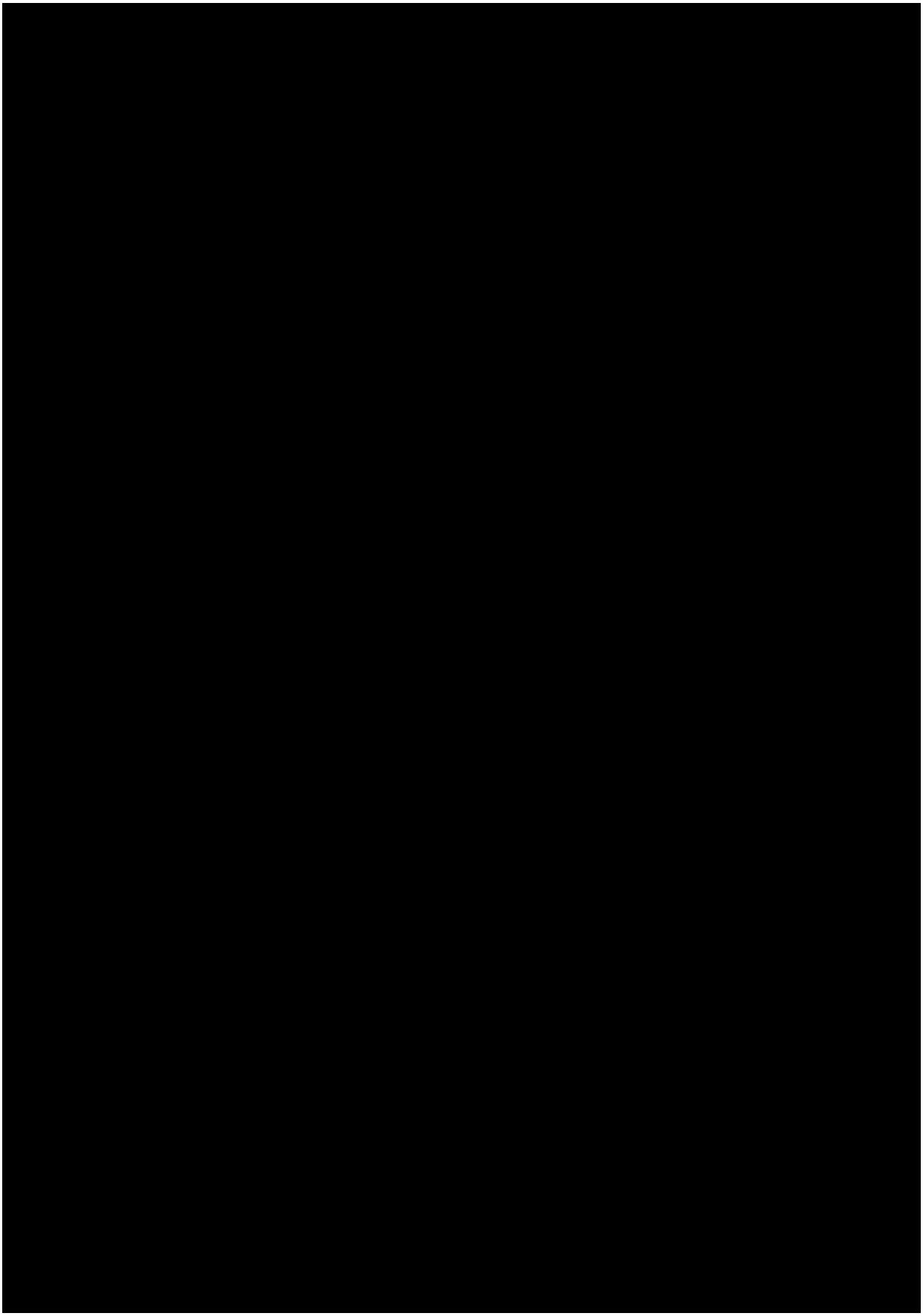
13.5 Appendix 5 Laboratory Parameters

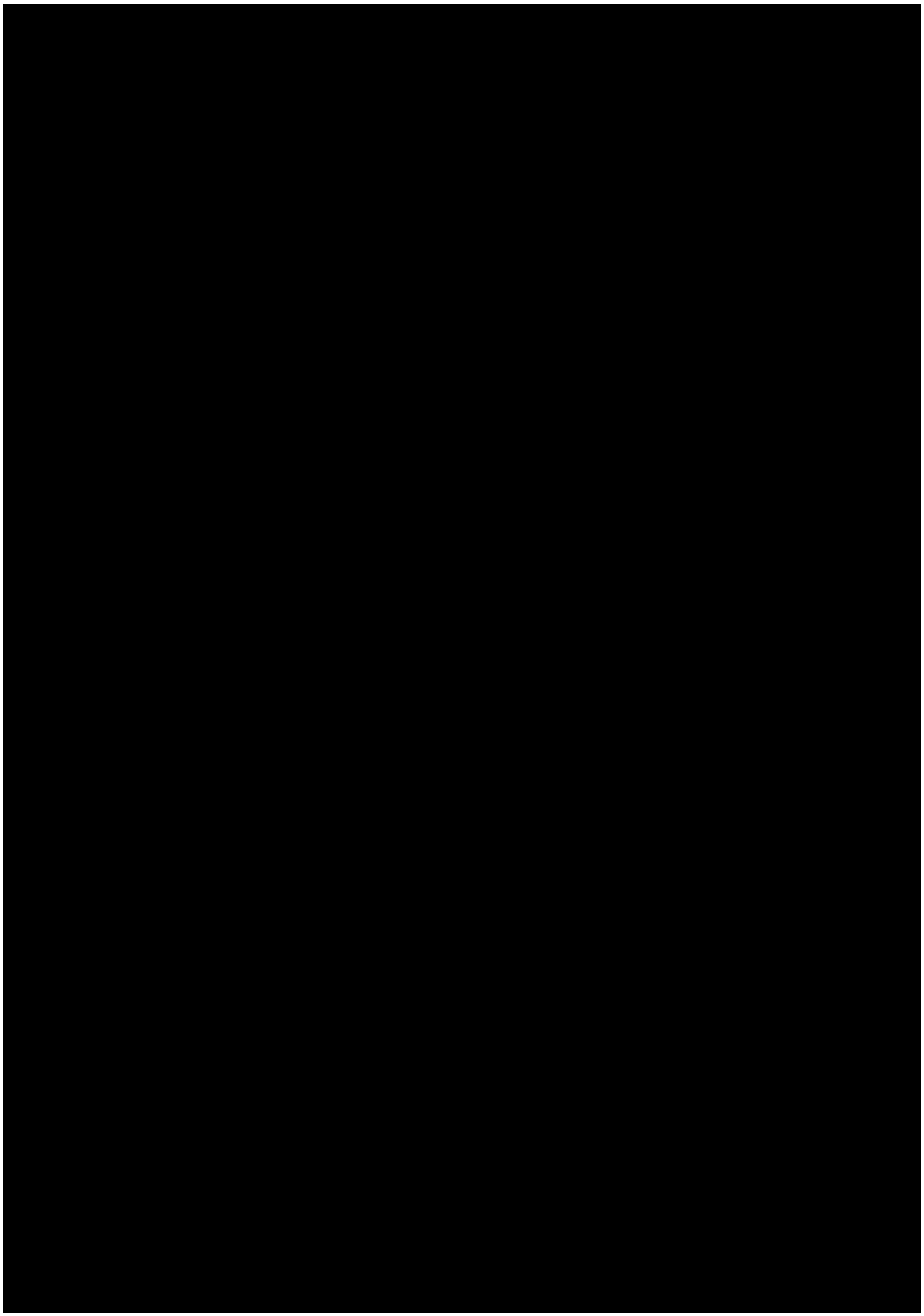
The following clinical laboratory tests will be performed:

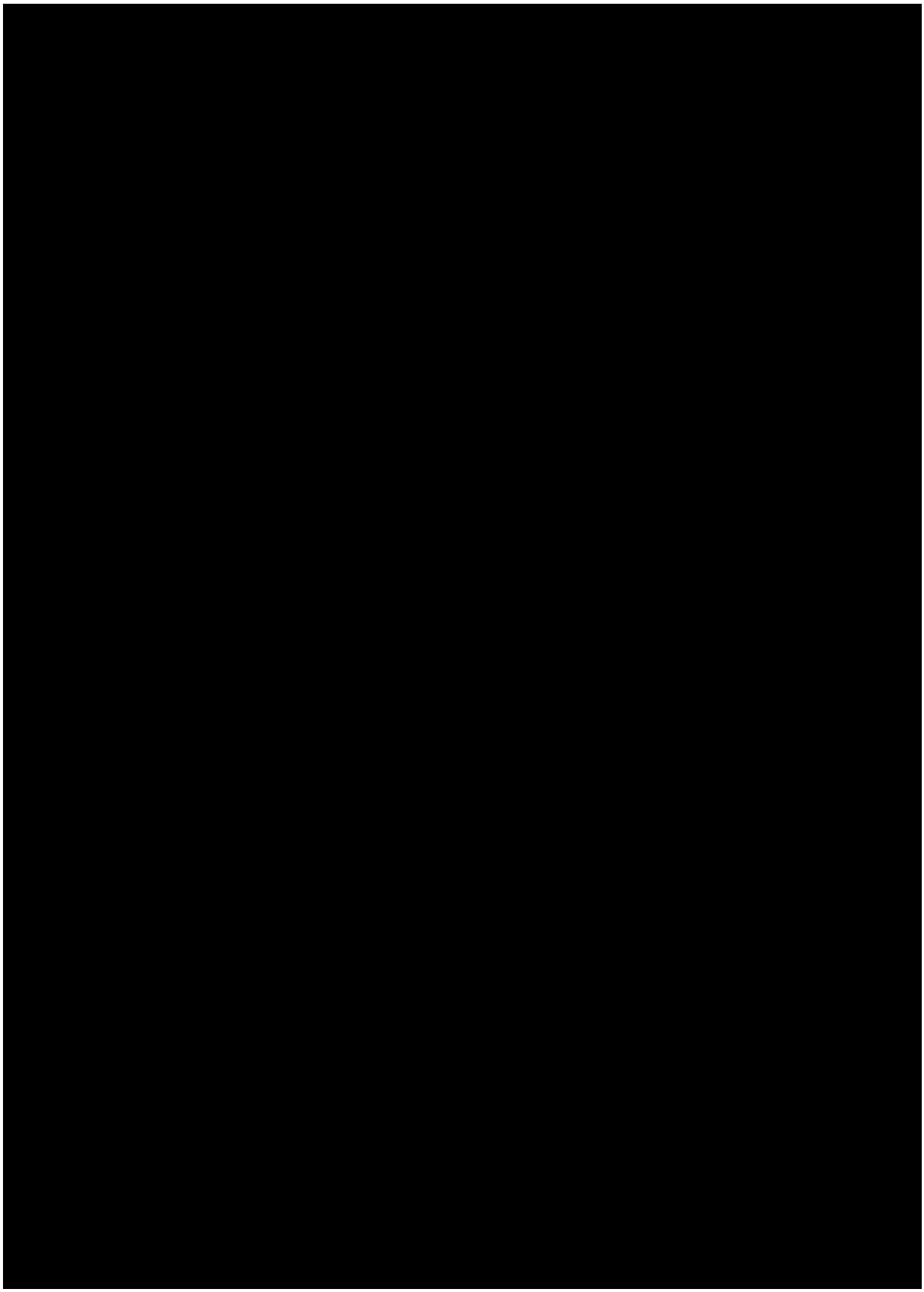
13.6 Appendix 6 Protocol Amendments

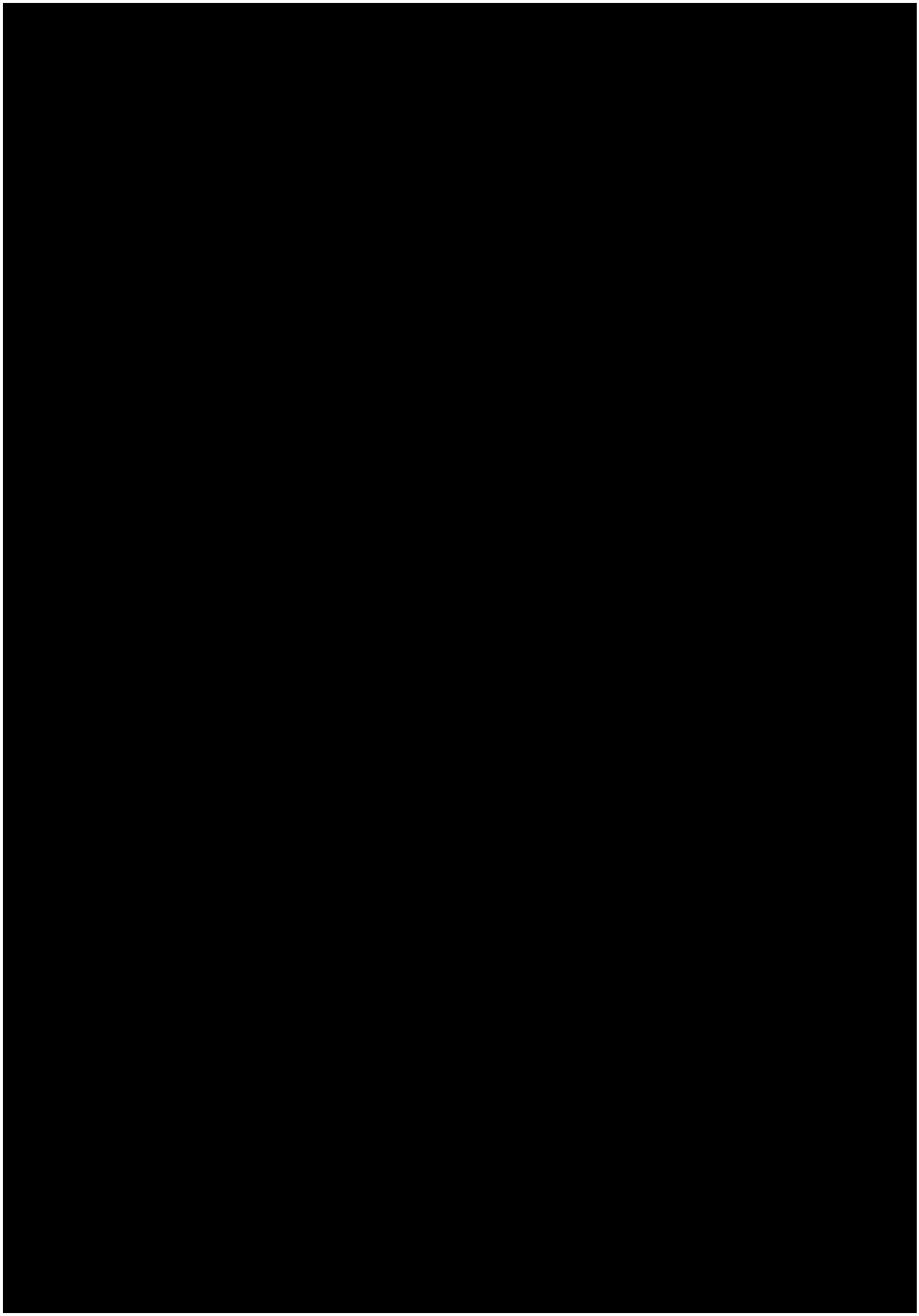












13.7 Appendix 7 ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Oken MM, *et al*. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5(6):649–655.

13.8 Appendix 8 Revised Recommendations of the International Working Group for Response Criteria in Acute Myeloid Leukemia

Journal of Clinical Oncology, Vol 21, No 24 (December 15), 2003

Response Criteria AML

Response Criterion	Time of Assessment	Neutrophils (μL)	Platelets (μL)	Bone Marrow Blasts (%)	Other
Early treatment assessment	7-10 days after therapy	NA	NA	< 5	
Morphologic leukemia-free state	Varies by protocol	NA	NA	< 5	Flow cytometry EMD
Morphologic CR	Varies by protocol	> 1,000	> 100,000	< 5	Transfusion EMD
Cytogenetic CR	Varies by protocol	> 1,000	> 100,000	< 5	Cytogenics—normal, EMD
Molecular CR	Varies by protocol	> 1,000	> 100,000	< 5	Molecular—negative, EMD
Partial remission	Varies by protocol	> 1,000	> 100,000	> 50 or decrease to 5-25	Blasts < 5% if Auer rod positive

Abbreviations: AML, acute myelogenous leukemia; EMD, extramedullary disease; CR, complete remission.

Treatment failure includes: (1) resistant disease, (2) aplasia, (3) indeterminate cause and recurrence due to (4) morphologic relapse, (5) molecular or cytogenetic relapse.

Definitions of Endpoints for Clinical Trial

Outcome	Response Category	Point of Measurement	Definition
Overall survival	All patients	Entry onto trial	Death from any cause
Relapse-free survival	CR	Leukemia-free state	Disease relapse or patient death from any cause
Event-free survival	All patients*	Entry onto trial	Treatment failure, disease relapse, or patient death from any cause
Remission duration	CR	Date of CR	Disease relapse

NOTE. Complete blood counts should be evaluated at least monthly, or more often if clinically indicated, to establish the durability of responses.
Abbreviations: AML, acute myelogenous leukemia; CR, complete remission.
*Under circumstances where presentation of event-free survival may be appropriate for responders only, this point should be clearly stated.

13.9 Appendix 9 Modification of the International Working Group for Response Criteria in Myelodysplasia (Part A Only)

Blood. 2006; 108: 419-425

Response Criteria MDS

Proposed modified International Working Group response criteria for altering natural history of MDS7

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100 × 10^9/L
	Neutrophils ≥ 1.0 × 10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new 1s
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

***** Dysplastic changes should consider the normal range of dysplastic changes (modification).

† Modification to IWG response criteria.

‡ In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

13.10 Appendix 10 NCI CTCAE Version 4.03

In the present study, toxicities will be graded according to the NCI CTCAE, version 4.03.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov.

Investigators will receive a copy prior to the start of the study.

13.11 Appendix 11 Calculation of Creatinine Clearance (CrCl)

Donald W Cockcroft and M. Henry Gault. Nephron. 1976:16:31-41

Standard Cockcroft and Gault Formula
For Male:

$$CrCl = \frac{(140 - age) \times (wt)}{72 \times \text{serum creatinine (mg/dL)}}$$

For Female:

$$CrCl = \frac{(140 - age) \times (wt) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

Age in years, Weight (wt) in kilograms

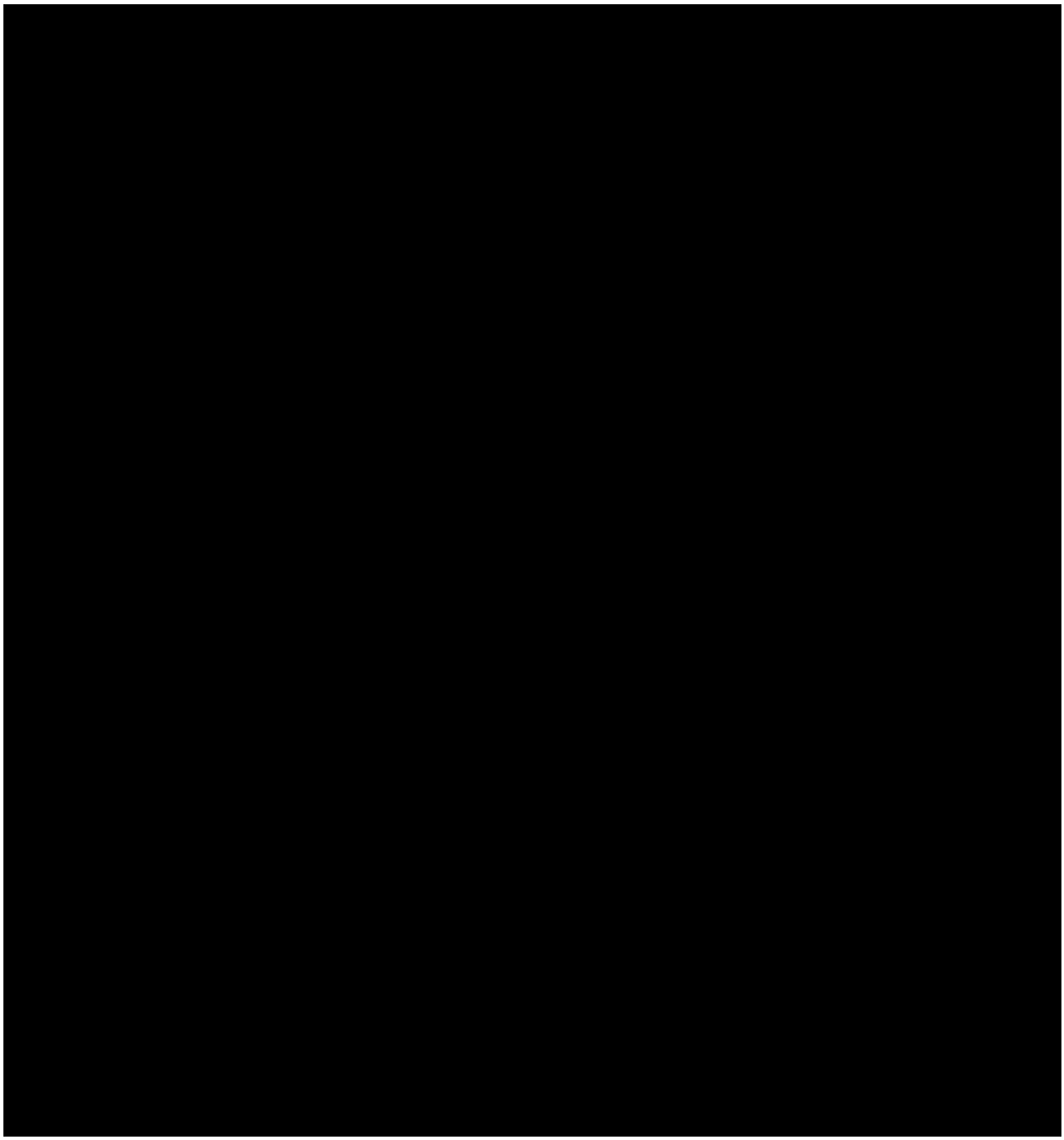
13.12 Appendix 12 Fundus Photography (Part A only)

From URL: https://www.ophth.wisc.edu//wp-content/uploads/2017/03/7Std-D.pdf

13.13 Appendix 13 Drug-Interactions List

Lists of drugs with potential for interaction below have been taken from FDA HP Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (Content current as of 10/MAR/2020).

FDA HP link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2.



13.14 Appendix 14 Breakfast Recommendation for the Assessment of Food on the Pharmacokinetics of ONO-7475 (Part A Only)

According to the FDA guidance, a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food effect assessment. This test meal should derive approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively. An example test meal would be 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

13.15 Appendix 15 [redacted]

13.16 Appendix 16 [redacted]

[redacted]