Title: AURORA: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis

Protocol Number: 3152-301-002
Amendment Number: 4
Product: Cenicriviroc mesylate (CVC)

Phase of Study: 3

Sponsor Name and:
Legal Registered Address Tobira Therapeutics, Inc., a subsidiary of Allergan plc
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EudraCT Number: 2016-004566-26

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SAE Reporting Fax Number/Email:

Business Unit /Legacy Organization	Email	Phone	Fax
Allergan	[redacted]	Not applicable	[redacted]

Approval Date: 25 April 2019

[redacted]

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	25 Apr 2019
Amendment 3	10 Apr 2018
Amendment 2	29 Jun 2017
Amendment 1	04 May 2017
Original Protocol	05 Dec 2016

The purpose of Global Protocol Amendment 4 is to provide additional clarification and updates to the previous Global Protocol Amendment 3 (dated 10 Apr 2018, details provided in Section 12.19). These changes will not impact the safety assessment of CVC or alter the risk-benefit ratio for study subjects.

The following is a summary of content-oriented changes that were made. Strikethrough text denotes text removed and bolded text denotes added text. Additional administrative edits were also made, but not specifically noted (eg, corrected spelling, punctuation, grammar, abbreviation, and style errors) including global edits required for consistency.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Protocol Section(s)	Summary of Changes	Rationale for Changes
General	• All instances of 8 weeks changed to 3 months • All instances of 180 days changed to 6 months	In response to request from the sites to increase duration of 8 weeks for timing of Screening visit to facilitate enrollment. All instances of "weeks" has been changed to "months" for clarification and consistency with current practice.
Cover page and Section 1 Emergency Contacts	• Updated emergency contact and SAE reporting information • Added address for Allergan international office in Marlow • Added "Allergan Global Patient Safety and Epidemiology" under SAE/Pregnancy/AEoSI Reporting	To align with current Allergan template
Section 1 Emergency Contacts	Updated information for Syneos Medical Monitoring Team	Updated to reflect change in CRO to Syneos
Section 4 Synopsis	• All relevant changes made below in subsequent sections in the body have been carried up to the synopsis • Increase in number of sites from 425 up to 600	To align with the body of the protocol To increase the number of subjects who will be randomized
Section 5.3 Clinical Studies with CVC	• Updated exposure data	To reflect current information
Section 5.3.2 Phase 1 PK Study in Subjects with Hepatic Impairment	• Added details regarding patient population for 652-1-121 • Added details regarding Study 3152-102-002	• To provide additional clarity • To provided updated information regarding 3152-102-002, now completed
Section 5.3.3 Phase 2b Study in Subjects with NASH and Liver Fibrosis	Updated results for year 2 CENTAUR based on final CSR	To reflect final results for CENTAUR as provided in the final CSR
Section 5.4 Study Rationale, Section 7.1 Overall Study Design and Plan, Section 8 Study Population	Re-worded for clarification and added details regarding newly randomized Stage 3 subjects in Part 2	For clarification [redacted]

Protocol Section(s)	Summary of Changes	Rationale for Changes
Section 6 Objectives, Section 6.1 Part 1	• Redefined primary efficacy objective and endpoint for Part 1: Primary Objective (Part 1): Demonstrate the superiority of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy in adult subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) as confirmed by an independent central pathologist. Primary Efficacy Endpoint: Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade). • Reorganized secondary efficacy objectives for Part 2 (Section 6.2) by moving 5th and 6th bullet up. There was no change in text.	[redacted]
Section 7.1 Overall Study Design and Plan	• Re-worded for clarification and to add details regarding newly randomized Stage 3 subjects in Part 2: Part 2 of the study will focus on assessing the effect of CVC on clinical outcomes (Section 7.1.2) and will include approximately 2000 subjects, of which up to 1200 subjects will have been randomized in Part 1. In Part 2, approximately 800 subjects will be newly enrolled and randomized 2:1 to receive CVC or placebo. The study population will include the following: • Part 1: adult subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) as confirmed by an independent central pathologist • Part 2: subjects who continue on from Part 1 as well as newly randomized adult subjects with a liver biopsy diagnosis of NASH and Stage ~~2 or~~ 3 liver fibrosis (by NASH CRN system)	[redacted]
Section 7.1 Overall Study Design and Plan	• Added a statement clarifying subsequent study visits • Revised Figure 1, and revised footnote a, g, and h • Added text regarding source of liver fibrosis • Added description of PRO assessment via electronic tablet • Added description of the subjects to be newly enrolled and randomized to Part 2 • Table 4 was edited to reflect these are subjects in Part 2 and instructions	For clarification

Protocol Section(s)	Summary of Changes	Rationale for Changes
	were clarified	
Section 8.1 Number of Subjects	Added details regarding patient population Part 2	[redacted]
Section 8.2 Inclusion Criteria	• Added details in IC #4 regarding newly randomized Stage 3 subjects in Part 2	For clarification
Section 8.3 Exclusion Criteria	• Added "at Screening" for EC #12-16 • Defined stable weight in EC #18 • EC#23: Added additional details regarding immunomodulating agents, vaccines, and steroids • EC#24: Added exception for subjects in stable therapy with GLP-1 receptor agonists for more than 6 months • EC#25: Added details regarding disallowed medication use and washout period	For clarification
Section 9.1 Treatments Administered	Added details regarding newly randomized Stage 3 subjects in Part 2	[redacted]
Section 9.2 Study Drug; Section 9.2.8 Part 2	Re-worded for clarification and to add details regarding newly randomized Stage 3 subjects in Part 2	
Section 9.4 Blinding	Clarify that individual subject treatment assignments will not be provided to sites, subjects, or study staff/sponsor until analysis of Part 2	For clarification
Section 9.5 Prior, Concomitant, and Subsequent Therapy	• Added details regarding disallowed medication use and washout period • Added details regarding disallowed antidiabetic agents • Added clarification on Fentanyl use	For clarification and update
Section 10.1 Part 1 and Part 2: Screening (Month 2; Visit 1)	Text added to allow retest for subjects who do not meet laboratory eligibility criteria during the Screening period	To clarify retest requirements for subjects who do not meet laboratory eligibility criteria during the Screening period
[redacted]		

Protocol Section(s)	Summary of Changes	Rationale for Changes
[redacted]		
Section 10.6 Part 2: On-Treatment Evaluations Post Biopsy	Add details regarding newly randomized subjects in Part 2	To align with changes made above regarding patient population in Part 2
Section 11.2 Assessment of Efficacy	• Add details regarding newly randomized subjects in Part 1 and 2 • Serum hepatic fibrosis indices: Added text clarifying process to be implemented	To align with changes made above regarding patient population in Part 2
Section 11.3.2.2 Clinically Significant Laboratory Abnormalities	Clarified resolution of abnormal values	For clarification
Section 11.3.3 Vital Signs	Added exception to obtaining vital signs at the Early Discontinuation visit	For clarification
Section 11.3.6.4	Revision made in table to correct typo for "≤ 5 × baseline"	Correction of typo in previous amendment
[redacted]		
Section 14.4 Subject Confidentiality	Added text relevant to EU requirement: ...European Union Data Protection Directive 95/46/EC).	To align with current guidelines
Section 15.2.3 Study Monitoring and Access to	Added text regarding role and responsibilities of the study monitor	For clarification

Protocol Section(s)	Summary of Changes	Rationale for Changes
Source Documents		
Section 20.1 Schedule of Assessments	• Added confirmation of inclusion/exclusion criteria to Screening Visit • Revised footnote "a" to clarify rescreening and eligibility • Revised footnote "c" to clarify calculation of visit window • Added footnote "dd": Prior use of and outcomes associated with diet and exercise, prior use of and outcomes associated with NAFLD or NASH treatment	For clarification
Section 20.3 Information on Contraception Effectiveness	• Text was revised to address concerns from specific country health authorities but which the sponsor determined could be applicable to all countries	To address health authority concerns
Section 20.4 Disallowed Medications	• Added information for BCRP substrates and disallowed medications due to possible confounding effect on efficacy	For clarification
Section 20.5	• Added text to table titles clarifying enrolled and randomized subjects under Part 2	To align with changes made above regarding patient population in Part 2

1. EMERGENCY CONTACTS

In emergency situations, the investigator should contact the contract research organization (CRO) medical monitor, indicated below:

Syneos Medical Monitoring Team

Email:
Fax:
Back-up Fax:

[redacted]

Serious Adverse Event/Pregnancy/Adverse Events of Special Interest Reporting
Allergan Global Patient Safety and Epidemiology

Email:
Fax:
Back-up Fax:

[redacted]

2. TABLE OF CONTENTS

[redacted]

[redacted]

2.1. List of In-Text Tables

[redacted]

2.2. List of In-Text Figures

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
A1AT	alpha-1-antitrypsin
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event(s) of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANCOVA	analysis of covariance
APRI	aspartate aminotransferase to platelet count ratio index
AST	aspartate aminotransferase
$AUC_{0\text{-}tau}$	area under the concentration-time curve up to the last measurable concentration
BCRP	breast cancer resistance protein
BMI	body mass index
CCL	chemokine (C-C motif) ligand
CCR	C-C chemokine receptor
CI	confidence interval
CLDQ-NAFLD	Chronic Liver Disease Questionnaire for NAFLD
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
C_{min}	minimum plasma concentration
CPK	creatine phosphokinase
CRN	Clinical Research Network
CRO	contract research organization
CVC	cenicriviroc mesylate
CYP	cytochrome P450
DCIS	ductal carcinoma in situ
DILI	drug-induced liver injury
DPP-4	dipeptidyl peptidase 4
DSMB	Data and Safety Monitoring Board
DSUR	Development Safety Update Report

Abbreviation	Definition
ECG	electrocardiogram
EC_{min50}	C_{min} associated with half-maximal response
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EU	European Union
FDA	Food and Drug Administration
FIB-4	noninvasive hepatic fibrosis index score combining standard biochemical values (platelets, ALT, AST) and age
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide 1
GPP2	Good Publications Practice for Communicating Company Sponsored Medical Research
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HDPE	high-density polyethylene
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL	interleukin
INR	international normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
ITT	intent-to-treat
IxRS	interactive response system
LC1	liver cytosol type 1
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LKM1	liver/kidney microsome type 1
MCP-1	monocyte chemotactic protein-1
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for end stage liver disease
MIP	macrophage inflammatory protein
mITT	modified intent-to-treat
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	nonalcoholic steatohepatitis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NFS	NAFLD fibrosis score
OR	odds ratio
P-gp	P-glycoprotein
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PP	per protocol
PPI	proton pump inhibitor
PR	time between the start of the P wave to the start of the QRS complex (ECG)
[redacted]	
QD	once daily
QT	time between the start of the Q wave and the end of the T wave (ECG)
QTc	QT interval corrected for heart rate
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RANTES	regulated on activation normal T-cell expressed and secreted

Abbreviation	Definition
RNA	ribonucleic acid
SAE	serious adverse event
SAR	suspected adverse reaction
[redacted]	
SGLT2	sodium–glucose cotransporter 2
SMA	smooth muscle antibodies
sDILI	suspected drug-induced liver injury
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
T2DM	type 2 diabetes mellitus
TE	transient elastography
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
TZD	thiazolidinedione
ULN	upper limit of normal
US(A)	United States (of America)
VLDL	very low-density lipoprotein
WHO	World Health Organization

4. SYNOPSIS

Title	AURORA: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis
Clinical Phase	3
Indication	Treatment of liver fibrosis in adult subjects with nonalcoholic steatohepatitis (NASH)
Objectives **Part 1**	Primary Objective (Part 1): Demonstrate the superiority of cenicriviroc (CVC) compared to placebo on liver histology at Month 12 relative to the Screening biopsy in adult subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) as confirmed by an independent central pathologist • Primary Efficacy Endpoint: Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade). Key Secondary Objective (Part 1): • Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis of at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) Secondary Objectives (Part 1): • Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis • Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on steatohepatitis • Evaluate the safety and tolerability of CVC for the treatment of liver fibrosis in adult subjects with NASH
Objectives **Part 2**	Primary Objective (Part 2): • Demonstrate the superiority of CVC compared to placebo on the composite endpoint of histopathologic progression to cirrhosis (defined by NASH CRN Fibrosis Stage 4), liver-related clinical outcomes, and all-cause mortality, as measured by the time to first occurrence of any of the listed adjudicated events (clinical outcomes composite endpoint) – (all subjects)

	Secondary Objectives (Part 2): • Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) – (subjects newly randomized in Part 2) • Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis – (subjects newly randomized in Part 2) • Evaluate the effect of CVC compared to placebo on liver histology at Month 60 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) – (all subjects) • Evaluate the effect of CVC compared to placebo on liver histology at Month 60 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis – (all subjects) • Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) – (for subjects newly randomized in Part 2) • Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) regardless of effect on steatohepatitis – (for subjects newly randomized in Part 2) • Evaluate the effect of CVC compared to placebo on liver histology at Month 60 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) – (all subjects) • Evaluate the effect of CVC compared to placebo on liver histology at Month 60 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on steatohepatitis – (all subjects) • Evaluate the safety and tolerability of CVC for the treatment of liver fibrosis in adult subjects with NASH – (all subjects)

<table>
<tr>
<td>Study Design
Overall</td>
<td>This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of CVC for the treatment of Stage 2 or 3 liver fibrosis in adult subjects with NASH. The study will be conducted in 2 parts: Part 1 (surrogate endpoint) and Part 2 (clinical outcomes) as described below.
A Data and Safety Monitoring Board (DSMB) will be formed to review ongoing data from Part 1 and Part 2 of this study.
The study will be terminated when adjudicated events have been accrued in 367 unique subjects overall. All subjects who complete the study or are terminated from the study early due to an adjudicated clinical endpoint or due to any other reason, will have an End of Study visit at that time and will return to the clinic for a Follow-up visit 30 days after the last dose of study drug.
Subjects who permanently discontinue study drug, for any reason, before the planned end of study are encouraged to complete all subsequent study visits for assessment of clinical outcomes (at the discretion of the investigator, subjects who permanently discontinue study drug may be followed every 6 months unless otherwise specified by the protocol).
Subjects who undergo early termination from the study will return to the clinic within 48 hours for an early discontinuation visit and will return to the clinic for a Follow-up visit 30 days after the last dose of study drug.
Survival data will be collected for all study subjects at the end of the study.</td>
</tr>
<tr>
<td>Study Design
Part 1</td>
<td>Part 1 will assess the effect of CVC on the surrogate endpoint at Month 12 in approximately 1200 subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) as confirmed by an independent central pathologist. Subjects will be randomized 2:1 to receive CVC or placebo and will receive the same treatment for the duration of the study.

At Baseline (Day 1), eligible subjects will be assigned to the treatment arms using permuted block randomization and presence or absence of documented type 2 diabetes mellitus (T2DM) (yes or no). Eligible subjects will be randomized 2:1 to one of the following 2 treatment arms and will receive the same treatment for the duration of the study:
<table>
<tr><th>Arm</th><th>N</th><th>Treatment</th></tr>
<tr><td>A</td><td>800</td><td>CVC 150 mg, once daily</td></tr>
<tr><td>B</td><td>400</td><td>Placebo, once daily</td></tr>
</table>
All subjects will undergo safety assessments at the Baseline visit and at Months 1, 3, 6, 9, and 12.
The liver biopsy, used to evaluate the efficacy endpoints, must be performed within ± 2 weeks of the Month 12 visit (Visit 7).
Subjects who remain in Part 1 at Month 12 will continue to be evaluated</td>
</tr>
</table>

<table>
<tr><td></td><td>in Part 2 of the study and will continue the same treatment through the end of Part 2. Individual subject treatment assignments will not be revealed until the completion of Part 2 of the study.</td></tr>
<tr><td>Study Design
Part 2</td><td>Part 2 of the study will focus on assessing the effect of CVC on clinical outcomes in approximately 2000 subjects, including up to 1200 subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) previously randomized in Part 1 and an additional 800 adult subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis (by NASH CRN system) newly randomized 2:1 to receive CVC or placebo in Part 2.
Subjects who enter Part 2 from Part 1 of the study will have study visits every 3 months until Part 2 is completed. Study drug will be dispensed and adverse events (AEs), concomitant medications, and adherence to study drug will be reviewed at every visit (every 3 months). Safety laboratory assessments will be performed every 6 months through the end of the study.
At Baseline (Day 1), eligible subjects who newly enroll in Part 2 of the study will be assigned to the treatment arms using permuted block randomization, and presence or absence of documented T2DM (yes or no). Newly enrolled subjects will be randomized 2:1 to one of the following 2 treatment arms to achieve a total of approximately 2000 randomized subjects in the study (of which up to 1200 subjects will have been randomized in Part 1 and 800 in Part 2.
<table>
<tr><th>Arm</th><th>Newly Randomized Subjects <u>in Part 2</u>
N</th><th>Total Subjects (Randomized in Part 1 or Part 2)
N</th><th>Treatment</th></tr>
<tr><td>A</td><td>534</td><td>1334</td><td>CVC 150 mg, once daily</td></tr>
<tr><td>B</td><td>266</td><td>666</td><td>Placebo, once daily</td></tr>
</table>
Newly enrolled subjects in Part 2 will undergo safety laboratory assessments at Months 1, 6, and 12 and every 6 months thereafter through the end of the study. Beginning at Month 3, AEs, concomitant medications, and adherence will be reviewed every 3 months through the end of the study.
Newly enrolled subjects in Part 2 will undergo a liver biopsy at Screening for assessment of eligibility and a further liver biopsy at Month 12 (within ± 2 weeks).
Newly enrolled subjects will undergo a liver biopsy at Screening for assessment of eligibility and performed at Month 12 visit (within ± 2 weeks). All subjects (newly randomized subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis [by NASH CRN system] and those who continue from Part 1) will undergo a liver biopsy at</td></tr>
</table>

	Month 60 (within ± 2 weeks) after the first dose of study drug.
Treatment Duration	Estimated to be 60 months for subjects participating in the study. Actual treatment duration will vary depending on the time to accrue adjudicated events in 367 unique subjects in the CVC and placebo arms combined.
Number of Subjects	Part 1: Approximately 1200 subjects will be included in Part 1: • Treatment Arm A (CVC 150 mg, once daily): approximately 800 subjects or • Treatment Arm B (placebo, once daily): approximately 400 subjects). Subjects who remain in Part 1 at Month 12 will continue to be evaluated in Part 2 of the study and will continue the same treatment through the end of Part 2. Part 2: Approximately 2000 subjects will be included in Part 2,, including up to1200 from Part 1 and approximately 800 newly randomized in Part 2. Approximately 60% or more of subjects with Stage 3 fibrosis will be enrolled in the study overall. • Treatment Arm A (CVC 150 mg, once daily): approximately 1334 subjects of which approximately 534 are newly enrolled • Treatment Arm B (placebo, once daily): approximately 666 subjects of which approximately 266 subjects are newly enrolled
Number of Study Centers	A total of 2000 subjects will be enrolled in the study at up to 600 centers in North, Central, and South America; Europe; and Asia Pacific region. It is expected that at least 30% of subjects will be randomized in the United States (US). ~~and at least 30% of subjects will be randomized in the EU.~~
Target Population	Part 1: Adult subjects with liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) –Part 2: Subjects newly enrolled and randomized in Part 2 will include adult subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis (by NASH CRN system).
Inclusion Criteria	1. Male and female subjects aged between 18-75 years 2. Ability to understand and sign a written informed consent form (ICF) 3. Histological evidence of NASH based on central reading of the Screening liver biopsy [redacted]

	iv. Subjects must have been metabolically stable since the biopsy (no significant weight loss [≥ 7% of body weight], no major deterioration of glycemic control, and no introduction of new or investigational drugs for the treatment of T2DM) 4. Subjects included in Part1 must have histopathological evidence of Stage 2 or 3 liver fibrosis per the NASH CRN System based on central reading of the Screening biopsy slides. Subjects newly randomized in Part 2 must have histological evidence of Stage 3 liver fibrosis per the NASH CRN System, based on central reading of the Screening period biopsy slides. Historical biopsy can be used, provided the criteria listed on Item 3a above are fulfilled. **5**. Females of childbearing potential and males participating in the study must agree to use at least 2 approved methods of contraception throughout the duration of the study and for 30 days after stopping study drug. Females who are postmenopausal must have documentation of cessation of menses for ≥ 12 months without an alternative medical cause. Follicle-stimulating hormone (FSH) level in the postmenopausal range (≥ 30 mU/mL at Screening) [redacted]
Exclusion Criteria	1. Inability to undergo a liver biopsy safely 2. Hepatitis B surface antigen (HBsAg) positive 3. Hepatitis C antibody (HCVAb) positive [redacted] 4. Human immunodeficiency virus (HIV)-1 or HIV-2 infection 5. Prior or planned liver transplantation 6. Other known causes of chronic liver disease [redacted]

[redacted]

7. History or presence of cirrhosis (NASH CRN Fibrosis Stage 4) and/or hepatic decompensation including ascites, hepatic encephalopathy or variceal bleeding
8. Alcohol consumption greater than 21 units/week for males or 14 units/week for females [redacted]
9. Aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN) at Screening
10. Alanine aminotransferase (ALT) > 5 × ULN at Screening
11. Hemoglobin A1c (HbA1c) > 9% at Screening
12. Serum albumin < 3.5 g/dL at Screening
13. Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) equation at Screening
14. Platelet count < 100,000/mm^3 at Screening
15. Total bilirubin > 1.3 mg/dL (subjects with hyperbilirubinemia associated with documented Gilbert's syndrome may be eligible upon review by the medical monitor) at Screening
16. International normalized ratio (INR) > 1.3 at Screening
17. Model for end stage liver disease (MELD) score > 12
18. Weight reduction, defined as ≥ 7% of body weight, through bariatric surgery in the past 5 years or bariatric surgery planned during the conduct of the study (including gastric banding and sleeve surgery)
19. [redacted] history of malignancy within the past 5 years or ongoing malignancy other than: basal cell carcinoma, resected noninvasive cutaneous squamous cell carcinoma. [redacted]
20. Active, serious infections that require parenteral therapy (antibiotic or antifungal) within 30 days prior to Screening visit
21. Clinically significant cardiovascular or cerebrovascular disease within the past 3 months [redacted]

	22. Females who are pregnant or breastfeeding 23. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents and immune-modulating agents (such as interleukins and interferons) 24. Receiving a glucagon-like peptide 1 (GLP-1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium–glucose cotransporter 2 (SGLT2) and/or SGLT1 inhibitor, or a thiazolidinedione (TZD), for less than 6 months prior to the Screening period liver biopsy. Subjects on a stable therapy with a GLP-1 receptor agonist, DPP-4 inhibitor, SGLT1 and/or SGLT2 inhibitor, or a TZD for at least 6 months prior to the Screening liver biopsy may be considered eligible. (**Important Note:** if a historical biopsy is to be used, subjects need to be on stable therapy for at least 6 months **prior** to the day historical liver biopsy was performed).

[redacted]

Test Article	CVC 150-mg tablet
Dosage and Administration	CVC 150 mg administered orally once daily with food
Placebo	Matching placebo
Dosage and Administration	Matching placebo administered orally once daily with food

Study Procedures/ Frequency	During Part 1 and Part 2, a Screening visit is to occur within 3 months before the Baseline visit. In Part 2, the Screening visit will only be required for newly enrolled subjects. The Screening visit will not be required for subjects continuing their previously assigned blinded treatment from Part 1. As part of Screening, assessment of serum laboratory tests (hematology and chemistry panels), serum hepatic fibrosis indices including FIB-4, APRI, and NFS, and evaluation of liver stiffness via transient elastography (TE) or liver imaging (performed no more than 6 months prior to the first day of Screening at sites where available) will be performed to aid in identifying subjects with clinically significant liver fibrosis prior to proceeding with a new liver biopsy. A historical liver biopsy obtained no more than 6 months prior to the first day of Screening that meets protocol-required specifications will be evaluated for all subjects as part of Screening to confirm histologic evidence of NASH and Fibrosis Stages 2 or 3. Subjects meeting all other eligibility criteria and with suspicion of significant liver fibrosis (through clinical evaluation, hepatic fibrosis indices, and/or liver stiffness assessment [performed no more than 6 months prior to the first day of Screening]) will undergo a liver biopsy during the Screening period; randomized subjects will undergo, a second post-treatment liver biopsy at the Month 12 visit (± 2 weeks). Newly enrolled subjects will undergo a liver biopsy at Screening for assessment of eligibility and a second post-treatment liver biopsy will be collected within ± 2 weeks of the Month 12 visit. All subjects (newly randomized subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis [by NASH CRN system] and those who continue from Part 1) will undergo a liver biopsy at Month 60 (within ± 2 weeks) after the first dose of study drug. Fasting metabolic parameters will be measured at Baseline, at Months 3, 6, and 12 in Part 1 and at Baseline for newly randomized subjects and every 6 months through the end of study for all subjects. Samples for biomarkers of systemic inflammation will be collected at Baseline, at Months 3, 6, and 12 in Part 1, and at Baseline for newly randomized subjects in Part 2, and every 6 months through the end of the study for all subjects. At selected sites where available, non-invasive assessment of liver fibrosis by TE will be performed at Baseline (if not performed at Screening), at Months 6 and 12 in Part 1, and annually in Part 2. Pharmacokinetic samples for CVC will be collected at Months 3, 6, and 12 in Part 1. Weight, waist circumference, and hip circumference will be performed at Screening, Baseline, at Months 3, 6, and 12 in Part 1, and every 6 months in Part 2. Height will be performed at Screening. Physical examinations, vital signs, and laboratory analyses (serum chemistries and hematology) will be performed at Screening, Baseline, Months 1, 6 and 12 for subjects who are newly randomized in Part 2, and every 6 months thereafter through the end of the study for all

	subjects. Electrocardiograms (ECG) will be performed at Baseline and annually for all study subjects. Clinical outcomes, AEs, and concomitant medications will be assessed at each visit. An ultrasound exam to screen for HCC and presence of ascites will be performed at Month 60. [redacted]
Efficacy Evaluation **Part 1**	Primary Efficacy Endpoint (Part 1): • Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver histology at Month 12 relative to the Screening biopsy Key Secondary Efficacy Endpoint (Part 1): • Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver histology at Month 12 relative to the screening biopsy Secondary Efficacy Endpoints (Part 1): • Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis, at Month 12 relative to the Screening biopsy • Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on steatohepatitis, at Month 12 relative to the screening biopsy
Efficacy Evaluation **Part 2**	Primary Efficacy Endpoint (Part 2): • Time to first occurrence of any of the following adjudicated events (all subjects): o Death (all cause) o Histopathologic progression to cirrhosis (defined by NASH CRN Fibrosis Stage 4) o Liver transplant o MELD score ≥ 15 o Ascites (requiring intervention, ie, large volume paracentesis ≥ 1L or initiation of a diuretic)

	○ Hospitalization (as defined by a stay of ≥ 24 hours) for onset of: variceal bleed, hepatic encephalopathy (defined by a West Haven Stage of ≥ 2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis with positive ascitic fluid bacterial culture) Each component of this endpoint will be considered by the independent adjudication committee, and only events confirmed by the committee will be included in the primary analysis. If any of the above events occur in Part 1, they will be included in this primary efficacy endpoint for Part 2. Secondary Efficacy Endpoints (Part 2): • Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver biopsy at Month 12 relative to the Screening biopsy – (subjects newly randomized in Part 2) • Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis, on liver biopsy at Month 12 relative to the Screening biopsy – (subjects newly randomized in Part 2) • Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver biopsy at Month 12 relative to the screening biopsy – (subjects newly randomized in Part 2) • Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) regardless of effect on steatohepatitis on liver biopsy at Month 12 relative to the screening biopsy – (subjects newly randomized in Part 2) • Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver biopsy at Month 60 relative to the Screening biopsy – (all subjects) • Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis, on liver biopsy at Month 60 relative to the Screening biopsy – (all subjects) • Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver biopsy at Month 60 relative to the screening biopsy – (all subjects) • Proportion of subjects with improvement in fibrosis by at least

	2 stages (NASH CRN system), regardless of effect on steatohepatitis on liver biopsy at Month 60 relative to the screening biopsy – (all subjects)
Safety Evaluation	Safety endpoints (Part 1 and Part 2): • Clinically evident adverse events, including major adverse cardiovascular events (MACE) and new-onset T2DM • Clinical laboratory tests (hematology, chemistry, and fasting metabolic parameters) • Physical examination • Vital signs • 12 lead ECG
Pharmacokinetic Evaluation **Part 1**	• Characterization of the population PK of CVC and possible metabolites in subjects with NASH • Evaluation of covariates that impact the PK of CVC and possible metabolites (age, sex, weight, race, ethnicity, fibrosis stage, etc.)
[redacted]	
Statistical Analysis	
Analysis Sets	**Intent-to-treat (ITT) analysis set:** All subjects randomly assigned to a treatment group will be included in ITT analysis set. Subjects will be included with the randomly assigned treatment, if they receive treatment other than that to which they are randomly assigned. This will be a supportive analysis set for selected efficacy analyses. Subjects with

	missing Screening biopsy data should not be randomized in the study, hence will not be included in the ITT analysis set, should such subjects exist. **Modified intent-to-treat (mITT) analysis set:** All subjects in the ITT analysis set who receive at least one dose of study drug will be included in the mITT analysis set. Subjects will be included with the randomly assigned treatment, if they receive treatment other than that to which they are randomly assigned. This will be the primary analysis set for the efficacy analyses. **Month 12 per protocol (PP1) analysis set:** All subjects randomly assigned to a treatment group who have an evaluable biopsy at Screening and another after at least 6 months but before 15 months of follow-up, receive at least 6 months of assigned study drug and have no significant protocol deviations that potentially influence the primary efficacy assessment will be included in the PP1 analysis set. This will be a supportive analysis set for selected efficacy analyses of Part 1 and Part 2. **Month 60 per protocol (PP2) analysis set:** All subjects randomly assigned to a treatment group who have an evaluable biopsy at Screening, have no significant protocol deviations that potentially influence the primary efficacy assessment, and either: • Have an adjudicated event that is a component of the primary composite endpoint within 24 months after randomization **OR** • Have at least 24 months of follow-up for clinical events **AND** one of the following: o Have an adjudicated event that is a component of the primary composite endpoint within 6 months of last intake of study drug **OR** o Have a biopsy at least 24 months after randomization and within 6 months of last intake of study drug. This will be a supportive analysis set for selected efficacy analyses of Part 2. **Safety analysis set:** All subjects randomly assigned to a treatment group who receive at least one dose of study drug will be included in the safety analysis set. Subjects will be included with the treatment group according to treatment actually received, if they receive treatment other than that to which they are randomly assigned. Subjects who inadvertently receive both treatments will be included with the CVC group. This will be the primary analysis set for the safety analyses. **Pharmacokinetic analysis set:** All subjects who are randomized and receive at least one dose of study drug and have at least one post-dose PK sample will be included in the PK analysis set.
Efficacy **Part 1**	The significance level of both 0.00125 (2-sided) and 0.05 (2-sided) will be applied to hypothesis testing in this study, with the former to

	manifest strong evidence from a single confirmatory study and the latter for study success. To manifest strong evidence from a single confirmatory study, the familywise type I error rate (between the surrogate endpoint and the clinical outcome endpoint) will be controlled at the 0.00125 level by initial assignment of 0.0012 to the surrogate endpoint and 0.00005 to the clinical outcome endpoint, and the clinical outcome endpoint will be tested at 0.00125 level if the test of surrogate endpoint is successful. The testing procedure will be the same for study success, except the familywise type I error rate will be controlled at the 0.05 level instead of 0.00125 level, in which an initial alpha level of 0.048 to the surrogate endpoint and of 0.002 to the clinical outcome endpoint will be allocated. The primary analysis of Part 1 will occur when approximately 1200 randomized subjects have been followed for at least 12 months. Subjects who will contribute to the primary analysis of Part 1 will be identified before unblinding of any subjects for Part 1 analysis. Individual subjects' treatment group assignments will not be disseminated to the sites until the end of Part 2 to allow for continued blinded assessment during Part 2. For the primary efficacy analysis in Part 1, using the mITT analysis set, any available liver biopsy after baseline will be used as the Month 12 biopsy, no matter when it was obtained relative to the first dose of study drug. Subjects who do not have an evaluable liver biopsy at both Screening and Month 12 will be included in the analyses as non-responders. Subjects with multiple liver biopsies will have the evaluable biopsy closest to the Month 12 visit included in the analysis. The proportion of subjects who meet the primary efficacy endpoint in Part 1, and each component, will be summarized by treatment group. Two-sided 95% confidence intervals (CI) for the proportion who meet the primary efficacy endpoint, calculated using Wilson's method for CI, will also be reported. Part 1 testing hierarchy includes 2 tests, one for the primary endpoint and the other for the key secondary endpoint. Within Part 1 testing, the key secondary endpoint is to be tested only when the primary endpoint result is significant. Analysis of the primary and the key secondary endpoints of Part 1 will use the Cochran-Mantel-Haenszel (CMH) test, stratified by randomization strata (fibrosis stage [2 vs 3] and presence or absence of T2DM at Baseline, for a total of 4 strata), to compare the rates in the 2 randomized treatment arms. Sensitivity analyses for the primary efficacy endpoint will also be performed. Subgroup analyses using the CMH test will be reported for selected subgroups. Analysis of other secondary efficacy endpoints of Part 1 will use similar methods to the primary endpoint analysis. Results for the mITT and PP1 analysis sets will be reported for secondary efficacy endpoints. Binary endpoints will be analyzed with the CMH procedure, stratified by randomization strata. Continuous endpoints will be analyzed with

	analysis of covariance, with randomization strata included as covariates. [redacted]
Efficacy **Part 2**	Part 2 of this study will include all subjects randomized to this study. The primary analysis for Part 2 will occur when adjudicated events have been accrued in 367 unique subjects overall (regardless of treatment assignment). Because many events may be observed from the Month 60 liver biopsy and given that all reported events will need to undergo independent adjudication prior to being included or excluded from the analysis, it is possible that more than or fewer than 367 events will be included in the analysis. All subjects and events in the database at the time of Part 2 database lock and unblinding, and only those events, will be included in the primary analysis of Part 2. If multiple events are observed in a single subject, only the first observed event will be used in the analysis. For the primary efficacy analysis in Part 2 using the mITT analysis set, any available liver biopsy after baseline will be used for assessment of components of the clinical endpoint that require a biopsy, no matter when obtained. Subjects who do not have an evaluable liver biopsy at both Screening and postbaseline will be included in the analyses as having an event only if they meet a component that does not require a biopsy; otherwise they will be included as not having an event and censored at the last visit. Subjects with multiple liver biopsies will be included as an event if any (one or more) biopsy meets the definition of the primary endpoint, as determined by the adjudication committee. The proportion of subjects who meet the primary efficacy endpoint in Part 2, and each component, will be summarized by treatment group. Two-sided 95% CIs for the proportion who meet the primary efficacy endpoint, calculated using Wilson's method for CI, will also be reported. Additionally, Kaplan-Meier product-limit estimates will be presented as graphs to show the event rates over time and a table will present Kaplan-Meier estimates for the probability of an event at specific time intervals. Subjects will be censored for analysis at the last recorded study visit. Analysis of the primary endpoint of Part 2 will use the logrank test, stratified by randomization strata (fibrosis stage [2 vs 3] and presence or absence of T2DM at Baseline, for a total of 4 strata), to compare the rates in the 2 randomized treatment arms. The p-value for the test of no difference between treatment arms (hazard ratio = 1) will be presented as well as the hazard ratio from a proportional hazards model (CVC divided by placebo) and corresponding 95% CI. Analysis of secondary efficacy endpoints of Part 2 will use similar methods to the primary endpoint analysis in Part 2. The primary endpoint in Part 1, improvement in fibrosis by at least one stage and no worsening of steatohepatitis at Month 12, will be reported for subjects not in the Part 1 analysis (subjects newly randomized in Part 2), and for all subjects in the study (Month 12 results from Part 1 and Part 2 combined). Results for the mITT and PP2 analysis sets will be reported

	for the secondary endpoints in Part 2. Binary endpoints will be analyzed with the CMH procedure, stratified by randomization strata. Continuous endpoints will be analyzed with analysis of covariance, with randomization strata included as covariates. Time to event endpoints will be analyzed with the stratified logrank test, stratified by randomization strata. [redacted]
Safety	No statistical hypotheses are pre-specified for safety endpoints. Analyses will be primarily descriptive, with any p-values post-hoc and any comparative conclusions requiring confirmation. Any event reported on the electronic case report form (eCRF) that occurs or worsens on or after the initiation of study drug and through 30 days after the last intake of study drug is defined as treatment-emergent. Any event reported on the eCRF that occurs or worsens after last intake of study drug + 30 days is defined as subsequent. AEs will be categorized by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system-organ classification. The occurrence of treatment-emergent adverse events (TEAEs) will be summarized by treatment group for the safety analysis set using MedDRA preferred terms, system organ classifications, and severity. All AEs (including nontreatment-emergent events) recorded on the eCRF will be listed for individual subjects showing both verbatim and preferred terms. The number of subjects with at least one TEAE, at least one severe TEAE, at least one serious TEAE, at least one TEAE judged by the investigator to be related to study drug, and with a TEAE leading to death will be summarized by treatment group. Summaries of TEAEs will also be presented by subgroups of age, sex, race, and ethnicity. Descriptive summaries of clinical laboratory results will be presented by study visit. Laboratory abnormalities will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by treatment group and severity grade. Change from baseline in laboratory tests will be summarized for each treatment group. Any abnormal findings in the physical examination or vital signs that are considered clinically significant in the opinion of the investigator will be recorded as AEs or be captured as medical history, if already present at Screening. Descriptive summaries of vital signs will be presented by study visit. Descriptive summaries of quantitative changes in vital signs will be presented by treatment group and study visit. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria. Subjects exhibiting Grade 3 or 4 PR or QT interval corrected for heart rate (QTc) interval will be summarized. Abnormalities in Fridericia's corrected QT interval (QTcF) interval, Bazett's corrected QT interval (QTcB) interval, QRS, PR, and heart rate (HR) will be will be summarized.

	Prior, concomitant, and subsequent (taken more than 30 days after permanent discontinuation of study drug) medications will be mapped to a World Health Organization (WHO) preferred term and drug classification. The number and percent of subjects taking prior, concomitant, and subsequent medications will be summarized by treatment group using preferred terms and drug classifications.
Pharmacokinetics	A population PK analysis of CVC will be performed by using pre-dose and post-dose PK samples collected at steady state throughout Part 1 of the study. Population PK modeling of measured plasma CVC concentrations will be conducted using nonlinear mixed effects modeling. An analysis of subject covariates will be conducted.
[redacted]	
Sample Size **Part 1**	The sample size for the primary endpoint of Part 1 is based on the primary binary endpoint at the end of Month 12 comparing treatment with CVC versus placebo. The planned sample size of 1200 subjects (800 in treatment Arm A and 400 in treatment Arm B) for Part 1 of this study is expected to provide 84% power to demonstrate strong evidence with a single study (2-sided alpha level of 0.0012), assuming a 15% response rate for the placebo arm and a 25% response rate for CVC according to the results from the Phase 2b Study 652-2-203 (CENTAUR). The planned 800 subjects in treatment Arm A and 400 subjects in treatment Arm B is expected to provide 97% power to demonstrate strong evidence with a single study (2-sided alpha level of 0.0012) in the key secondary endpoint, assuming a 2.2% response rate for the placebo arm and an 8.6% response rate for CVC according to the results from the Phase 2b Study 652-2-203 (CENTAUR). PASS 8.0 was used to calculate the sample size. These response rates reflect the primary analysis, in which subjects missing the post-baseline liver biopsy will be included as non-responders. The anticipated proportion of subjects with missing Month 12 liver biopsies, as a result of either premature subject discontinuation or non-evaluable liver biopsy results (ie, biopsy sample deemed inadequate for evaluation of efficacy endpoints by an independent central pathologist), is estimated to be 15% of subjects at Month 12, compared to approximately 13% of missing post-treatment liver biopsies in the Phase 2b study.

Sample Size **Part 2**	The sample size for the primary endpoint analysis in Part 2 is based on the estimated event-free survival rate of 80% for the placebo group and detection of a hazard ratio of 0.62 by the anticipated end of the study at Month 60 (corresponding to a median event-free survival time of approximately 15 years for placebo and 25 years for CVC). A total of 2000 subjects (2:1 randomization ratio between CVC and placebo) enrolled approximately uniformly over 2 years for an overall study duration of approximately 8 years (2 years of accrual period plus 5 to 6 years of follow-up) will lead to about 367 events, after accounting for an overall dropout rate of 20%. With these events, there will be 85% power to demonstrate strong evidence of superiority of CVC over placebo (at a 2-sided 0.00125 significance level, for a single registration study), and 99% power to test the superiority of CVC over placebo (at the 2-sided test 0.05 significance level for a registration study). EAST 6.4 was used for the calculation.

5. INTRODUCTION

Cenicriviroc mesylate (CVC) is a novel, once-daily, orally active and potent inhibitor of ligand binding to C-C chemokine receptor (CCR) type 2 (CCR2) and type 5 (CCR5), currently in clinical development for the treatment of liver fibrosis in adult subjects with nonalcoholic steatohepatitis (NASH).

5.1. Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) is a common, often "silent", liver disease associated with obesity related disorders, such as type-2 diabetes mellitus (T2DM) and the metabolic syndrome, occurring in people who consume little or no alcohol and is characterized by the accumulation of fat in the liver with no other apparent causes.[1-11] At the beginning of the NAFLD spectrum is simple or bland steatosis, which is characterized by a build-up of fat within the liver. Liver steatosis without inflammation is usually described as benign or non-progressive. NASH is usually described as a severe form of NAFLD where steatosis is complicated by liver-cell injury and inflammation, with or without fibrosis. The rising prevalence of obesity-related disorders has contributed to a rapid increase in the prevalence of NASH. Approximately 10% to 20% of subjects with NAFLD will progress to NASH.[12] Due to the growing epidemic of obesity and diabetes worldwide, NASH is projected to become the most common cause of advanced liver disease and the most common indication for liver transplantation.[13-16] The burden of NASH, combined with a lack of any approved therapeutic interventions, represents an unmet medical need.

5.2. CVC Mechanism of Action

In vitro data with CVC have demonstrated that it blocks the binding of C-C motif chemokine ligand 2 (CCL)2 (also known as monocyte chemotactic protein 1 [MCP-1]) to CCR2, and also blocks the binding of CCR5 ligands, CCL3 (also known as macrophage inflammatory protein [MIP]-1α), CCL4 (also known as MIP-1β) and CCL5 (also known as regulated on activation normal T-cell expressed and secreted [RANTES]), to CCR5. Ex vivo experiments showed that nanomolar concentrations of CVC achieved 98% receptor occupancy of CCR2 on human monocytes and ~90% receptor occupancy for CCR5 on human CD4+ and CD8+ T-cells. Additionally, CVC was an efficient inhibitor of monocyte and human lymphocyte (primarily T-cells) migration in vitro.

The mechanism of action of CVC, as an anti-inflammatory and anti-fibrotic agent, supports its use in liver diseases, such as liver fibrosis associated with NASH. CVC treatment decreases the recruitment and migration of CCR2-expressing monocytes to the site of liver injury, mainly via CCR2 antagonism, thereby reducing the infiltration of pro-inflammatory, monocyte-derived macrophages into the liver.[17,18] In addition, CCR5 antagonism by CVC is expected to impair the migration, activation and proliferation of collagen−producing activated hepatic stellate cells and myofibroblasts, therefore reducing fibrogenesis.[19,20]

5.3. Clinical Studies with CVC

Overall, as of January 2019, approximately 1579 subjects have been exposed to CVC in completed and ongoing clinical studies (January 2018 Development Safety Update Report [DSUR] cutoff).

5.3.1. Phase 1 Pharmacokinetic Studies in Healthy Subjects

Initial human pharmacokinetic (PK) data for CVC was obtained in 2003 when the molecule was being developed by Takeda Pharmaceutical. The first 2 Phase 1 studies of CVC (Study 2080/16 [RCP-001] and Study 001 [01-03-TL-652-001]) established CVC's bioavailability in humans and demonstrated that CVC was not excreted in urine, that plasma drug exposure was nearly dose proportional up to single doses of 400 mg, and that M-II and M-I were the major and minor metabolites, respectively, in humans. More importantly, the studies established rapid attainment of clinically significant drug levels, with a time to maximum plasma concentration (t_{max}) of 3 to 6 hours, and the possibility of once-daily dosing with a half-life ($t_{1/2}$) of 34 to 42 hours.

Tobira conducted its first clinical study with CVC tablet formulation at doses up to 800 mg in 2008 (Study 652-1-101) and confirmed that CVC was readily absorbed with median t_{max} occurring about 3 to 6 hours post-dose across the dose levels. CVC was eliminated from plasma with a mean $t_{1/2}$ of approximately 30 to 40 hours across the wide dose range studied, suggesting linear elimination kinetics. Evaluation of single oral dose administration of the Phase 3 formulation of CVC 150 mg in Study 3152-101-002 suggested that food increases exposure of CVC by 5.2-fold with a mean $t_{1/2}$ of approximately 40 hours.

CVC was well tolerated in all of the single-dose studies, with no clinically important findings with respect to vital signs, electrocardiogram (ECG) findings, physical examinations, or laboratory tests for any subject. A few subjects had mild, usually isolated elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) while on CVC.

Study 102 (652-1-102) was the first multiple-dose study in humans. This randomized, double-blind, placebo-controlled, multiple-dose study was conducted in cohorts of 12 healthy adult male and female subjects. In Part 2 of Study 102, CVC at doses of 25 to 200 mg once daily was readily and well absorbed following single (Day 1) or repeated (Day 10) doses with a high-fat meal, achieving peak plasma concentrations about 3 to 6 hours post-dose. The mean $t_{1/2}$ of CVC following repeated doses was similar to that after a single dose, averaging approximately 35 to 40 hours across dose regimens, indicating that the elimination kinetics of CVC were unchanged following repeated doses.

In Study 102, 2 subjects experienced adverse events (AEs) that resulted in discontinuation of study drug: Grade 4 AST/ALT in 1 subject, and a Grade 2 AST elevation and an elevated lactate dehydrogenase (LDH) in the other subject.

The safety, tolerability, and PK of the Phase 3 formulation following once daily escalating doses of CVC (450 and 900 mg) and combination with a single dose of 100 mg ritonavir

were evaluated in Study 3152-107-002. Steady state levels of CVC, M-1, and M-II metabolites were achieved with once daily dosing of 450 or 900 mg CVC with a high-fat meal for 7 days. Comparison of PK parameters suggested dose-proportional increase in C_{max} and $AUC_{0-\tau}$ of CVC and M-1 metabolite, while M-II exposure increased less than proportionally. Coadministration of CVC with a single dose of 100 mg ritonavir resulted in increased CVC C_{max} and $AUC_{0-\tau}$ by 33.5% and 20.4%, respectively. Overall, multiple-dose administration of 450 and 900 mg CVC with a high-fat meal and coadministration with single dose of ritonavir 100 mg was safe and well tolerated.

The PK, safety, and tolerability of CVC were assessed in several drug-drug interaction studies. In clinical studies, potent cytochrome P450 (CYP)3A4 inhibitors such as ritonavir, darunavir/ritonavir combination, and atazanavir/ritonavir combination increased the exposure of CVC by 3.55-fold, 3.13-fold, and 3.89-fold, respectively. The exposure of midazolam, a substrate of CYP3A4, is increased by 1.84-fold when co-administered with 150 mg CVC. CVC increased the exposure of rosuvastatin (breast cancer resistance protein [BCRP] substrate) by 3.52-fold, atorvastatin and simvastatin (CYP3A4 substrates) by 1.37-fold and 2.48-fold, respectively. However, no significant increase in the exposure of digoxin (P-glycoprotein [P-gp] substrate) and caffeine (CYP1A2 substrate) was observed (Study 652-124).

Based on clinical data as well as in vitro drug interaction studies, potent CYP3A4 inhibitors could significantly increase CVC exposure. Since CYP2C8 is identified to contribute to metabolism of CVC, potent CYP2C8 inhibitors may increase exposure of CVC. CVC was identified as a P-gp substrate in vitro; however, based on currently available exposure-safety CVC data (Study 3152-107-002), co-administration of CVC with P-gp inhibitors is not expected to result in any clinically meaningful increase in CVC exposure. CVC can be co-administered with P-gp substrates such as digoxin. Caution is recommended while co-administering substrates of CYP3A4 with narrow therapeutic index (eg, midazolam). It is also recommended not to exceed the suggested maximum daily dose of rosuvastatin (BCRP substrate) and other statins (atorvastatin, lovastatin, pravastatin and simvastatin). The detailed list of disallowed medications and the list of medications that are allowed but with specific restrictions are provided in Appendix 20.4.

5.3.2. Phase 1 Pharmacokinetic Study in Subjects with Hepatic Impairment

A Phase 1 open-label study (Study 121 [652-1-121]) in subjects with differing levels of hepatic impairment was conducted. This study was designed to evaluate the PK, safety, and tolerability of CVC in subjects with mild and moderate hepatic impairment (Child Pugh class A and B) compared to subjects with normal hepatic function. CVC exposures were not increased in subjects with mild hepatic impairment relative to matched healthy control subjects. CVC exposures were increased in subjects with moderate hepatic impairment relative to matched healthy control subjects. On Day 14, subjects with moderate hepatic impairment had CVC exposures approximately 29% (maximum plasma concentration [C_{max}]) to 55% (area under the concentration-time curve up to the last measurable concentration [AUC_{0-tau}]) higher compared to healthy matched controls. In subjects with hepatic impairment, a longer half-life was observed compared to healthy control subjects with

normal hepatic function (Day 14, $t_{1/2}$ geometric mean: 37.6 hours [moderate] and 29.7 hours [mild] versus 22.4 hours [matched healthy controls, moderate] and 22.0 hours [matched healthy controls, mild]). Based on the magnitude of these observed differences in exposure in subjects with mild or moderate hepatic impairment, it is unlikely that a CVC dose adjustment will be required. In another study, the effect of severe hepatic impairment on PK of CVC and its metabolites was evaluated following single dose administration (Study 3152-102-002). While the C_{max} of CVC decreased by 26.39%, the AUC_{0-t} and $AUC_{0-\infty}$ increased by 39.67% and 77.75%, respectively.

In Study 121, CVC showed a favorable safety profile with few treatment-related AEs and with only 1 AE (mild vomiting; mild hepatic impairment subject) leading to treatment discontinuation. Two subjects (both with long-standing history of hepatitis C and liver cirrhosis) experienced Grade 3 (5.1 to 10.0 × upper limit of normal [ULN]) or Grade 4 (> 10.0 × ULN) elevations in liver transaminases during the study; however, these returned to their prior grade of abnormality, and both subjects completed the 14-day dosing period and all study visits with no further sequelae. Both of these subjects had bilirubin levels within normal limits.

5.3.3. Phase 2b Study in Subjects with NASH and Liver Fibrosis

The Phase 2b study (CENTAUR; Study 652-2-203) was a randomized, double-blind, placebo-controlled, multinational, 2-year study. The study was designed to determine the efficacy and safety of CVC for the treatment of NASH in adult subjects with liver fibrosis. The study population included subjects with a nonalcoholic fatty liver disease activity score (NAS) ≥ 4 and liver fibrosis Stage 1 to 3 based on the NASH Clinical Research Network (CRN) criteria who were at increased risk of disease progression due to the presence of T2DM, body mass index (BMI) > 25 kg/m^2 and meeting at least 1 of the criteria for metabolic syndrome, or bridging fibrosis (NASH CRN Stage 3) and/or definite NASH (NAS ≥ 5). Subjects were randomized in a 2:1:1 ratio to receive 1 of 3 treatments as follows:

- CVC 150 mg once daily for 2 years (Arm A; CVC/CVC group)
- Placebo once daily for 1 year followed by CVC 150 mg once daily for an additional 1 year (Arm B; placebo/CVC group)
- Placebo once daily for 2 years (Arm C; placebo/placebo group)

Fibrosis stage, NASH status, and NAS were assessed in serial liver biopsies read by an independent central pathologist at baseline, Year 1, and Year 2. The independent central pathologist remained blinded to individual subject treatment assignment throughout the conduct of the study.

A total of 289 subjects (intent-to-treat [ITT] population) were randomized into the CENTAUR study.[21] Overall, 39 of 289 subjects (13.5%) withdrew early during Year 1 (Treatment Period 1), with the most commonly reported reasons for early discontinuation during Year 1 being due to AEs and withdrawal of consent. A total of 250 subjects (86.5%) completed Year 1, and 242 subjects (83.7%) entered Year 2 (Treatment Period 2). During

Year 2, 16 subjects (5.5%) withdrew early, with the most commonly reported reason for early discontinuation during Year 2 being due to AEs, which were more commonly reported in the CVC/CVC group (3.4%, 5 subjects) compared with the placebo/CVC group (1.4%, 1 subject) and the placebo/placebo group (0 subjects).

Overall, 47.4% (137/289) of subjects were male and 52.6% (152/289) were female. Most subjects were white (86.5% [250/289]) and not Hispanic or Latino (82.4% [238/289]). The mean age at screening was 54.1 years. Except for documented evidence of T2DM, the treatment groups were well balanced with respect to demographics and baseline characteristics. A higher percentage of subjects in the CVC/CVC group (58.6%) and placebo/CVC group (52.8%) than in the placebo/placebo group (40.3%) had documented evidence of T2DM.

Results

Although the primary endpoint of the CENTAUR study was not met, this study demonstrated that treatment with CVC resulted in a clinically meaningful antifibrotic benefit in participants with NASH. Twice as many participants treated with CVC 150 mg once daily, compared with placebo, achieved the key secondary outcome of improvement in fibrosis by ≥ 1 stage and no worsening of steatohepatitis at Year 1.

The CENTAUR Year 2 analysis results confirm the antifibrotic effect of CVC observed at Year 1, as reflected in several analyses performed using 2 independent subgroups (ie, Year 1 placebo nonresponders subgroup, in the placebo/CVC group versus placebo/placebo group over Year 1 to Year 2; and pooled participants treated with CVC for 1 year in the CVC/CVC and placebo/CVC groups versus the placebo/placebo group). The antifibrotic benefit associated with CVC treatment compared with placebo was most evident in the following clinical endpoints:

- Improvement in fibrosis by ≥ 1 stage and no worsening of steatohepatitis at Year 1
- Improvement in fibrosis by ≥ 2 stages and no worsening of steatohepatitis, with greater treatment effects observed at Years 1 and 2
- Improvement in fibrosis by ≥ 1 stage regardless of effect on steatohepatitis

The majority of CVC-treated participants achieving at least a 1-stage improvement in fibrosis at Year 1 maintained the antifibrotic effect at Year 2. Furthermore, the greatest antifibrotic effect and durability of response was observed in NASH patients with advanced disease (eg, Stage 3 fibrosis at baseline).

Overall, the safety profile of CVC (150 mg QD) was comparable to that in participants treated with placebo and was well tolerated over 2 years. The types, severity, and frequency of TEAEs reported after 2 years of CVC treatment was consistent with those reported after 1 year of treatment. The overall incidence of TEAEs during the study was similar across the treatment groups (≥ 95.0% of participants in each group). No deaths occurred during the study. The frequency and types of TEAEs reported were comparable between treatment groups during Year 1 and Year 2. The incidence of treatment-emergent Grade 3 or 4 laboratory abnormalities during Year 2 was generally similar across the treatment groups. In

total, 3.3% (4/121) subjects in CVC/CVC group (Arm A), 3.3% (2/61) subjects in the placebo/CVC group (Arm B), and 3.3% (2/60) subjects in the placebo/placebo group (Arm C) met any protocol-defined biochemical criterion for suspected DILI. Hepatobiliary disorders during Treatment Period 2 were reported in 5/242 (2.1%) subjects overall. Of note, among the subjects who met the criteria for suspected DILI during Year 1, 2 hepatobiliary adverse events of "autoimmune hepatitis" were reported during Year 1 (1 subject in CVC Arm A group [Grade 3] and 1 subject in the Placebo Arm C [Grade 3]), and these subjects did not continue treatment during Year 2. One additional subject in the CVC group (Arm A) had a postbaseline liver biopsy "suggestive of autoimmune hepatitis or a drug hepatoxicity mimicking autoimmune hepatitis," which was performed in the context of treatment emergent Grade 3 elevations in liver transaminases.

In conclusion, CVC treatment over 2 years resulted in a clinically meaningful, durable antifibrotic benefit and was generally well tolerated. Given that severity of fibrosis stage has been shown to be the only histological feature independently associated with clinical outcomes over the long term, these results provide additional evidence of CVC as a safe and efficacious pharmacologic treatment for liver fibrosis in adults with NASH. For further details, please refer to the most current CVC Investigator Brochure.

Pharmacokinetics/Pharmacodynamics

Findings from the pharmacokinetic/pharmacodynamic (PK/PD) analyses of CENTAUR were consistent with those of previous studies, which served as the basis for selection of the CVC dose of 150 mg evaluated in this study:

- Increases in CCL2 levels and decreases in fibrinogen levels were both found to be related to increases in CVC drug exposures, although most participants had attained a level of exposure where no additional changes in the biomarker would be expected
- Neither exposures nor changes in CCL2 levels could be linked to improvement in fibrosis and no worsening of steatohepatitis.

Results from a drug interaction study (Study 652-123) have shown that administration of a proton pump inhibitor (PPI) 90 minutes prior to CVC, dosed at 150 mg, resulted in significantly decreased CVC concentrations. In the CENTAUR study, PPIs were allowed with specific dosing instructions (ie, dosing of PPIs at least 2 hours after CVC 150 mg daily dose) and were used in 44% of all subjects. Although fewer subjects achieved an EC_{min50} of 40 ng/mL when using PPIs (84.5%) compared to those who did not (94.3%), a similar proportion of subjects in both groups achieved the key efficacy endpoint of improvement in fibrosis by at least 1 stage and no worsening of steatohepatitis: 21.0% for PPI users versus 25.0% for nonusers, respectively (mITT). Therefore, the dose of 150 mg appears sufficient when managing co-administration of CVC with commonly used concomitant medications, such as PPIs.

Taken together, along with the lack of apparent exposure-response for efficacy in this study, the main findings from the PK/PD analyses further support that the CVC 150 mg dose was

able to maximize CCR2/CCR5 blockade in most subjects and support its evaluation in the Phase 3 program.

5.4. Study Rationale

The clinically important results from the Phase 2b CENTAUR study are robust and suggest that CVC treatment may be disease modifying in adult patients with liver fibrosis as a result of NASH. This is particularly relevant when considering the comprehensive and clinically evidence which demonstrates that liver fibrosis, regardless of other histological components of steatohepatitis, is the only histologic feature independently associated with all-cause mortality and liver-related outcomes in patients with NAFLD.[22] Cenicriviroc appears to be safe with no notable differences observed in previous clinical studies in incidence of treatment-emergent AEs and laboratory abnormalities, including liver transaminase elevations, which were generally similar between treatment groups.

The AURORA study (Protocol 3152-301-002) will be conducted to confirm the efficacy and safety of CVC for the treatment of liver fibrosis in adult subjects with NASH.

The study will be conducted in 2 parts:

- Part 1: Evaluate the surrogate endpoint of improvement in fibrosis of at least 1 stage (nonalcoholic steatohepatitis clinical research network [NASH CRN]) and no worsening of steatohepatitis at Month 12 in subjects with Stage 2 and 3 liver fibrosis.
- Part 2: Determine the long-term clinical outcomes composed of histopathologic progression to cirrhosis (defined by NASH CRN Fibrosis Stage 4), liver-related clinical outcomes, and all-cause mortality in subjects from Part 1 who have continued into Part 2 and additional newly randomized subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis enrolled in Part 2.

5.5. Dose Rationale

A dose of CVC 150 mg will be evaluated for the treatment of liver fibrosis in adult subjects with NASH in the Phase 3 development program.

This dose was evaluated in the CENTAUR study (652-2-203) and selected based on the clinical activity, PK, pharmacodynamics (PD), and safety data from prior studies (652-1-110, 652-1-111, 652-120, 652-1-121, 652-1-122, 652-123, 652-124, 652-2-202, and 652-2-201), which together support:

- Evidence of meaningful clinical efficacy of CVC 150 mg in subjects with NASH and liver fibrosis in the CENTAUR study (Study 652-2-203)

- Evidence that CVC 150 mg is safe and well tolerated subjects with NASH and liver fibrosis in the CENTAUR study (Study 652-2-203)

- CVC dose of 150 mg provides an expectation of effective primary pharmacology (ie, CCR2 and CCR5 antagonism)

- Evidence of improvement in systemic inflammation biomarkers support underlying CVC pharmacology

6. STUDY OBJECTIVES

6.1. Part 1

Primary Objective (Part 1):

- Demonstrate the superiority of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy in adult subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) as confirmed by an independent central pathologist, by assessing the following composite primary endpoint:
    - Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade)

Key Secondary Objective (Part 1):

- Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis of at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade)

Secondary Objectives (Part 1):

- Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis
- Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on steatohepatitis
- Evaluate the safety and tolerability of CVC for the treatment of liver fibrosis in adult subjects with NASH

6.2. Part 2

Primary Objective (Part 2):

- Demonstrate the superiority of CVC compared to placebo on the composite endpoint of histopathologic progression to cirrhosis (defined by NASH CRN Fibrosis Stage 4), liver-related clinical outcomes, and all-cause mortality, as measured by the time to first occurrence of any of the listed adjudicated events (clinical outcomes composite endpoint) – (all subjects)

Secondary Objectives (Part 2):

- Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) – (subjects newly randomized in Part 2)

- Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis – (subjects newly randomized in Part 2)

- Evaluate the effect of CVC compared to placebo on liver histology at Month 60 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) – (all subjects)

- Evaluate the effect of CVC compared to placebo on liver histology at Month 60 relative to the Screening biopsy for the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis – (all subjects)

- Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) – (for subjects newly randomized in Part 2)

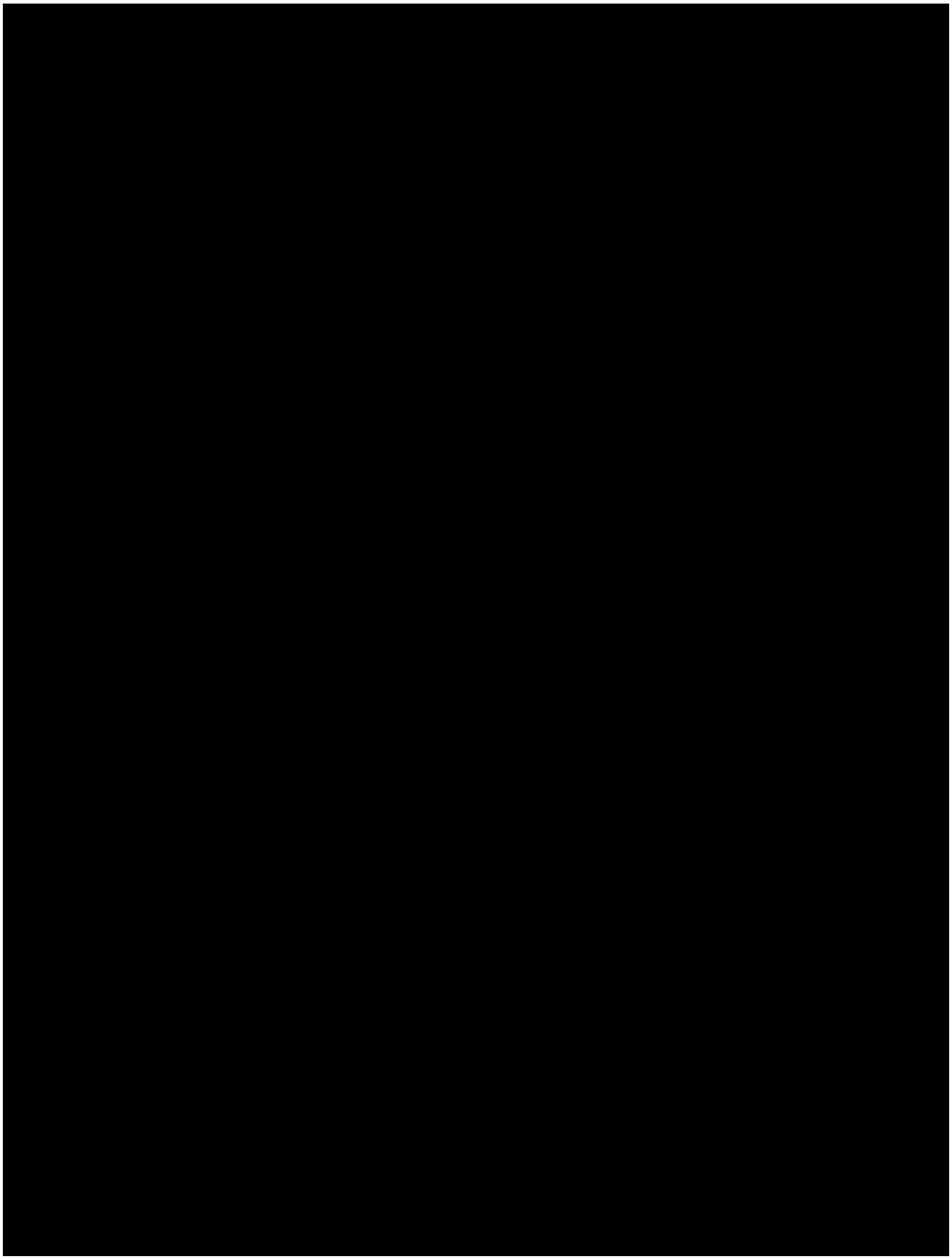
- Evaluate the effect of CVC compared to placebo on liver histology at Month 12 relative to the screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) regardless of effect on steatohepatitis – (for subjects newly randomized in Part 2)

- Evaluate the effect of CVC compared to placebo on liver histology at Month 60 relative to the screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) – (all subjects)

- Evaluate the effect of CVC compared to placebo on liver histology at Month 60 relative to the screening biopsy for the proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on steatohepatitis – (all subjects)

- Evaluate the safety and tolerability of CVC for the treatment of liver fibrosis in adult subjects with NASH – (all subjects)

[redacted]



7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of CVC for the treatment of Stage 2 or 3 liver fibrosis in adult subjects with NASH. The study will be conducted in 2 parts: Part 1 (surrogate endpoint) and Part 2 (clinical outcomes).

Part 1 will assess the effect of CVC on the surrogate endpoint at Month 12 (Section 7.1.1) in approximately 1200 subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) as confirmed by an independent central pathologist. Subjects will be randomized 2:1 to receive CVC or placebo and will receive the same treatment for the duration of the study.

Part 2 of the study will focus on assessing the effect of CVC on clinical outcomes in approximately 2000 subjects, including up to 1200 subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) previously randomized in Part 1 and an additional 800 adult subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis (by NASH CRN system) newly randomized 2:1 to receive CVC or placebo in Part 2 (Section 7.1.2).

A Data and Safety Monitoring board (DSMB) will be formed to review ongoing data from Part 1 and Part 2 of this study.

The study will be terminated when adjudicated events have been accrued in 367 unique subjects overall. All subjects who complete the study or are terminated from the study early due to an adjudicated clinical endpoint or due to any other reason, will have an End of Study visit at that time and will return to the clinic for a Follow-up visit 30 days after the last dose of study drug.

Subjects who permanently discontinue study drug, for any reason, before the planned end of study, are encouraged to keep participation in the study and complete all subsequent study visits (without treatment) for assessment of clinical outcomes (at the discretion of the investigator, subjects who permanently discontinue study drug may be followed every 6 months unless otherwise specified by the protocol).

Subjects who undergo early termination from the study drug will return to the clinic within 48 hours for an Early Discontinuation visit and will return to the clinic for a Follow-up visit 30 days after the last dose of study drug.

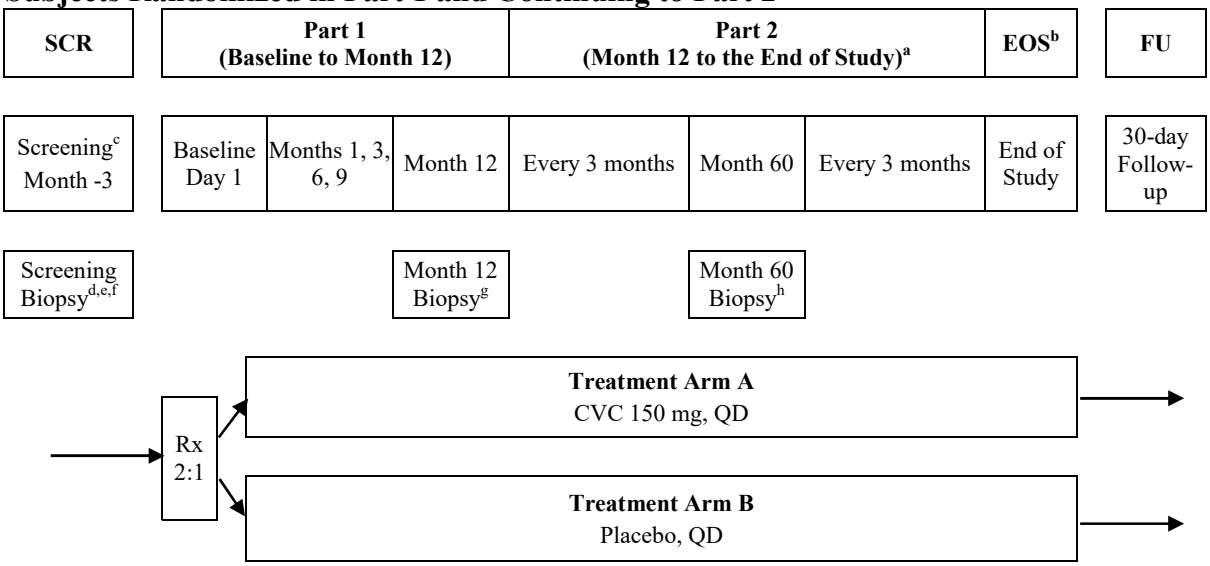
Survival data will be collected for all study subjects at the end of the study.

Subjects who progress to cirrhosis or reach a liver-related clinical outcome, which must be adjudicated by an independent adjudication committee, will complete the study and return to the clinic for a Follow-up visit 30 days after the last dose of study drug (Visit 98). After completion of the Follow-up visit (Visit 98), these subjects will become eligible for open-label access to CVC in a separate study (Clinical Study Protocol 3152-201-002).

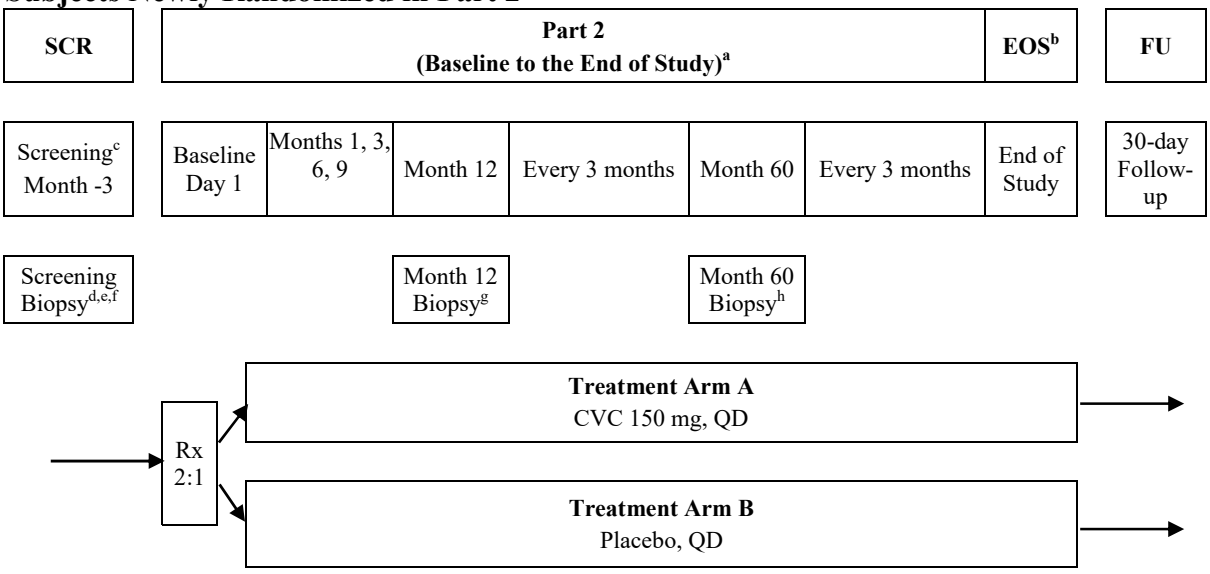
The study design is illustrated in Figure 1 and described briefly in Section 7.1.1 (Part 1) and Section 7.1.2 (Part 2). Study procedures are summarized across all study visits within the Schedule of Assessments for Part 1 (Table 20–1) and Part 2 (Table 20–2). Except for the End of Treatment and Follow-up visits, all subsequent visits are based on the Baseline visit date.

Figure 1 Study Design Schematic

Subjects Randomized in Part 1 and Continuing to Part 2



Subjects Newly Randomized in Part 2



AE = adverse event; CVC = cenicriviroc mesylate; EOS = End of Study; FU = Follow-up; QD = once daily; Rx = randomization; SCR = Screening

a The duration of treatment is estimated to be 60 months for subjects participating in the study. Actual treatment duration will vary depending on the time to accrue adjudicated events in 367 unique subjects in the CVC and placebo arms combined.

b The study will be terminated when adjudicated events have been accrued in 367 unique subjects overall. All subjects will have an End of Study visit at that time and will return to the clinic for a Follow-up visit 30 days after the last dose of study drug.

c Subjects who do not meet any of the laboratory eligibility criteria during the Screening period will be allowed to retest twice, with at least 1-week interval between the date of the first failed test and the date of subsequent test. However, if a subject fails to meet eligibility criteria upon these 2 retest opportunities, he or she will remain ineligible for the study. Subjects who continue from Part 1 to Part 2 will not require a Screening visit in Part 2.

d Screening laboratory tests, Screening serum hepatic fibrosis indices and evaluation of liver stiffness performed no more than 6 months prior to the first day of Screening will aid in identifying subjects with clinically significant liver fibrosis prior to proceeding with a new liver biopsy.

e A historical biopsy, obtained no more than 6 months prior to the first day of Screening, may be used if the criteria detailed in inclusion criterion 3a (Section 8.2) are met.

f Screening biopsy result is required before Baseline visit can be conducted and before subject can be randomized.

g The Month 12 biopsy will be collected within ± 2 weeks of the Month 12 visit.

h The Month 60 biopsy will be collected within ± 2 weeks of the Month 60 visit.

7.1.1. Part 1

Part 1 of the study will include approximately 1200 adult subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system).

In Part 1, eligible subjects will be randomized 2:1 to receive CVC or placebo, once daily for 12 months in order to assess the effect of CVC on the surrogate endpoint at Month 12.

At Baseline (Day 1), eligible subjects will be assigned to the treatment arms using permuted block randomization stratified by NASH CRN Fibrosis stage (2 or 3) and presence or absence of documented T2DM (yes or no). Eligible subjects will be randomized 2:1 to one of the following 2 treatment arms and will receive the same treatment for the duration of the study:

Table 7–1 Treatment Arms: Part 1

Arm	N	Treatment
A	800	CVC 150 mg, once daily
B	400	Placebo, once daily

CVC and placebo will be administered as double-blinded study drug. Study drug (CVC or placebo) must be taken once daily with food.

All subjects will undergo safety assessments at the Baseline visit and Months 1, 3, 6, 9, and 12.

The liver biopsy, used to evaluate the efficacy endpoints, must be performed within ± 2 weeks of the Month 12 visit (Visit 7).

Subjects who permanently discontinue study drug before planned end of study are encouraged to complete all subsequent study visits and participate (without treatment) in Part 2 of the study for assessment of clinical outcomes (at the discretion of the investigator,

subjects who permanently discontinue study drug may be followed every 6 months unless otherwise specified by the protocol). Subjects who undergo early termination from the study will return to the clinic within 48 hours for an Early Discontinuation visit and will return to the clinic for a Follow-up visit 30 days after the last dose of study drug.

Survival data will be collected for all study subjects at the end of the study.

Subjects who progress to cirrhosis or reach a liver-related clinical outcome, which must be adjudicated by an independent adjudication committee, will complete the study and return to the clinic for a Follow-up visit 30 days after the last dose of study drug (Visit 98). After completion of the Follow-up visit (Visit 98), subjects will become eligible for open-label access to CVC in a separate study (Clinical Study Protocol 3152-201-002).

Key Assessments

During Part 1 of the study:

- A Screening visit is to occur within 3 months before the Baseline visit. The informed consent form for Study 3152-301-002 (Parts 1 and 2) and patient education materials about NASH, liver fibrosis, liver biopsy procedures, and study retention tools will be reviewed at the Screening visit.

- As part of Screening, assessment of serum laboratory tests (hematology and chemistry panels), serum hepatic fibrosis indices (non-invasive hepatic fibrosis index score combining standard biochemical values, platelets, ALT, AST, and age [FIB-4]; AST to platelet count ratio index [APRI]; and NAFLD fibrosis score [NFS]) and evaluation of liver stiffness via transient elastography (TE) or liver imaging (performed no more than 6 months prior to the first day of Screening at sites where available) will aid in identifying subjects with clinically significant liver fibrosis prior to proceeding with a new liver biopsy.

- A historical liver biopsy, obtained no more than 6 months prior to the first day of Screening, that meets protocol-required specifications, or a new liver biopsy will be evaluated by an independent central pathologist for all subjects as part of Screening to confirm histologic evidence of NASH and fibrosis Stages 2 or 3.

- Subjects meeting all other eligibility criteria and with suspicion of significant liver fibrosis (through clinical evaluation, hepatic fibrosis indices, and/or liver stiffness assessment [performed no more than 6 months prior to the first day of Screening]) will undergo a new liver biopsy during the Screening period. In randomized subjects, a second post-treatment liver biopsy will be collected at the Month 12 visit (± 2 weeks).

- Fasting metabolic parameters, including lipid panel (triglycerides, total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], very low-density lipoprotein [VLDL]), glucose, insulin and hemoglobin A1c (HbA1c), will be measured at Baseline and at Months 3, 6, and 12.

- Samples for biomarkers of systemic inflammation, including interleukin (IL)-1β, IL-6, high-sensitivity C-reactive protein (hs-CRP), and fibrinogen will be collected at Baseline and at Months 3, 6, and 12.

- Samples of non-invasive serum hepatic fibrosis indices (FIB-4, APRI, NFS), ELF Score, and PRO-C3 will be collected at Months 6 and 12.

- At selected sites where available, non-invasive assessment of liver fibrosis by TE will be performed at Baseline (if not performed at Screening), and at Months 6 and 12.

- Pharmacokinetic samples for CVC will be collected at Months 3, 6, and 12 (pre-dose and at least 1-hour post-dose) (see Section 11.7)

- Weight, waist circumference, and hip circumference will be performed at Screening, Baseline and at Months 3, 6, and 12. Height will be performed at Screening.

- Physical examination, vital signs, and laboratory analyses (serum chemistry and hematology) will be performed at each visit. Serum immunoglobulin G (IgG), antinuclear antibody (ANA), anti-smooth muscle antibodies (SMA), anti-liver/kidney microsome type 1 (LKM1) and anti-liver cytosol type 1 (LC1) antibodies will be evaluated at Baseline. Electrocardiograms will be performed at Baseline and at Month 12.

- Adverse events and concomitant medications will be assessed at each visit.

[redacted]

7.1.2. Part 2

Part 2 of the study will focus on assessing the effect of CVC on clinical outcomes in approximately 2000 subjects, including up to 1200 subjects with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system) previously randomized in Part 1 and an additional 800 adult subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis (by NASH CRN system) newly randomized 2:1 to receive CVC or placebo in Part 2.

Subjects who remain in Part 1 at Month 12 will continue to be evaluated in Part 2 of the study and will continue the same treatment through the end of Part 2. Individual subject treatment assignments will not be revealed until the completion of Part 2 of the study.

Subjects who enter Part 2 from Part 1 of the study will have study visits every 3 months until Part 2 is completed. Study drug will be dispensed and AEs, concomitant medications, and adherence to study drug will be reviewed at every visit (every 3 months). Safety laboratory assessments will be performed every 6 months through the end of the study.

Subjects who are newly randomized in Part 2 of the study will complete the following visits: At Baseline (Day 1) eligible subjects will be randomized to treatment using permuted block randomization, and presence or absence of documented T2DM (yes or no). Newly enrolled subjects will be randomized 2:1 to one of the following 2 treatment arms to achieve a total of approximately 2000 randomized subjects in study (of which up to 1200 subjects will have been randomized in Part 1 and 800 in Part 2):

Table 7–2 Treatment Arms in Part 2

Arm	Randomized Subjects in Part 2 N	Total Subjects (Randomized in Part 1 or Part 2) N	Treatment
A	534	1334	CVC 150 mg, once daily
B	266	666	Placebo, once daily

Study drug will be administered as double-blinded treatment and must be taken once daily with food.

Newly enrolled subjects in Part 2 will undergo safety laboratory assessments at Months 1, 6, and 12 and every 6 months thereafter through the end of the study. Beginning at Month 3, AEs, concomitant medications, and adherence will be reviewed every 3 months through the end of the study.

Newly enrolled subjects will undergo a liver biopsy at Screening for assessment of eligibility and a second post-treatment liver biopsy will be collected within ± 2 weeks of the Month 12 visit. All subjects (newly randomized subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis [by NASH CRN system] and those who continue from Part 1) will undergo a liver biopsy at Month 60 (within ± 2 weeks) after the first dose of study drug.

Subjects who permanently discontinue study drug before planned end of study are encouraged to complete all subsequent study visits and participate (without treatment) in Part 2 of the study for assessment of clinical outcomes (at the discretion of the investigator, subjects who permanently discontinue study drug may be followed every 6 months unless otherwise specified by the protocol).

Subjects who undergo early termination from the study will return to the clinic within 48 hours for an Early Discontinuation visit and will return to the clinic for a Follow-up visit 30 days after the last dose of study drug.

Survival data will be collected for all study subjects at the end of the study.

Subjects who progress to cirrhosis or reach a liver-related clinical outcome, which must be adjudicated by an independent adjudication committee, will complete the study and return to the clinic for a Follow-up visit 30 days after the last dose of study drug (Visit 98). After completion of the Follow-up visit (Visit 98), these subjects will become eligible for open-label access to CVC in a separate study (Clinical Study Protocol 3152-201-002).

Key Assessments

During Part 2 of the study

- Screening will only be required for newly enrolled subjects and will not be required for subjects continuing their previously assigned blinded treatment from Part 1. A Screening visit is to occur within 3 months before the Baseline visit for any new subjects to be enrolled in Part 2. The informed consent and patient education materials about NASH, liver fibrosis, liver biopsy procedures, and study retention tools will be reviewed at the Screening visit for newly enrolled subjects.

- As part of Screening, assessment of serum laboratory tests (hematology and chemistry panels), serum hepatic fibrosis indices (including FIB-4, APRI, and NFS) and evaluation of liver stiffness via TE or liver imaging (performed no more than 6 months prior to the first day of Screening at sites where available) should be performed to aid in identifying subjects with clinically significant liver fibrosis prior to proceeding with a new liver biopsy.

- A historical liver biopsy, obtained no more than 6 months prior to the first day of Screening, that meets protocol-required specifications or a new liver biopsy will be evaluated for all subjects as part of Screening to confirm histologic evidence of NASH and fibrosis Stages 2 or 3.

- Subjects newly enrolled in Part 2 meeting all other eligibility criteria and with suspicion of significant liver fibrosis (through clinical evaluation, hepatic fibrosis indices, and/or liver stiffness assessment [performed no more than 6 months prior to the first day of Screening]) will undergo a new liver biopsy during the Screening period. Newly randomized subjects in Part 2 will undergo a further liver biopsy at Month 12 (within ± 2 weeks). A liver biopsy will be performed at the Month 60 visit (± 2 weeks) for all subjects.

- Fasting metabolic parameters, including lipid panel (triglycerides, total cholesterol, HDL, LDL, VLDL), glucose, insulin, and HbA1c, will be measured at Baseline for newly randomized subjects and every 6 months through the end of study for all subjects.

- Samples for biomarkers of systemic inflammation, including IL-1β, IL-6, hs-CRP, and fibrinogen, will be collected at Baseline for newly randomized subjects and every 6 months through the end of the study for all subjects.

- Samples for non-invasive serum hepatic fibrosis indices (FIB-4, APRI, NFS), Liver Stiffness, ELF Score, and PRO-C3 every 12 months for all subjects

- At selected sites where available, non-invasive assessment of liver fibrosis by TE will be performed at Baseline (if not performed at Screening) for newly randomized subjects and annually through the end of the study for all subjects.

- Weight, waist circumference, and hip circumference will be performed at Screening and Baseline for newly randomized subjects and every 6 months through the end of the study for all subjects. Height will be performed at Screening.

- Physical examinations, vital signs, and laboratory analyses (serum chemistries and hematology) will be performed at Screening, Baseline, Months 1, 6 and 12 for subjects who are newly randomized in Part 2, and every 6 months thereafter through the end of the study for all subjects. Serum IgG, ANA, anti-SMA, and anti LKM 1 and anti-LC1 antibodies will be evaluated at Baseline for subjects newly randomized in Part 2. Electrocardiograms will be performed at Baseline for newly randomized subjects and annually through the end of the study for all subjects.

- Clinical outcomes, AEs and concomitant medications will be assessed at each study visit.

- An ultrasound exam to screen for hepatocellular carcinoma (HCC) and presence of ascites will be performed at Month 60.

8. STUDY POPULATION

A total of 2000 subjects will be enrolled in the study at up to 600 centers in North, Central, and South America; Europe; and Asia Pacific region. It is expected that at least 30% of subjects will be randomized in the United States (US).

- Part 1: Adult subjects with liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system)
- Part 2: Subjects who remain in Part 1 at Month 12 will continue the same treatment through the end of Part 2. Subjects newly enrolled and randomized in Part 2 will include adult subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis (by NASH CRN system).

8.1. Number of Subjects

Part 1:

Part 1: Approximately 1200 subjects will be included in Part 1. They will be randomized 2:1 to the following treatment arms:

- Treatment Arm A (CVC 150 mg, once daily): approximately 800 subjects
- Treatment Arm B (placebo, once daily): approximately 400 subjects.

Subjects who remain in Part 1 at Month 12 will continue to be evaluated in Part 2 of the study and will continue the same treatment through the end of Part 2.

Part 2: Approximately 2000 subjects (including up to 1200 subjects who continue from Part 1 to Part 2) will be included in Part 2. Approximately 60% or more of subjects with Stage 3 fibrosis will be enrolled in the study overall.

- Treatment Arm A (CVC 150 mg, once daily): approximately 1334 subjects, of which approximately 534 are newly enrolled
- Treatment Arm B (placebo, once daily): approximately 666 subjects, of which approximately 266 subjects are newly enrolled

8.2. Inclusion Criteria: Part 1 and Part 2

For a subject to be eligible for participation in Part 1 or Part 2 of this study, *all* of the following criteria must apply.

1. Male and female subjects aged between 18 to 75 years

2. Ability to understand and sign a written informed consent form (ICF)

3. Histological evidence of NASH based on central reading of the Screening biopsy slides

    a. Historical biopsy may be substituted for Screening period biopsy to determine eligibility if the following are met:

        i. Historical biopsy was obtained no more than 6 months prior to the first day of screening

        ii. Hepatic tissue is available for central histologic evaluation

        iii. No new therapeutic intervention for NASH was made during the 6-month period (eg, obeticholic acid, vitamin E > 400 IU/day, pioglitazone, liraglutide, loss of ≥ 7% of body weight, bariatric surgery including gastric banding, investigational NASH agents)

        iv. Subjects must have been metabolically stable since the biopsy (no significant weight loss [≥ 7% of body weight], no major deterioration of

glycemic control, and no introduction of new or investigational drugs for the treatment of T2DM)

4. Subjects included in Part1 must have histopathological evidence of Stage 2 or 3 liver fibrosis per the NASH CRN System based on central reading of the Screening biopsy slides. Subjects newly randomized in Part 2 must have histological evidence of Stage 3 liver fibrosis per the NASH CRN System, based on central reading of the Screening period biopsy slides. Historical biopsy can be used, provided the criteria listed on Item 3a above are fulfilled.

5. Females of childbearing potential and males participating in the study must agree to use at least 2 approved methods of contraception throughout the duration of the study and for 30 days after stopping study drug. Females who are postmenopausal must have documentation of cessation of menses for ≥ 12 months without an alternative medical cause. Follicle-stimulating hormone (FSH) level in the postmenopausal range (≥ 30 mU/mL at Screening) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   a. Females on HRT and whose menopausal status is in doubt will be required to use the contraception methods in Appendix 20.3 if they wish to continue their HRT during the study. Otherwise, they must temporarily discontinue HRT to enable confirmation of postmenopausal status before study enrollment.

8.3. Exclusion Criteria: Part 1 and Part 2

A subject will not be eligible for participation in Part 1 and/or Part 2 of this study if *any* of the following criteria apply.

1. Inability to undergo a liver biopsy

2. Hepatitis B surface antigen (HBsAg) positive

3. Hepatitis C antibody (HCVAb) positive with the following 2 exceptions:

[redacted]

4. Human immunodeficiency virus (HIV)-1 or HIV-2 infection

5. Prior or planned liver transplantation

6. Other known causes of chronic liver disease, such as the following:

[redacted]

7. History or presence of cirrhosis (NASH CRN Fibrosis Stage 4) and/or hepatic decompensation including ascites, hepatic encephalopathy, or variceal bleeding

8. Alcohol consumption greater than 21 units/week for males or 14 units/week for females [redacted]

9. AST > 5 × ULN at Screening

10. ALT > 5 × ULN at Screening

11. HbA1c > 9% at Screening

12. Serum albumin < 3.5 g/dL at Screening

13. Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) equation at Screening

14. Platelet count < 100,000/mm^3 at Screening

15. Total bilirubin > 1.3 mg/dL at Screening (subjects with hyperbilirubinemia associated with documented Gilbert's syndrome may be eligible upon review by the medical monitor)

16. International normalized ratio (INR) > 1.3 at Screening

17. Model of end stage liver disease (MELD) score > 12

18. Weight reduction, defined as ≥ 7% of body weight, through bariatric surgery in the past 5 years or bariatric surgery planned during the conduct of the study (including gastric banding and sleeve surgery)

19. [redacted] history of malignancy within the past 5 years or ongoing malignancy other than: basal cell carcinoma, resected noninvasive cutaneous squamous cell carcinoma [redacted]

[redacted]

20. Active, serious infections that require parenteral therapy (antibiotic or antifungal) within 30 days prior to Screening visit

21. Clinically significant cardiovascular or cerebrovascular disease within the past 3 months,

[redacted]

22. Females who are pregnant or breastfeeding

23. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents and immunomodulating agents (eg, interleukins, interferons, cyclosporine, tacrolimus) except for vaccines or short-term corticosteroids.

24. Receiving a glucagon-like peptide 1 (GLP-1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium–glucose cotransporter 2 (SGLT2) and/or SGLT1 inhibitor, or a thiazolidinedione (TZD) for less than 6 months prior to the Screening period liver biopsy. Subjects on a stable therapy with a GLP-1 receptor agonist, DPP-4 inhibitor, SGLT1 and/or SGLT2 inhibitor, or a TZD for at least 6 months prior to the Screening liver biopsy may be considered eligible. (**Important Note:** if a historical biopsy is to be used, subjects need to be on stable therapy for at least 6 months **prior** to the day historical liver biopsy was performed).

[redacted]

assigned to placebo in such trials may be eligible immediately following completion of their participation in the previous trial)

29. Participation in any other clinical trial at Screening without approval from the sponsor

30. Any other clinically significant disorders or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements

9. TREATMENTS

9.1. Treatments Administered

At Baseline in Part 1 or Part 2 (newly randomized subjects), eligible subjects will be randomized 2:1 to one of 2 treatment arms:

Table 9–1 Treatment Arms: Part 1 and Part 2

Arm	Part 1 N	Part 2 Newly Randomized Subjects N	Part 2 Total Subjects (Randomized in Part 1 or Part 2) N	Treatment
A	800	534	1334	CVC 150 mg, once daily
B	400	266	666	Placebo, one daily

Subjects who remain in Part 1 of the study at Month 12 will continue their previously assigned blinded treatment from Part 1 into Part 2 and will continue to be evaluated in Part 2. In addition, new eligible subjects will be enrolled into Part 2 and randomized after the enrollment for Part 1 is completed. This will result in a total of approximately 2000 subjects in Part 2 (including up to 1200 subjects who were randomized in Part 1); approximately 1334 subjects treated with CVC and 666 subjects treated with placebo.

In Parts 1 and 2, CVC and placebo will be administered as double-blinded study drug. Study drug (CVC or placebo) must be taken once daily with food.

9.2. Study Drug

9.2.1. Investigational Product

Chemical Name:	(*S*)-8-[4-(2-Butoxyethoxy)phenyl]-1-isobutyl-*N*-(4-{[(1-propyl-*1H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide monomethane sulfonate
Generic Name:	Cenicriviroc mesylate
Abbreviated Name:	CVC
Laboratory Designation:	TBR-652
Trade Name:	Not applicable

The CVC drug product is formulated with fumaric acid (160 mg) and other excipients, including microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and Opadry® II yellow (film coating).

The CVC drug product is provided as 150-mg yellow-coated, immediate release tablets for oral administration.

The matching placebo tablet contains tartrazine E 102 (10 mg), as a component of 39 mg of the dye FD&C Yellow/Tartrazine Aluminum Lake.

WARNING: Tartrazine may cause allergic reactions.

9.2.2. Packaging and Labeling

The study drug, CVC and matching placebo, will be packaged in high-density polyethylene (HDPE) bottles containing 30 tablets per bottle with desiccant and induction sealed. The site pharmacist, investigator, or designee will dispense study drugs. When dispensed, supplies will contain sufficient drug to cover the visit window period.

All labels for CVC and placebo will meet all applicable requirements of the United States (US) Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices and/or all local regulations, as applicable.

9.2.3. Storage

All study drug should be stored at controlled room temperature (refer to the packaging or study/pharmacy manual). CVC tablets will continue to be monitored for stability at ICH recommended storage conditions. Detailed storage and handling information is provided in the Pharmacy Manual.

9.2.4. Study Drug Dispensing and Collection

Study drug (CVC or placebo) will be supplied in a bottle containing 30 tablets of medication for each subject, which is sufficient for 30 days dosing. At scheduled visits where visits are scheduled more than 1 month apart, multiple bottles will be supplied to ensure drug supply until the next scheduled visit.

Study drug will be assigned by interactive response system (IxRS) to study sites/subjects.

Subjects will be instructed that 1 tablet of study drug must be taken once daily with food.

Unused medication and empty medication bottles will be collected from each subject at each scheduled study visit, beginning with the Month 1 visit in Part 1 or Part 2.

9.2.5. Investigational Product Accountability

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and must

be readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug. The investigator or designee must maintain records that document the following:

- Study drug delivery to the study site
- Inventory at the site
- Storage conditions
- Use by each subject, including tablet counts from each supply dispensed
- Return of study drugs to the investigator or designee.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the study drug and study subjects.

The study drug must be used only in accordance with the protocol. The investigator will also maintain records adequately documenting that the subjects were provided the study drug specified.

Completed accountability records will be archived by the site. All used and unused bottles are to be sent back to the originating depot for destruction in accordance with the protocol-specific monitoring plan. Guidance and information regarding the final disposition of all study drug are provided in the Pharmacy manual.

Guidance and information regarding the final disposition of unused study drug are provided in the Pharmacy Manual.

9.2.6. Randomization

Randomization will be accomplished via IxRS.

9.2.7. Part 1

In Part 1, at Baseline (Day 1), following Screening evaluations, eligible subjects will be assigned to the treatment arms using permuted block randomization stratified by NASH CRN Fibrosis Stage (2 or 3) and presence or absence of documented T2DM (yes or no). Eligible subjects will be randomized 2:1 to receive the following double-blind treatment:

Table 9–2 Treatment Arms: Part 1

Arm	N	Treatment
A	800	CVC 150 mg, once daily
B	400	Placebo, one daily

Subjects who remain in Part 1 at Month 12 will continue the same treatment through the end of Part 2, and individual subject treatment assignments will not be revealed until the completion of Part 2 of the study.

9.2.8. Part 2

In Part 2, at Baseline (Day 1), following Screening evaluations, eligible subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis (by NASH CRN system) who are newly randomized in Part 2 of the study will be assigned to the treatment arms using permuted block randomization, and presence or absence of documented T2DM (yes or no). Newly enrolled, eligible subjects will be randomized 2:1 to receive the following double-blind treatment:

Table 9–3 Treatment Arms: Part 2

Arm	Newly Randomized Subjects N	Total Subjects (Randomized in Part 1 or Part 2) N	Treatment
A	534	1334	CVC 150 mg, once daily
B	266	666	Placebo, one daily

9.3. Study Drug Administration

Subjects will take 1 tablet of study drug daily for approximately 6 to 8 years of treatment.

Subjects will be instructed to take their medication (CVC or placebo) with food.

If a subject has missed a dose of study drug and is still within 12 hours of the time it is usually taken, the subject should take a dose of the missed drug as soon as possible, with food. The subject may then continue the usual dosing schedule. If the subject has missed a dose of study drug more than 12 hours after the time it is usually taken, the subject should not take the missed dose and should resume the usual dosing at the next scheduled time. The subject should not take a double dose to make up for a missed dose or take more than 1 tablet within 12 hours.

9.4. Blinding

Subjects, investigators, and all site personnel will be blinded to CVC and placebo individual treatment assignment until all subjects have completed Part 2 and the database has been locked for all study data up to the end of Part 2. Data will be unblinded at the end of Part 1 to

allow for analysis of Part 1 data only. Individual subject treatment assignments will not be provided to sites, subjects, study staff, or sponsor staff involved in the conduct of the study until analysis of Part 2, except in case of emergency unblinding described below.

Blinding of the oral investigational product will be accomplished by the sponsor providing CVC and matching placebo. Packaging for active and placebo product will be identical with the exception of a unique bottle identification number on the label.

Emergency Unblinding: In emergency situations, the investigator may need to break the blind if he/she finds it is in the best interest of the study subject. In the event that immediate knowledge of the treatment received (CVC versus placebo) is necessary for the management of the subject, the investigator may request unblinded treatment information using IxRS. The medical monitor should be notified promptly about the unblinding. (See Section 11.3.1.9 for unblinding procedures).

9.5. Prior, Concomitant and Subsequent Therapy

A prior medication is defined as a (nonstudy) medication taken at any time during 30 days before first study drug intake and stopped before the date of first dose of study drug. Any prior medication received within 30 days before the first dose of study drug will be recorded in the electronic case report form (eCRF).

Disallowed medication in use prior to enrollment will be required to be discontinued. **(**Note: subjects receiving allowed concomitant medications need to be on stable therapy for at least 30 days prior to the Baseline visit. Subjects receiving drugs with potential interaction with CVC, must respect a washout period of 14 days or 5 half-lives, whichever is longer, before CVC is started). For medications that are disallowed due to potential confounding effect on efficacy, a washout period of at least 6 months must be observed prior to the Screening liver biopsy. A list of disallowed medication is provided in Section 20.4. All medications (or treatments) other than study drug taken or received by the subject at any time during the study from first intake of study drug through the 30-day Follow-up visit after last study drug intake (or final visit, for subjects who do not complete a Follow-up visit) will be considered concomitant medications (or treatments). This includes medications ongoing at the time of first study drug intake and medications started after first study drug intake. A new concomitant medication will be a (nonstudy) medication started or for which the dose increased between first study drug intake through the 30-day Follow-up visit after last study drug intake (or final visit, for subjects who do not complete a Follow-up visit). All concomitant medications other than study drug, taken or received at any time during the study from first intake of study drug through to the 30-day Follow-up visit, will be recorded in the eCRF.

A subsequent medication is defined as a (nonstudy) medication taken after the date of the 30-day Follow-up visit (or 30 days after last intake of study drug, if no 30-day Follow-up visit occurs). Any subsequent medication taken after the 30-day Follow-up visit (or 30 days after last intake of study drug, if no 30-day Follow-up visit occurs) will be recorded in the eCRF.

Subjects will be allowed to continue their usual standard-of-care medications that are not specifically disallowed by the protocol.

The detailed list of disallowed medications and the list of medications that are allowed but with specific restrictions are provided in Appendix 20.4.

The following classes of medications are disallowed at any time during Part 1 and Part 2, from Screening through the 30-day Follow-up visit, if applicable:

- Potent CYP3A4 inhibitors and CYP3A4 inducers will be excluded
- Potent CYP2C8 inhibitors will be excluded
- Drugs with narrow therapeutic windows that are sensitive CYP3A4 substrates will be excluded (ie, drugs which should not be co-administered with weak CYP3A4 inhibitors such as CVC)
- Medications that may have confounding effects on the efficacy of CVC

The disallowed concomitant medications commonly administered to patients with NASH are provided in Appendix 20.4.

Should subjects have a need to initiate treatment with any disallowed concomitant medication, the medical monitor must be consulted prior to initiation of the new medication. In instances where a disallowed medication is initiated prior to discussion with the medical monitor, the investigator must notify the sponsor or designee as soon as he/she is aware of the use of the excluded medication to discuss the subject's continued participation in the study.

The following medications are allowed but should be used with caution as CVC (a weak CYP3A4 inhibitor and BCRP inhibitor) may increase exposure of these CYP3A4 and BCRP substrates or these medications may affect the absorption of CVC. If used, these medications should be used at the doses recommended in Appendix 20.4. Clinical monitoring and dose titration are recommended to achieve the desired clinical response.

- Lipid Lowering Agents: Atorvastatin, simvastatin, pravastatin, lovastatin (CYP3A4 substrates), and rosuvastatin (BCRP substrate) at recommended doses per Appendix 20.4
- Pitavastatin use is allowed without dose restriction.
- Intravenous midazolam use is allowed for sedation on the day of the liver biopsy or for surgical outpatient procedures; however, if given for biopsies performed at Month 12 and Month 60, or for any procedure requiring this medication after intake of study drug, the first dose should be reduced by 50% of the recommended dose and titrated according to the desired clinical response.
- Intravenous alfentanil or fentanyl may be used on the day of the Screening liver biopsy. These drugs are allowed with restrictions for biopsies performed at Month 12 and Month 60 or for any procedures requiring these medications after intake of study

drug. Fentanyl is to be administered under medical supervision and all precautions should be in place, including availability of antidote, to prevent complication from its use. It is recommended that the initial dose be decreased by 50% and titrated to the desired effect.

- Intravenous propofol use is allowed without dose restriction.
- When required, acid-reducing agents should be administered at least 2 hours after the CVC dose to ensure that adequate CVC concentrations are maintained. When possible, use of an H_2 receptor antagonist (except cimetidine) or antacids is preferred over a PPI. It is recommended to start with the lowest dose of these agents and titrate according to clinical response. See section 5.3.1 for further details.
  - If H_2 receptor antagonists (eg, famotidine or ranitidine) are used, these should preferably be given from 2 to 12 hours after administration of study drug at a dose that does not exceed doses comparable to famotidine 40 mg daily.
  - If antacids (eg, aluminum hydroxide, calcium carbonate, magnesium carbonate, magnesium hydroxide, or bismuth subsalicylate) are used, these should preferably be given at least 4 hours after administration of study drug due to their immediate effect in increasing gastric pH.
  - If PPIs (eg, omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, or dexlansoprazole) must be utilized, these should preferably be given approximately 3 hours after administration of study drug at a dose that does not exceed doses comparable to omeprazole 20 mg daily. Due to the prolonged acid-reducing effect of PPIs (~16 – 24 hours), it is advised to follow these dosing recommendations to reduce their potential impact on CVC absorption at subsequent dosing.

9.5.1. Antidiabetic Medications

- The benefits of intensive glycemic control on microvascular and neuropathic complications are well established for both type 1 and type 2 diabetes. The choice of therapies must be individualized based on attributes of the subject and the medications themselves (AACE/ACE Comprehensive diabetes management algorithm, 2015). For subjects participating in this study, the use of certain medications should be carefully considered, due to potential for confounding effects of the efficacy endpoint. If antidiabetic agents are used, the following ranking of medication is suggested (Table 9-4) in order to minimize the potential impact on the study efficacy assessments.
- Additional recommendations are provided in the ADA – Standards of Medical Care in Diabetes.

Table 9-4 Antidiabetic Medications

Rank	Medication	Route	Weight Change	Notes

1	Metformin	PO	Neutral	
2	Sulfonylureas (2nd generation)	PO	Gain	
3	DPP-4 Inhibitors	PO	Neutral	
4	SGLT1/2	PO	Loss	Discuss with medical monitor prior to introduction. Potential benefit in CVD
5	GLP-1 Agonists	SQ	Loss	Discuss with medical monitor prior to introduction. Potential benefit in CVD
6	Thiazolidinediones	PO	Gain	Pioglitazone disallowed per protocol

9.6. Additional Restrictions and Precautions

Subjects should refrain from alcohol consumption and strenuous physical activity (eg, weight lifting, strenuous yard work, intensive exercise workouts) for 48 hours prior to study visits and laboratory evaluations.

9.7. Treatment Adherence

Subjects will bring all of their study-supplied bottles of study drug to every clinic visit, and clinic staff will assess adherence based on the number of remaining tablets less any overage provided to cover the visit window. Subjects who miss doses must be counseled on the importance of adhering to their daily dosing schedule.

10. STUDY PROCEDURES

Study procedures are summarized across all study visits within the Schedule of Assessments for Part 1 (Table 20–1) and Part 2 (Table 20–2).

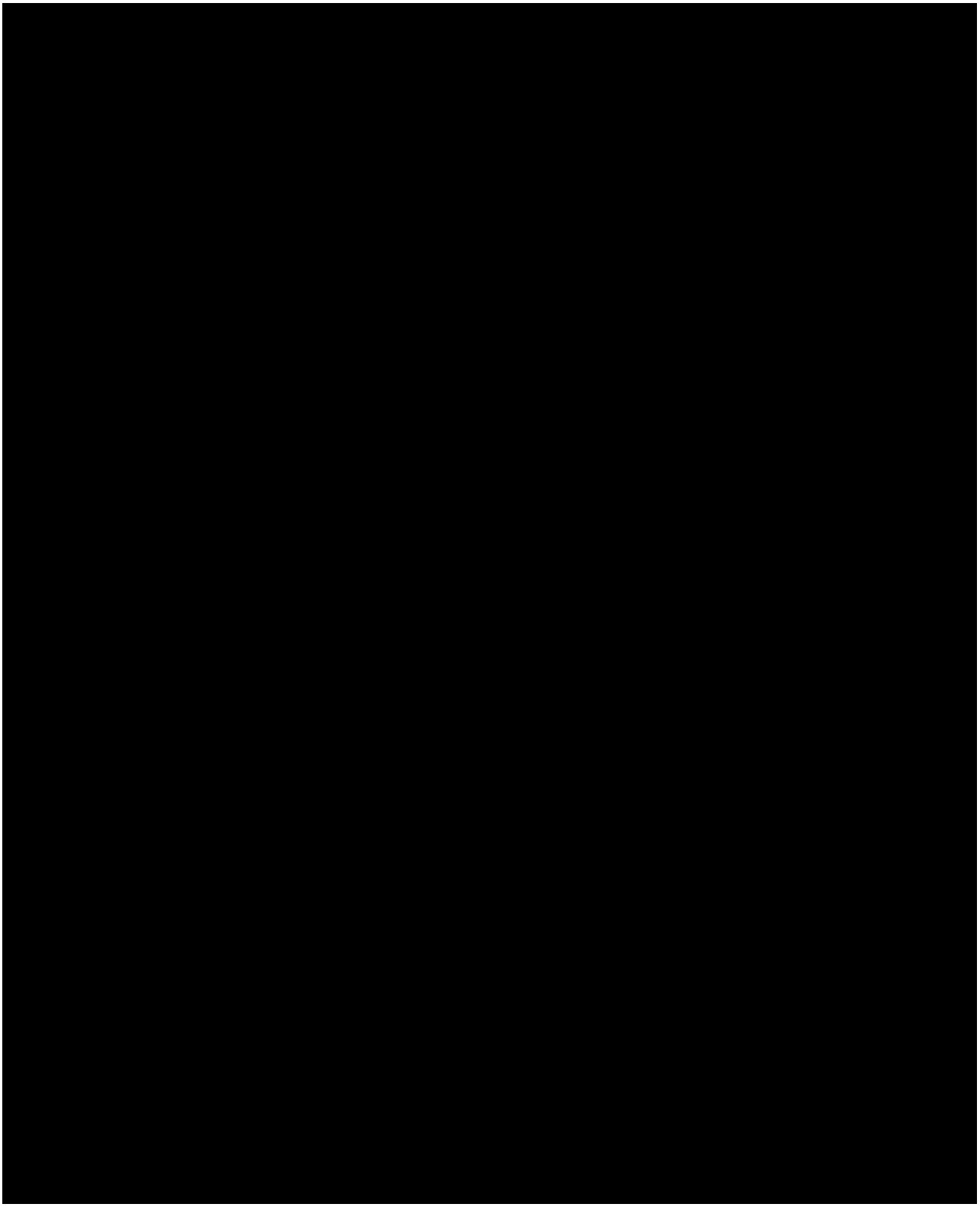
10.1. Part 1 and Part 2: Screening (Month -3; Visit 1)

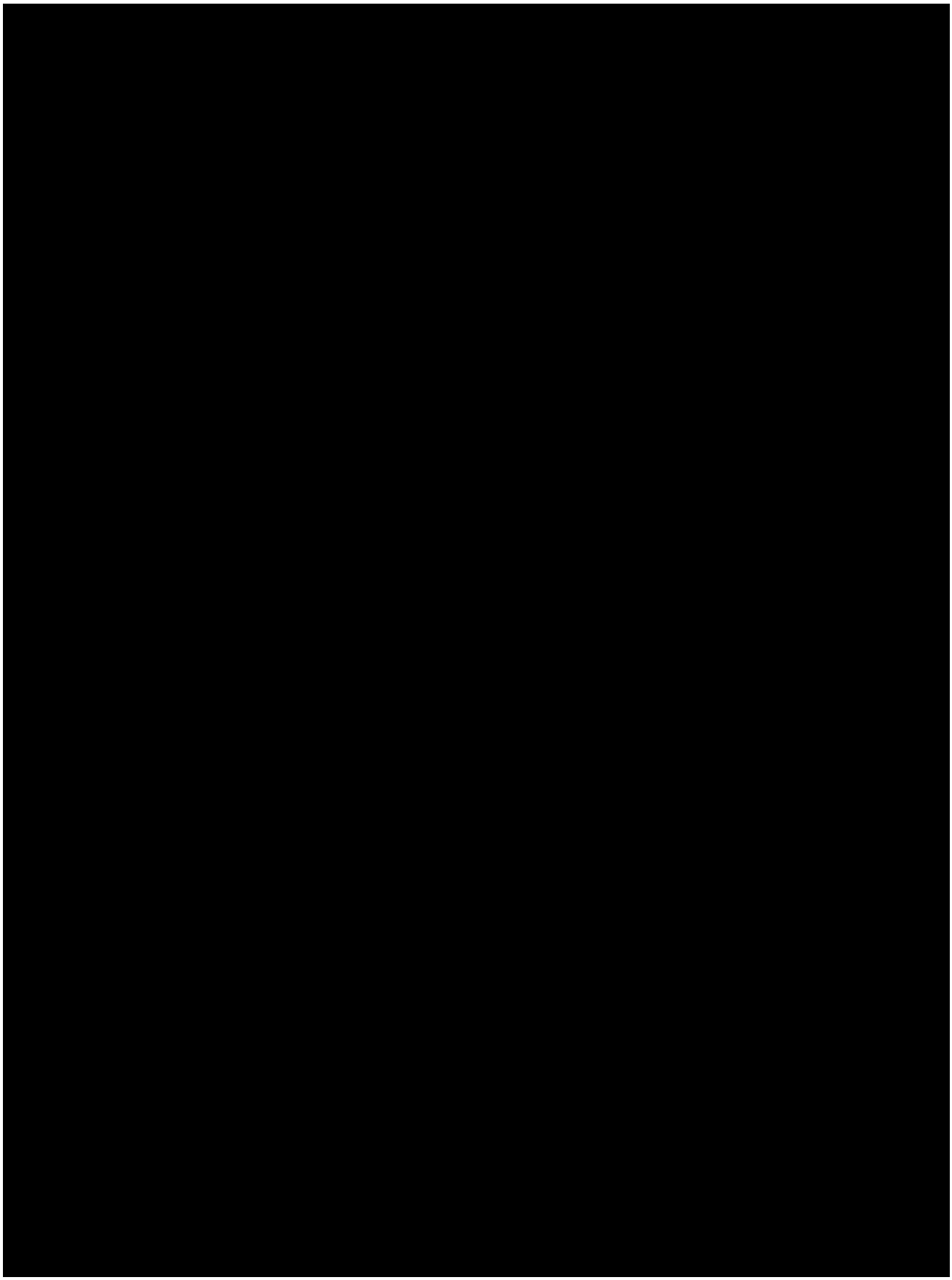
Prior to any clinical procedures and evaluations, written signed informed consent must be obtained. In Part 1 and Part 2, a Screening visit is to occur within 3 months before the Baseline visit (see Section 10.2).

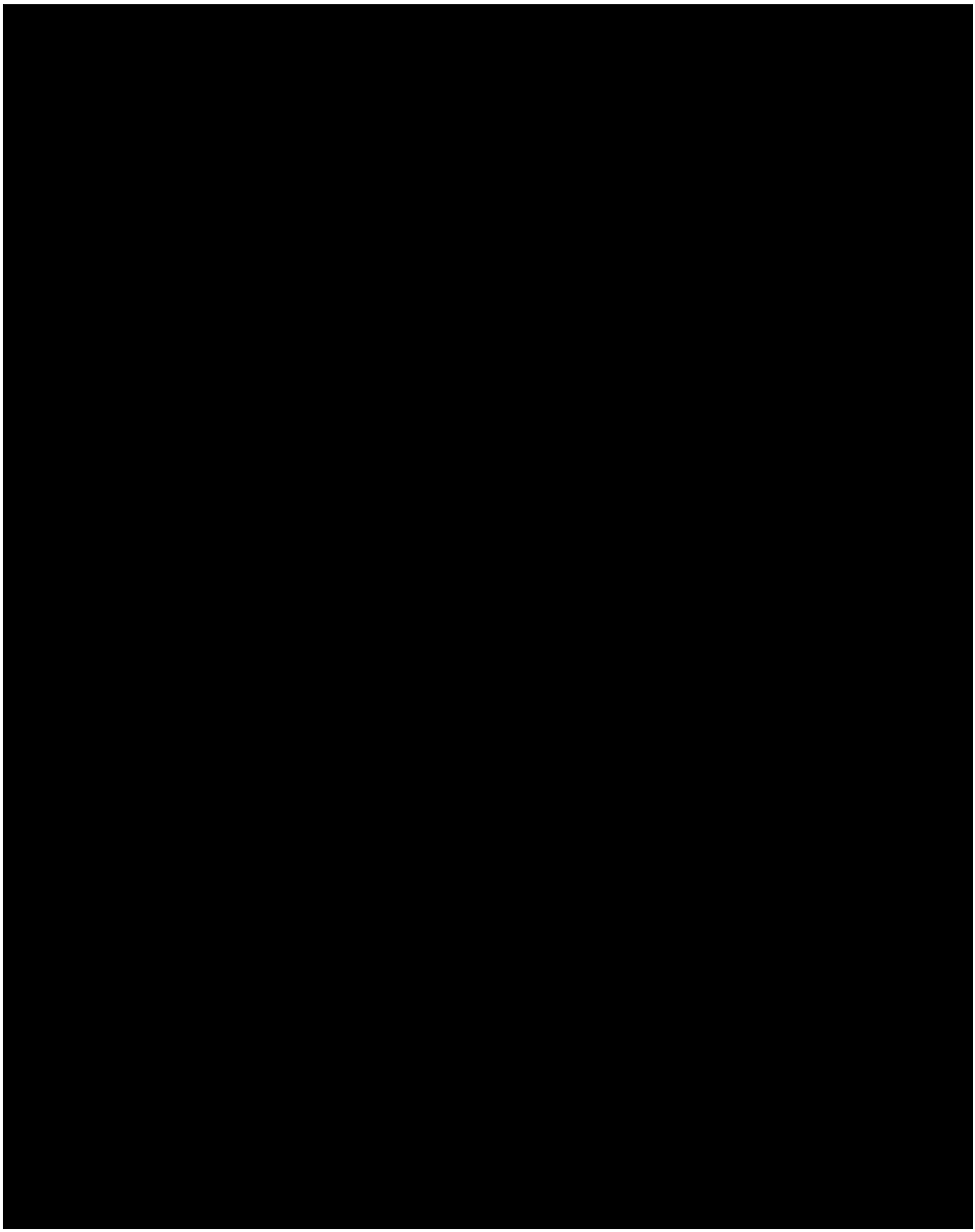
Subjects who do not meet **all eligibility criteria** at Screening will be allowed to rescreen twice. However, if a subject fails to meet eligibility criteria upon rescreening, he or she will remain ineligible for the study.

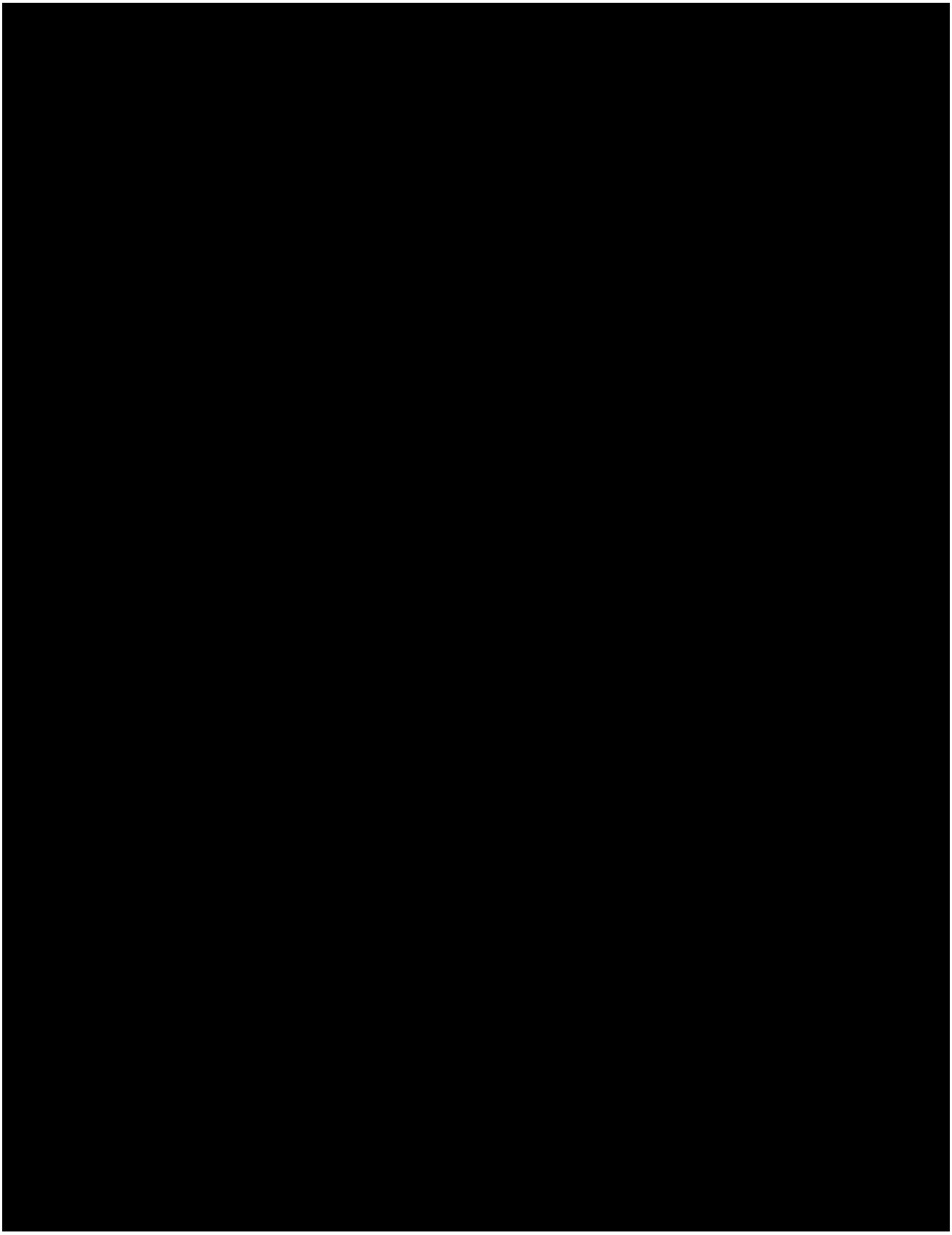
Subjects who do not meet any of the laboratory eligibility criteria during the Screening period will be allowed to retest twice, with at least 1-week interval between the date of the first failed test and the date of subsequent test. However, if a subject fails to meet eligibility

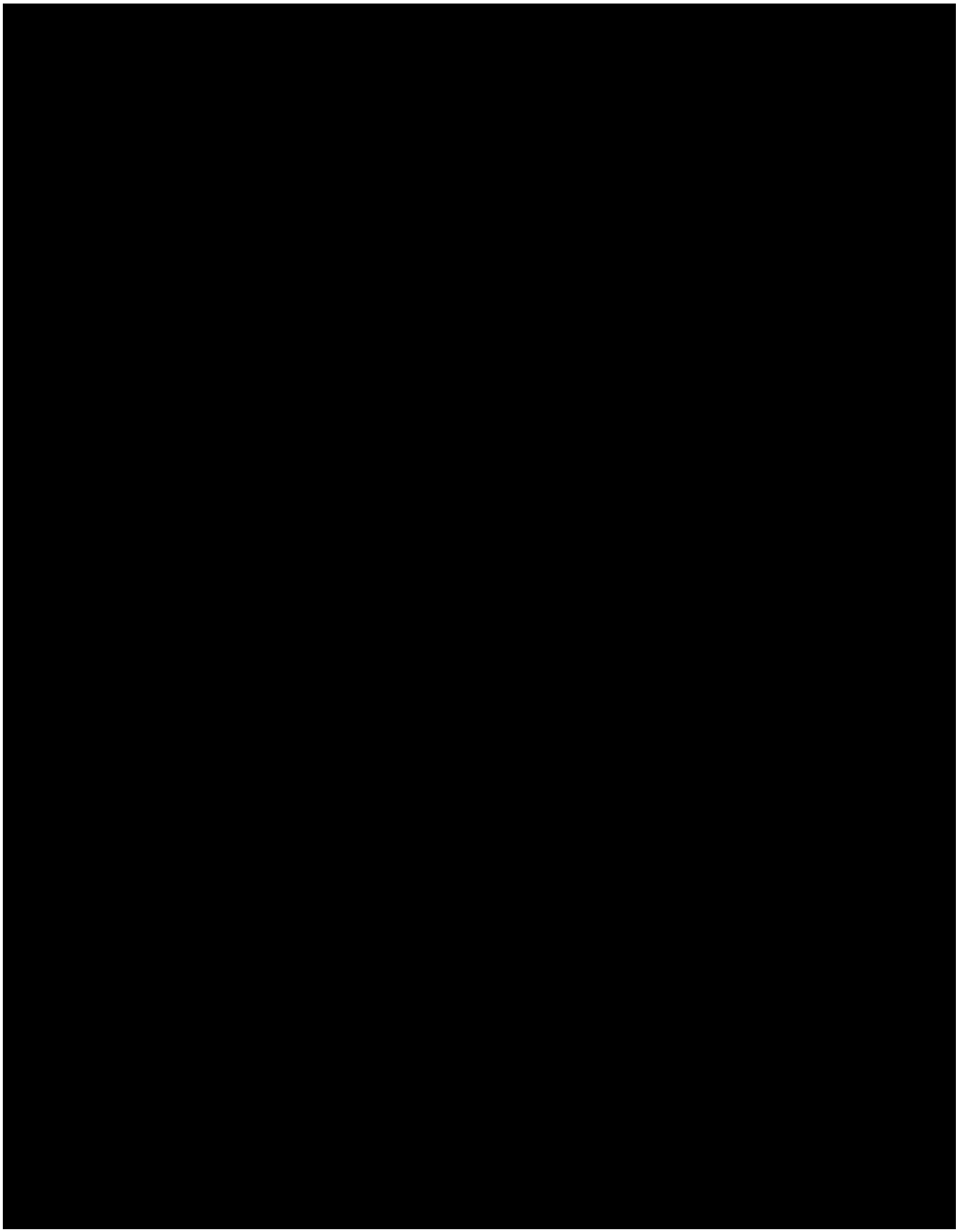
criteria upon these 2 retest opportunities, he or she will remain ineligible for the study. In Part 2, the Screening visit will only be required for newly enrolled subjects. The Screening visit will not be required for subjects continuing their previously assigned blinded treatment from Part 1.

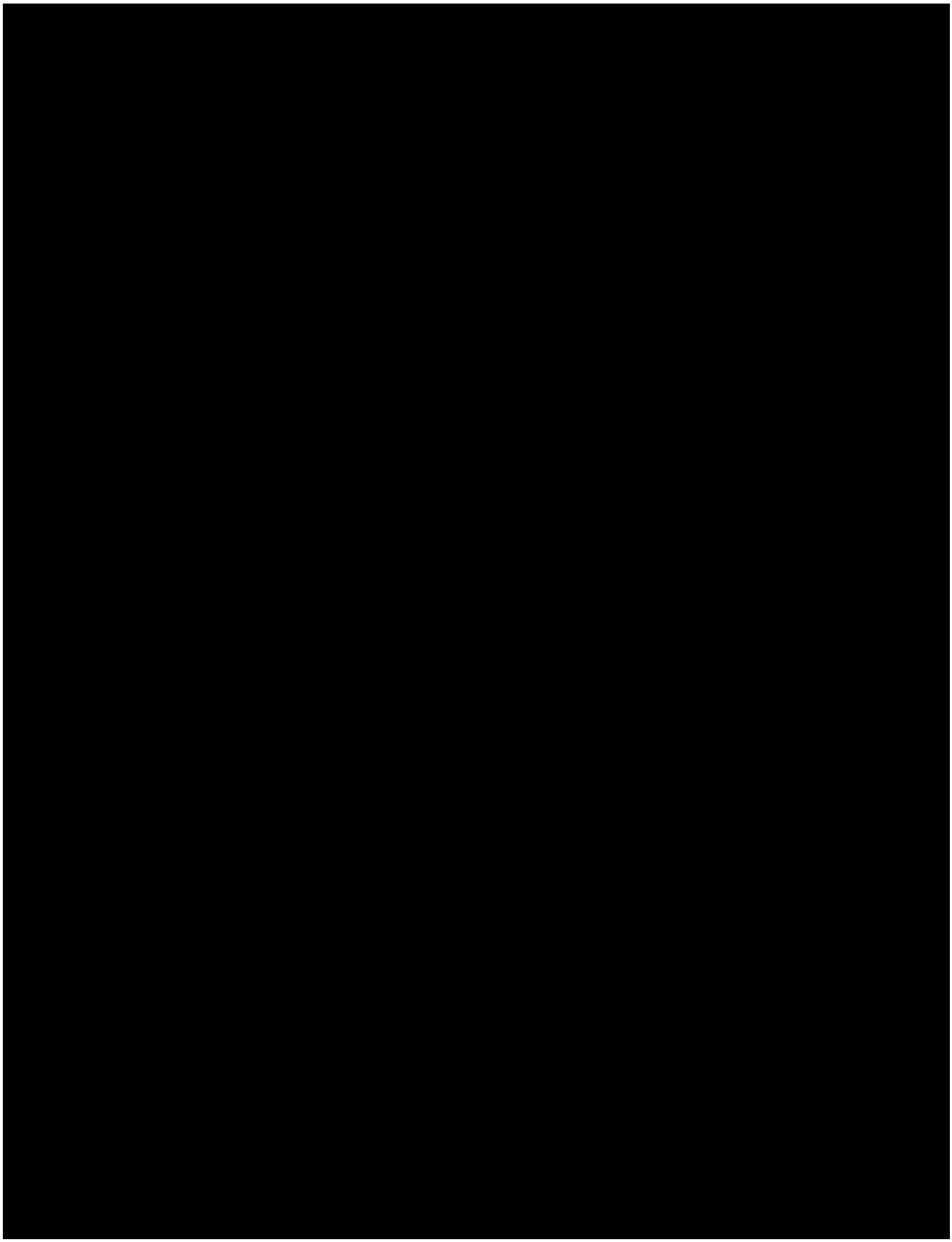


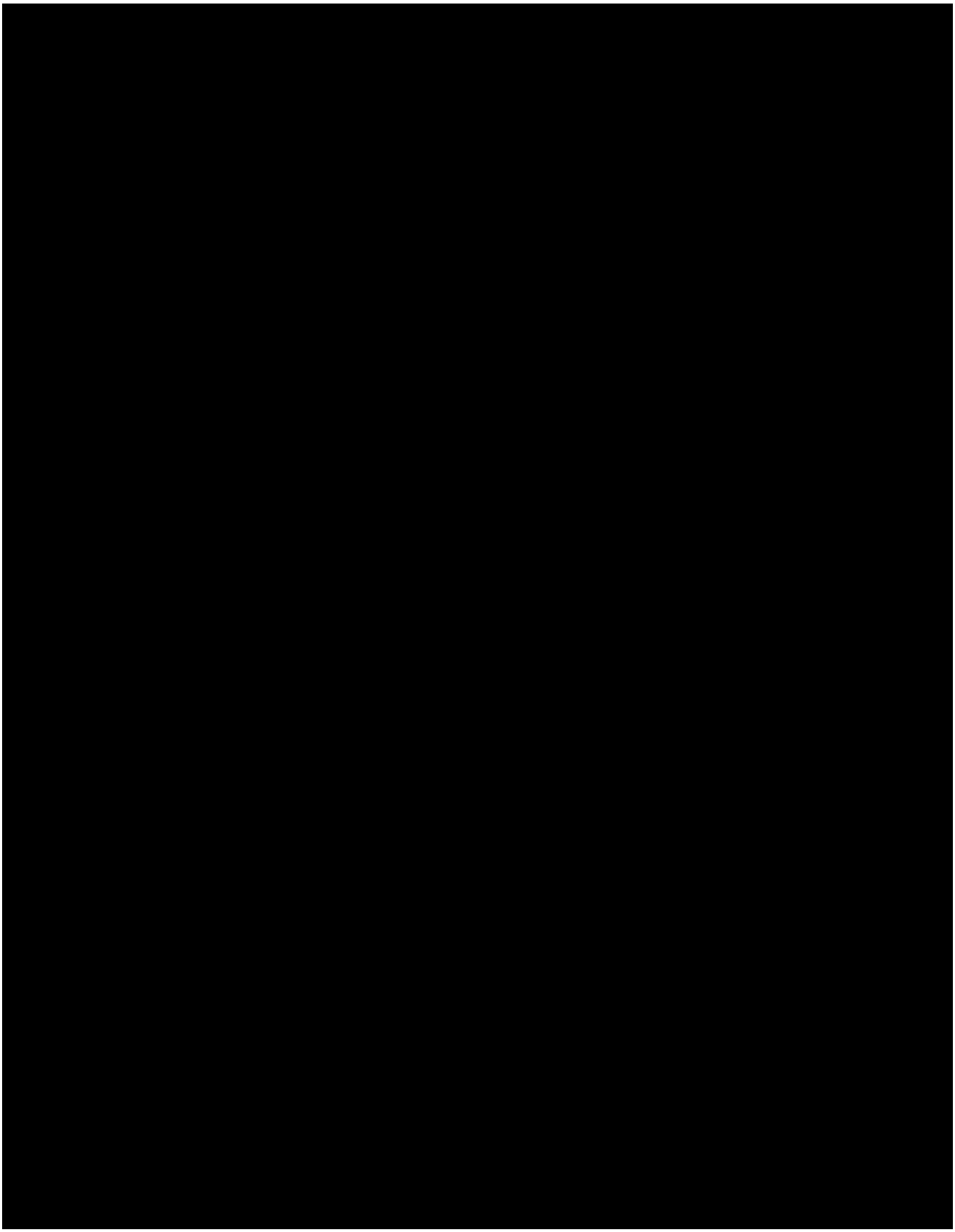


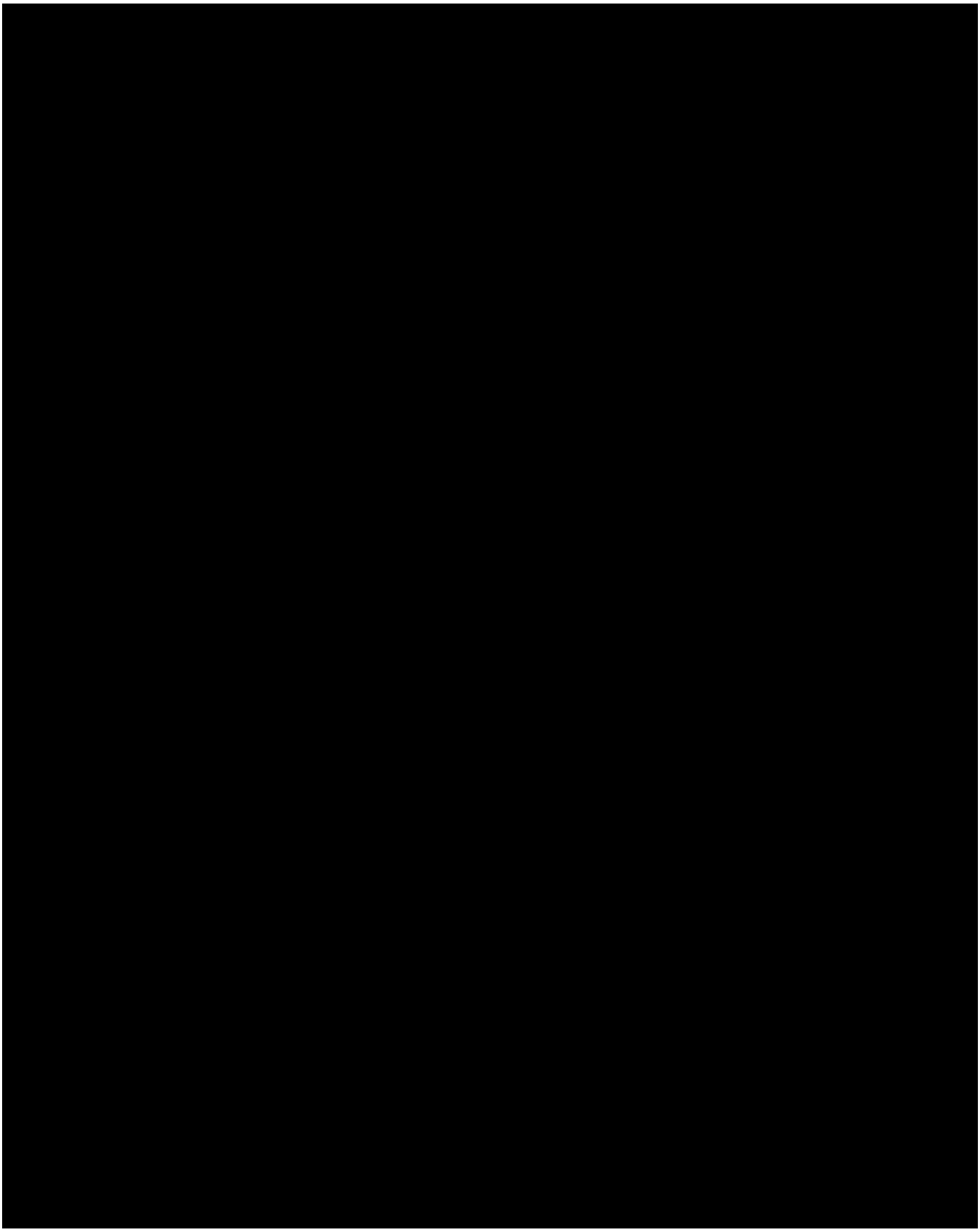


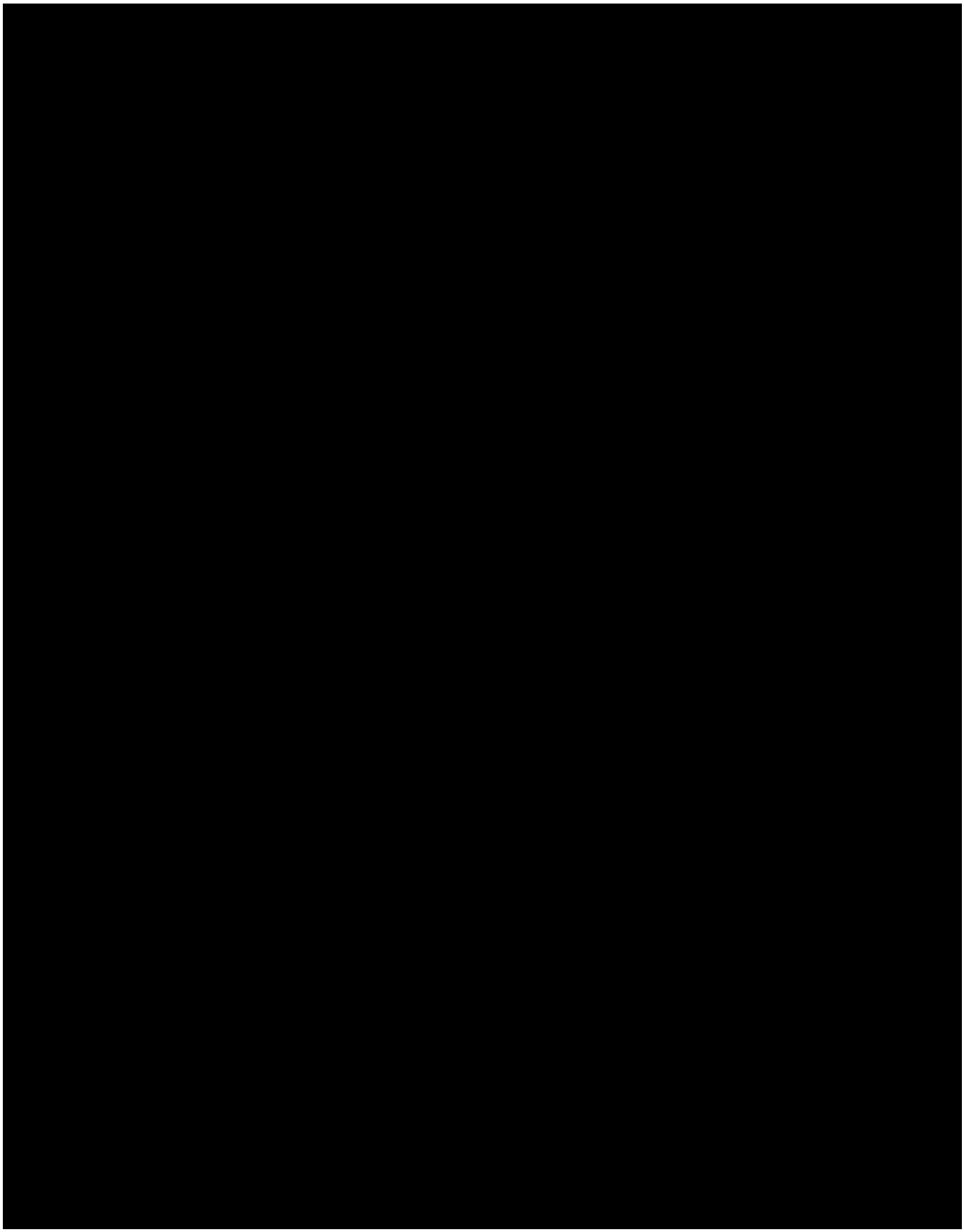


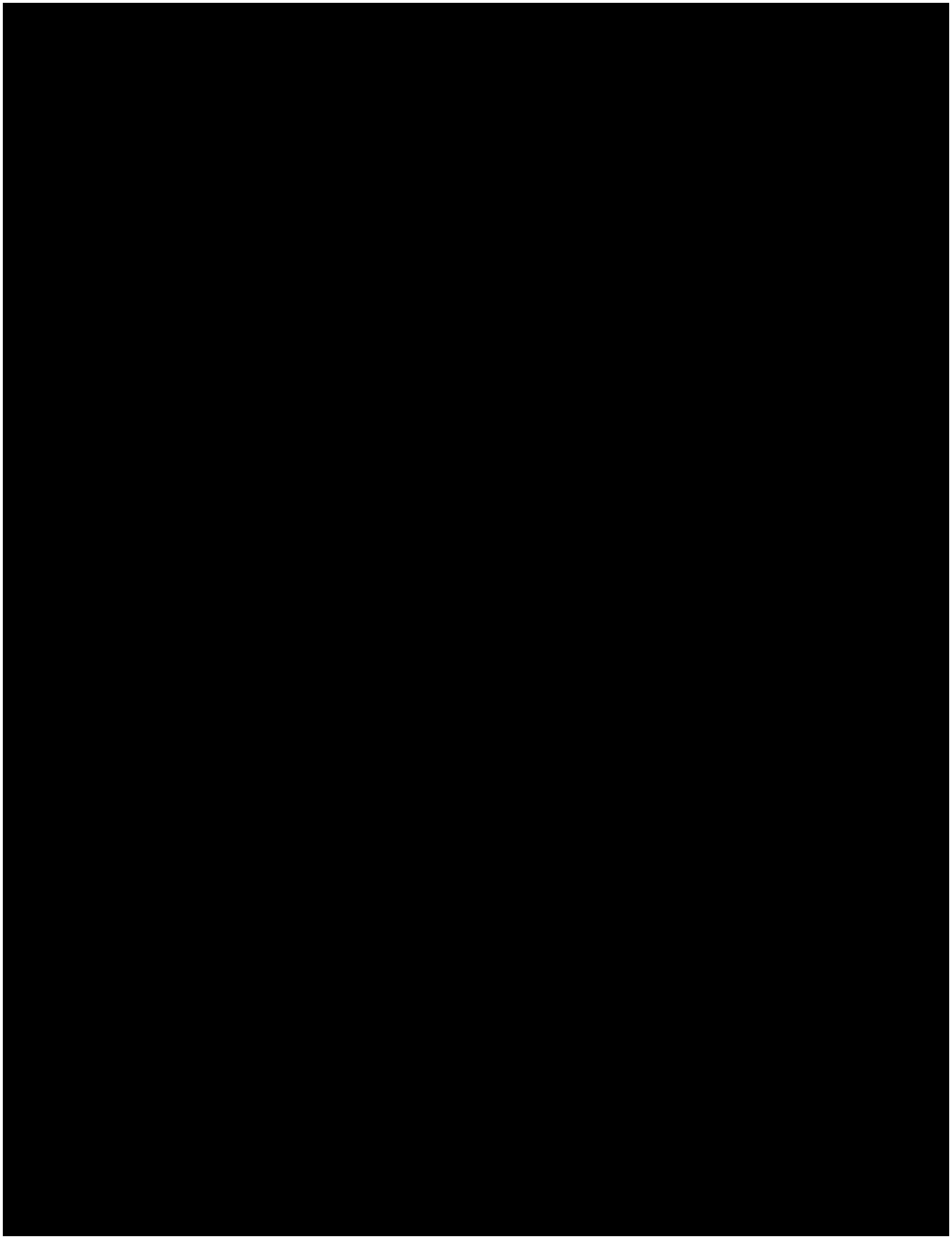


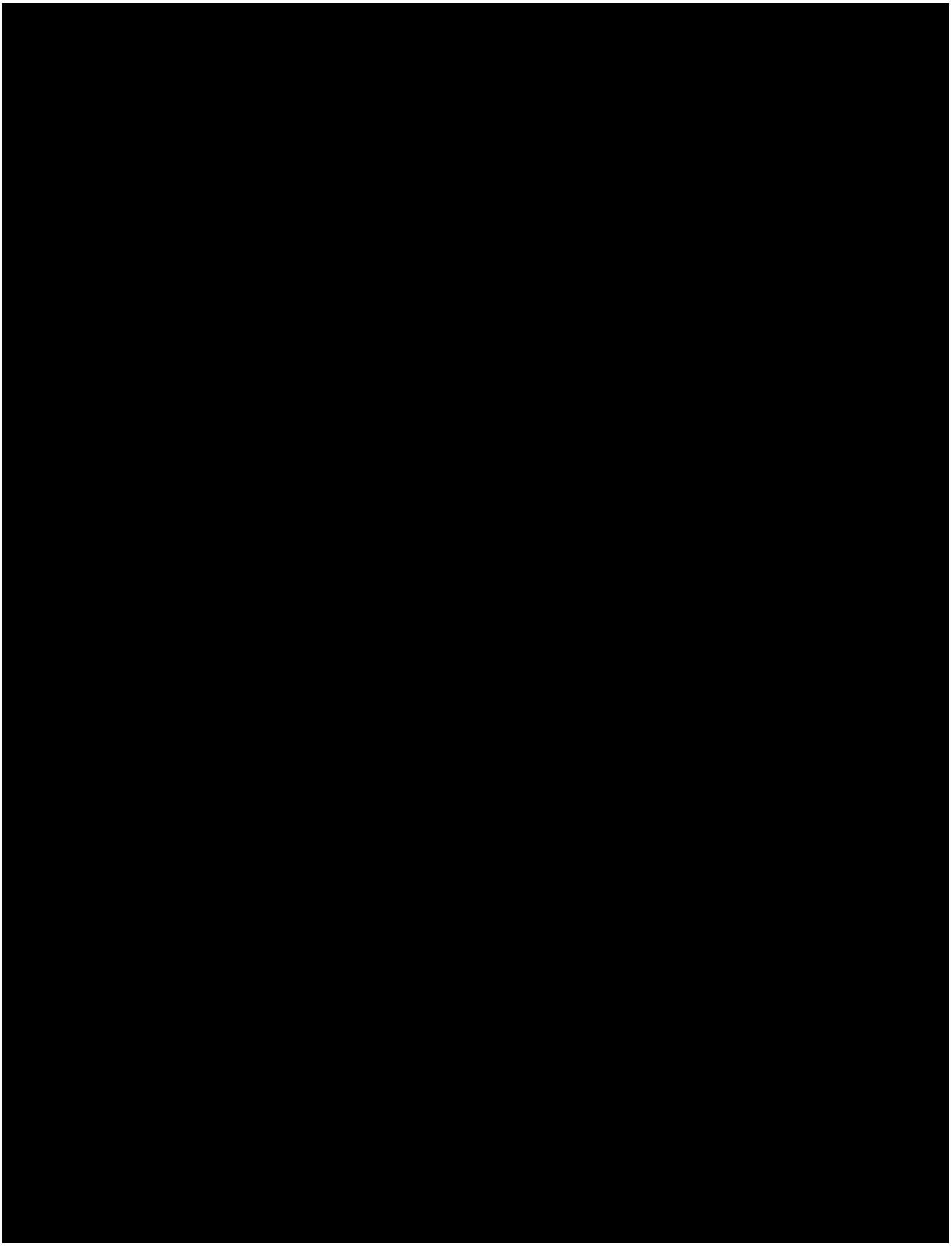


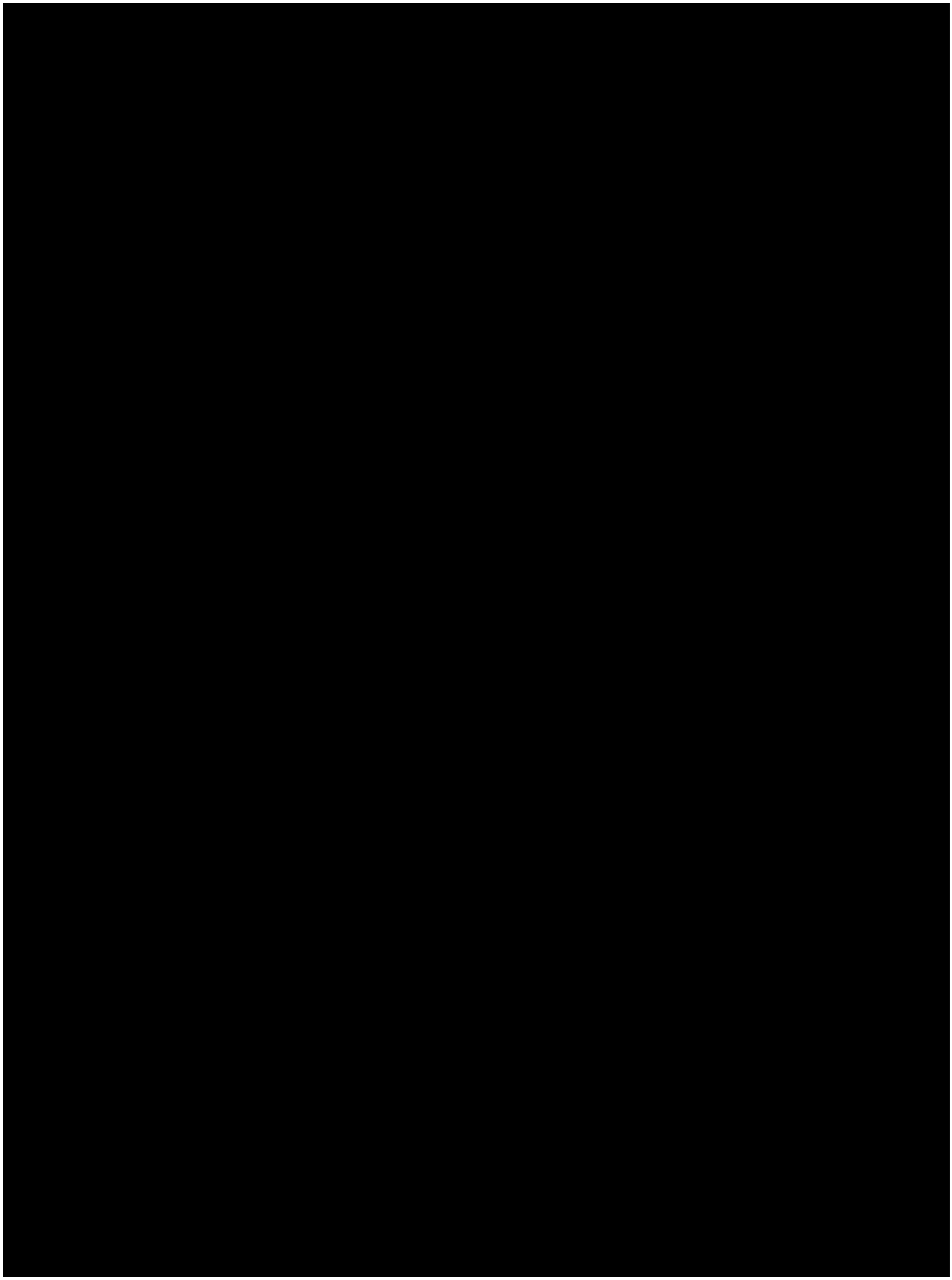


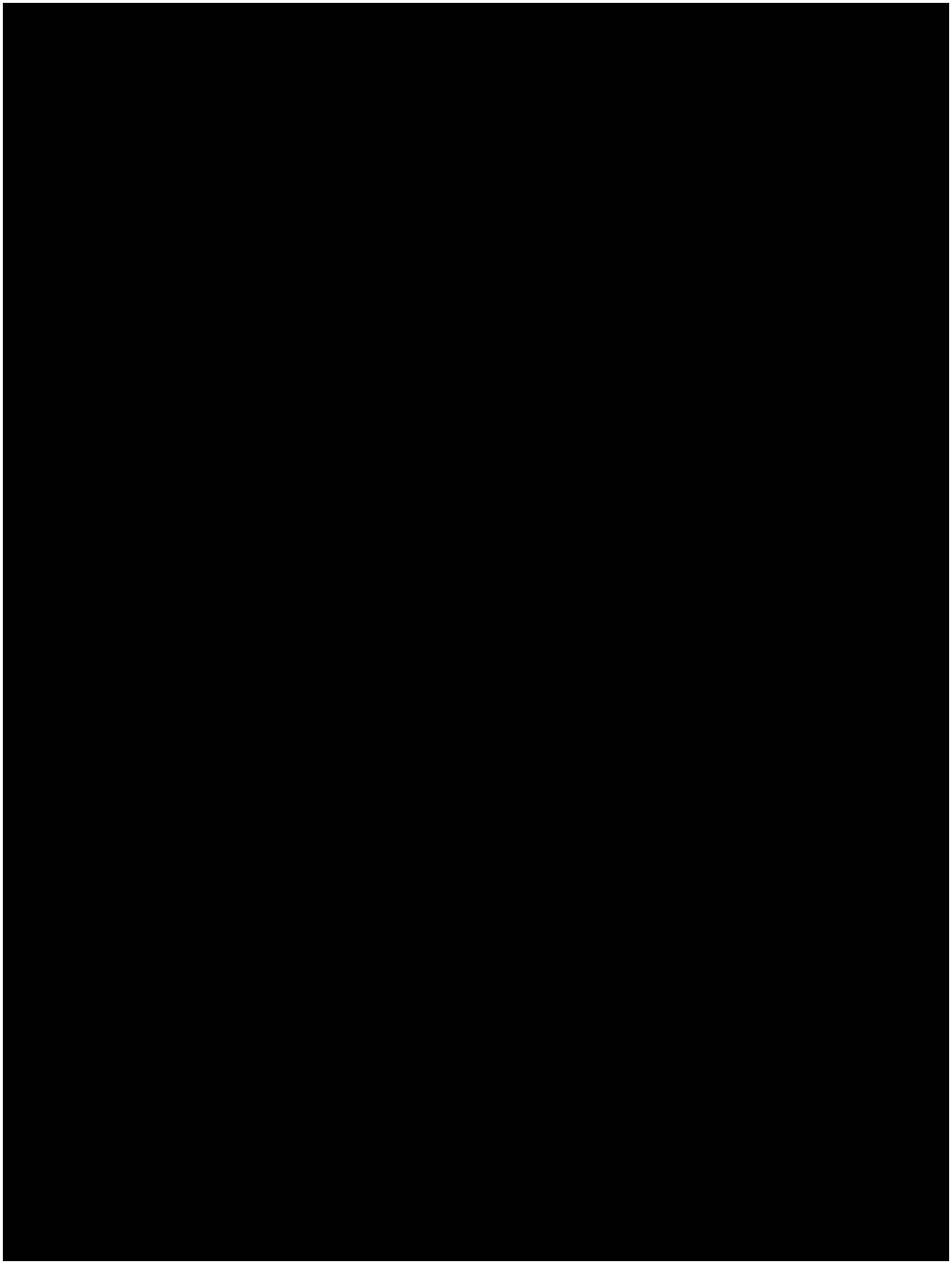


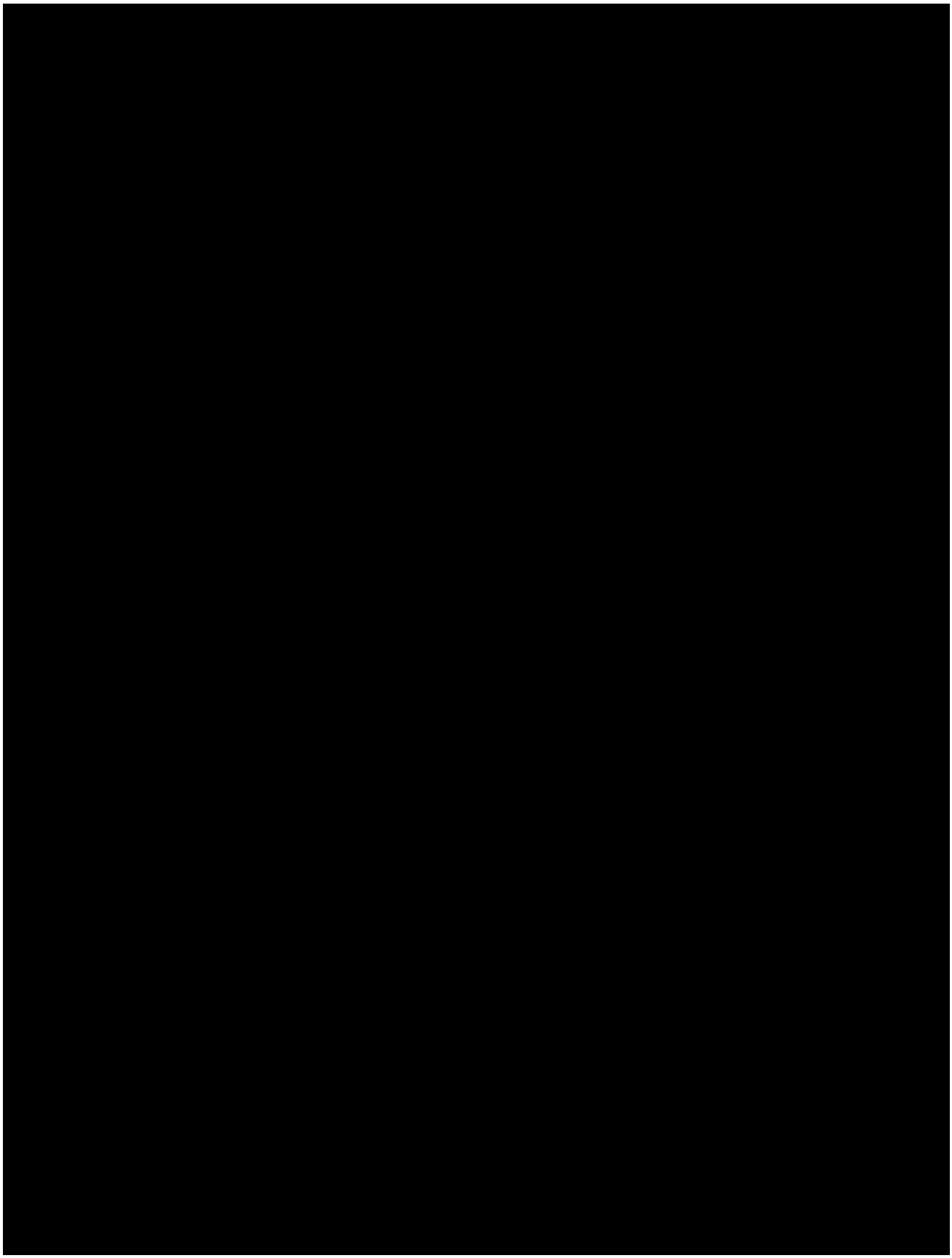


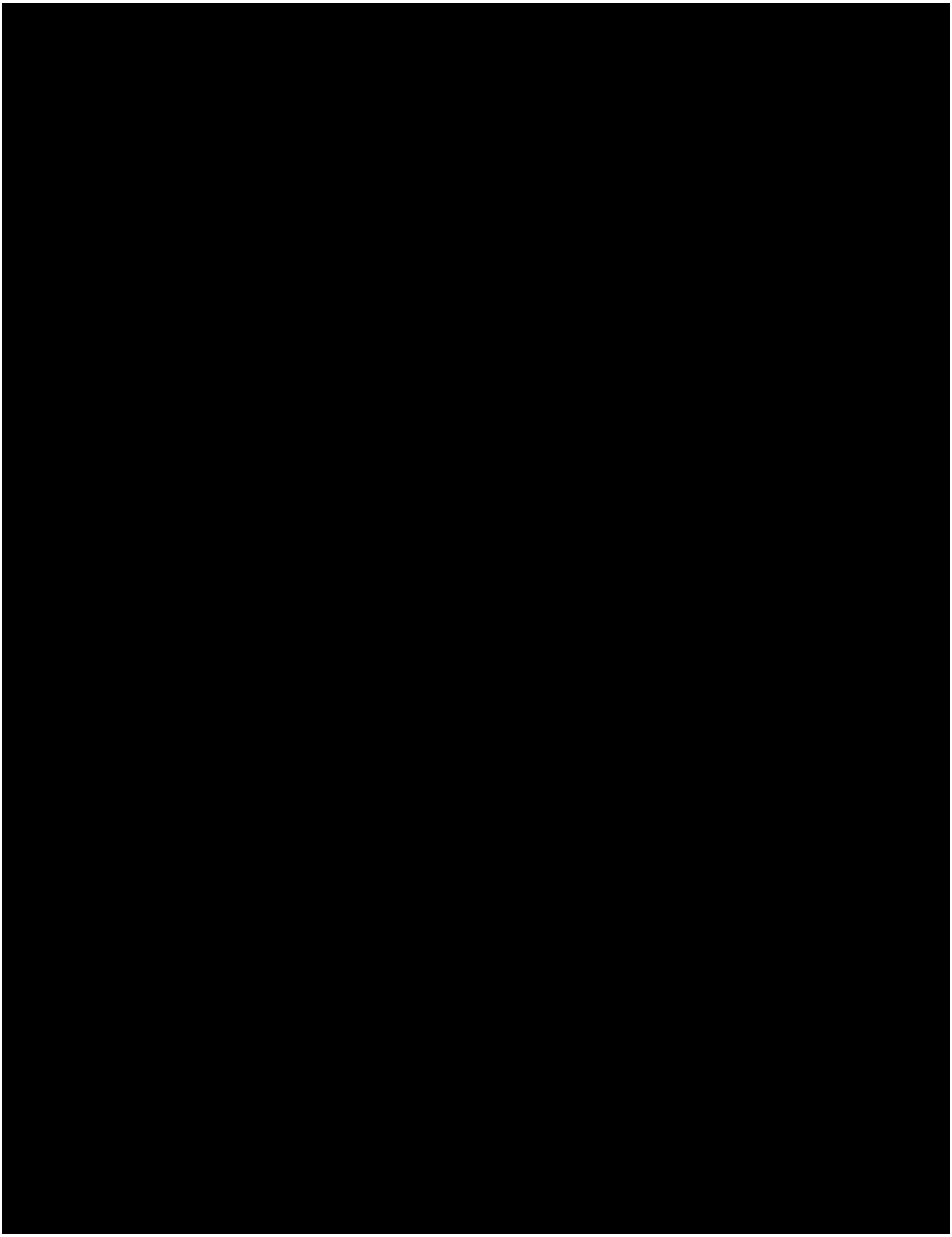


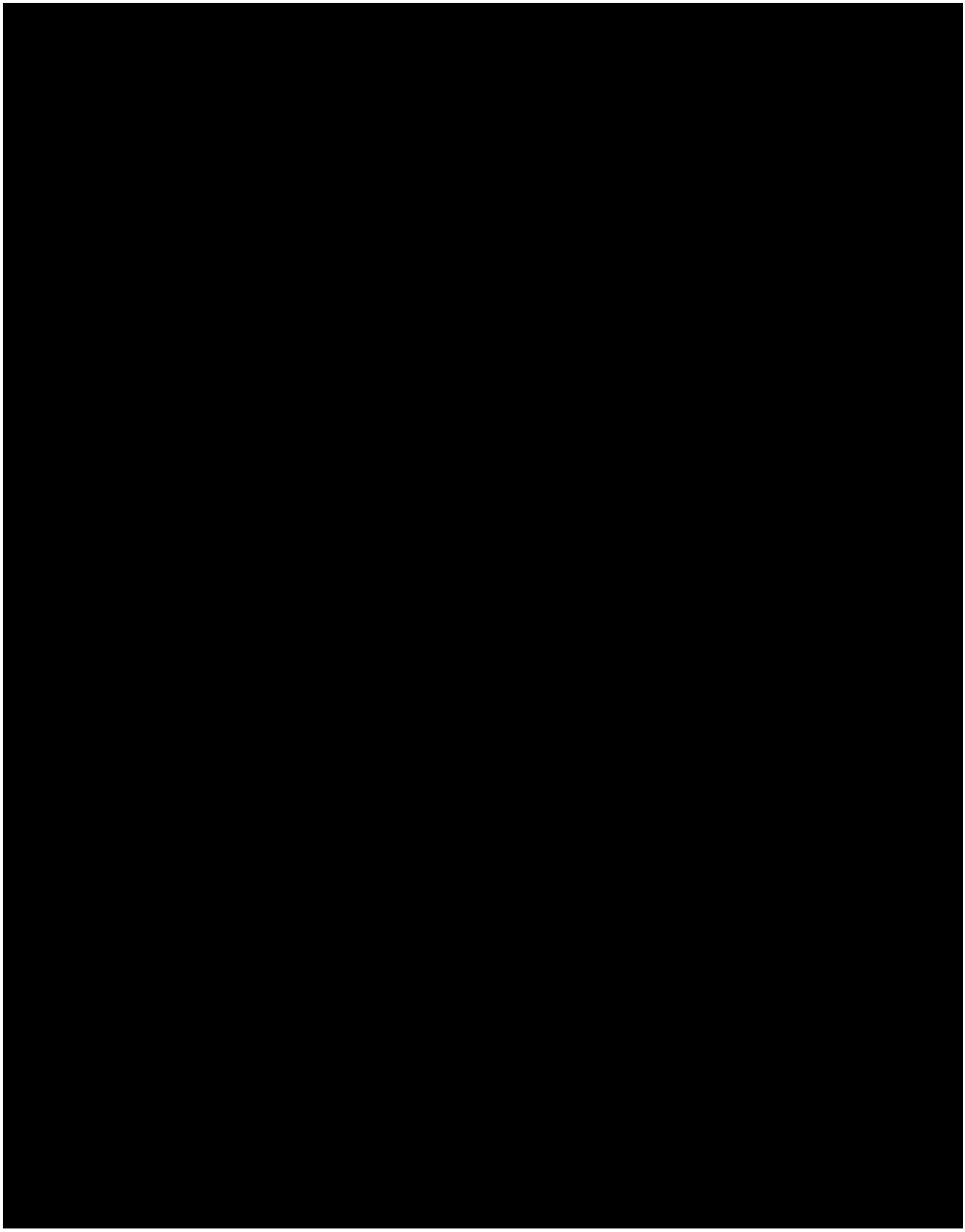


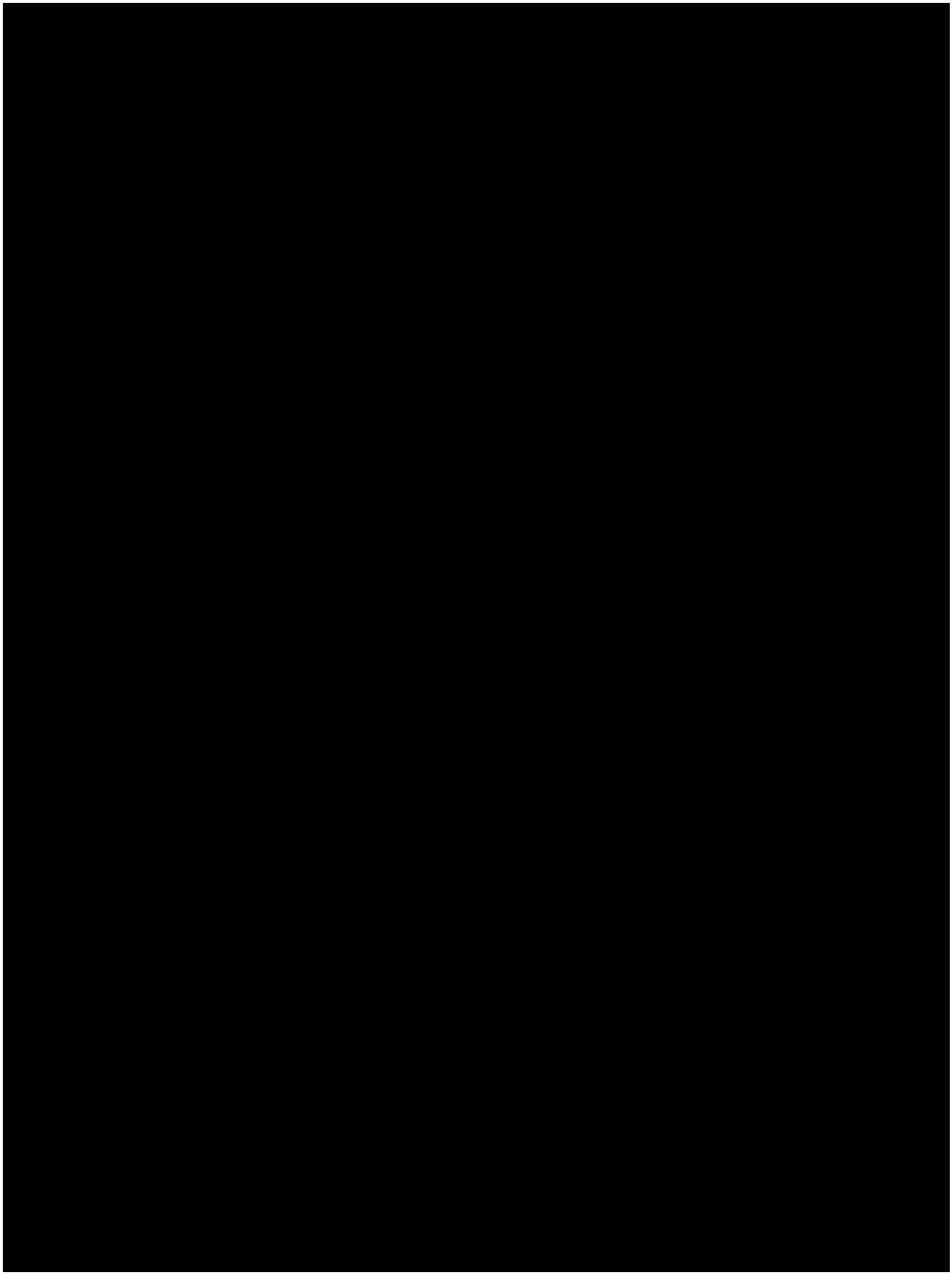


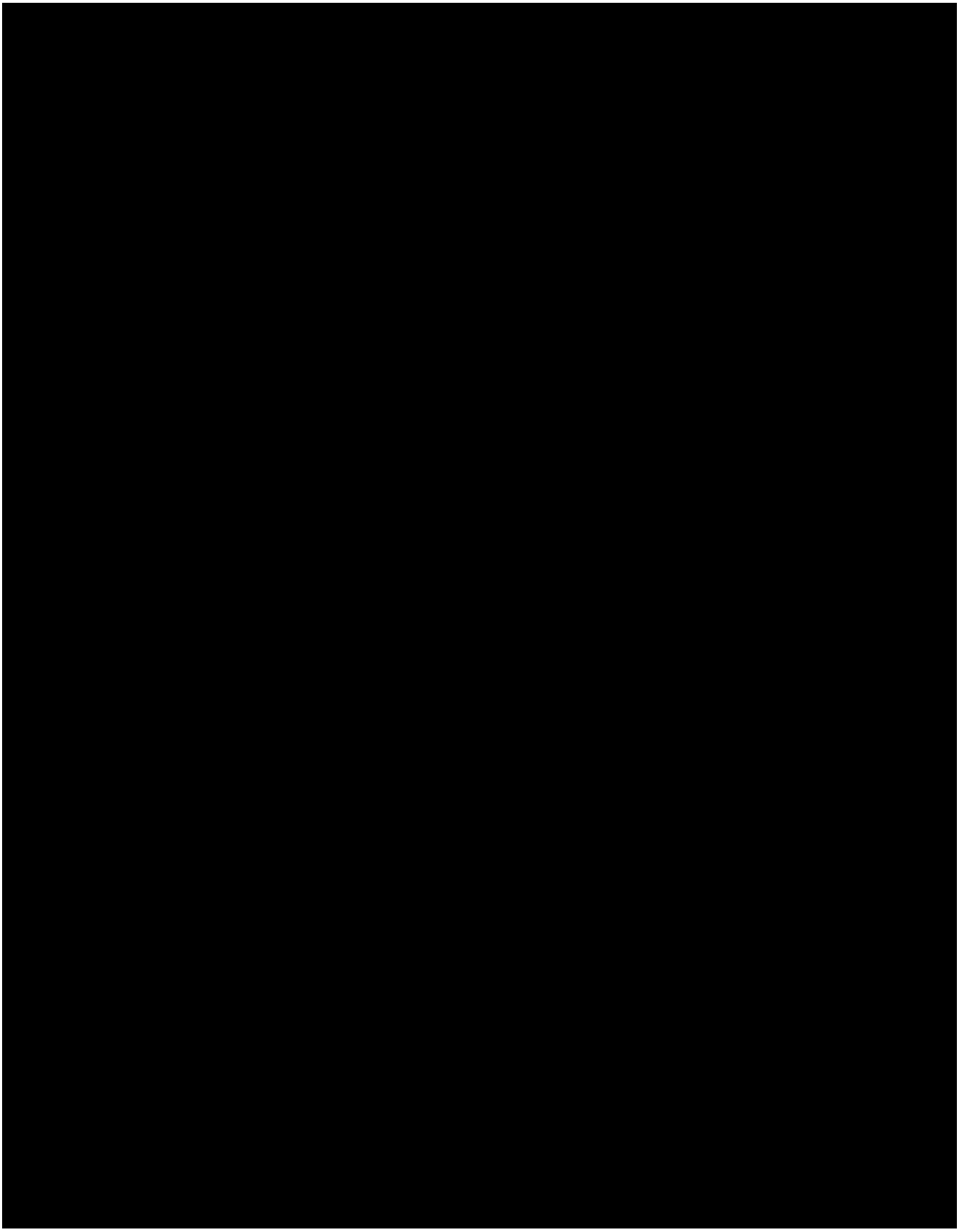


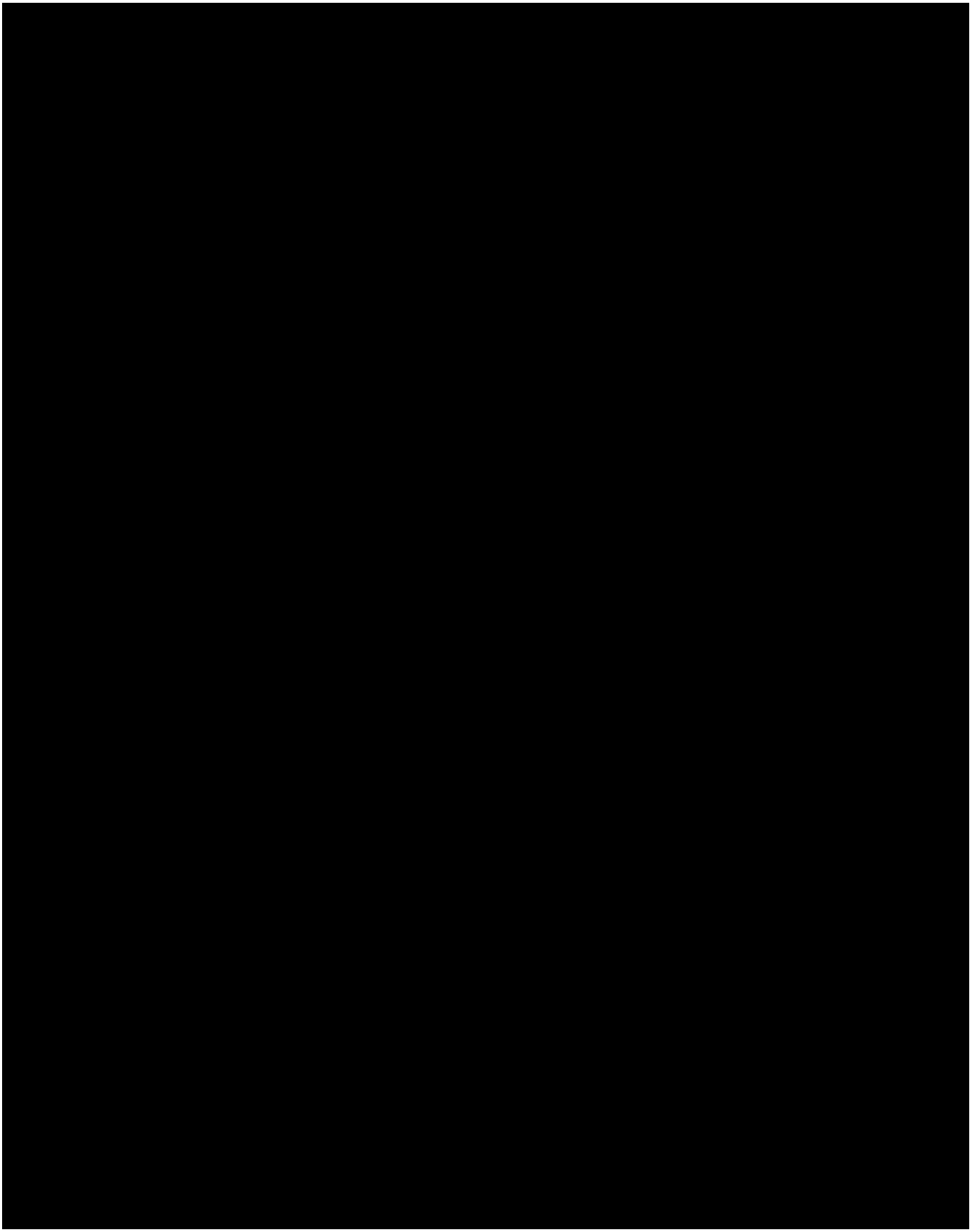


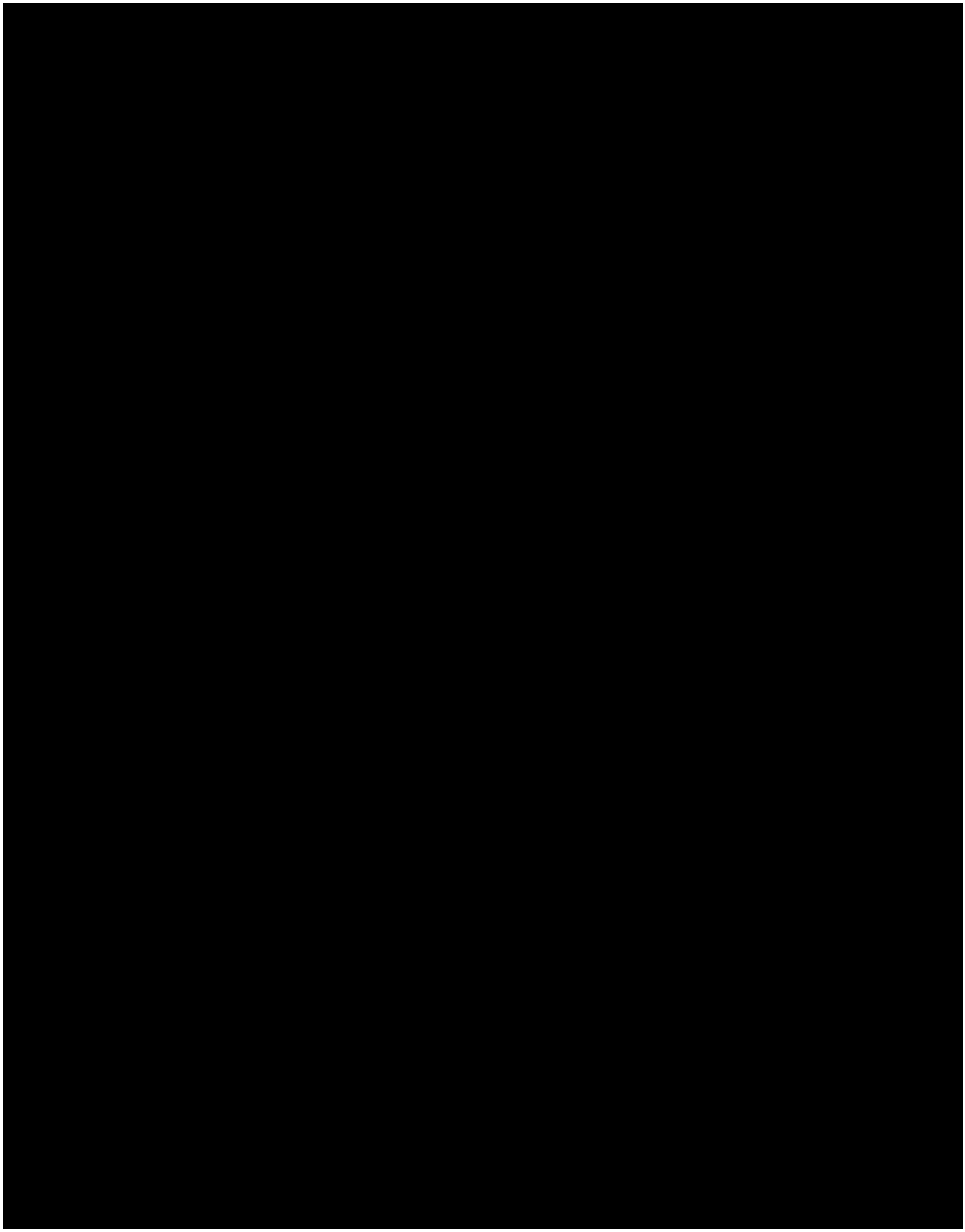


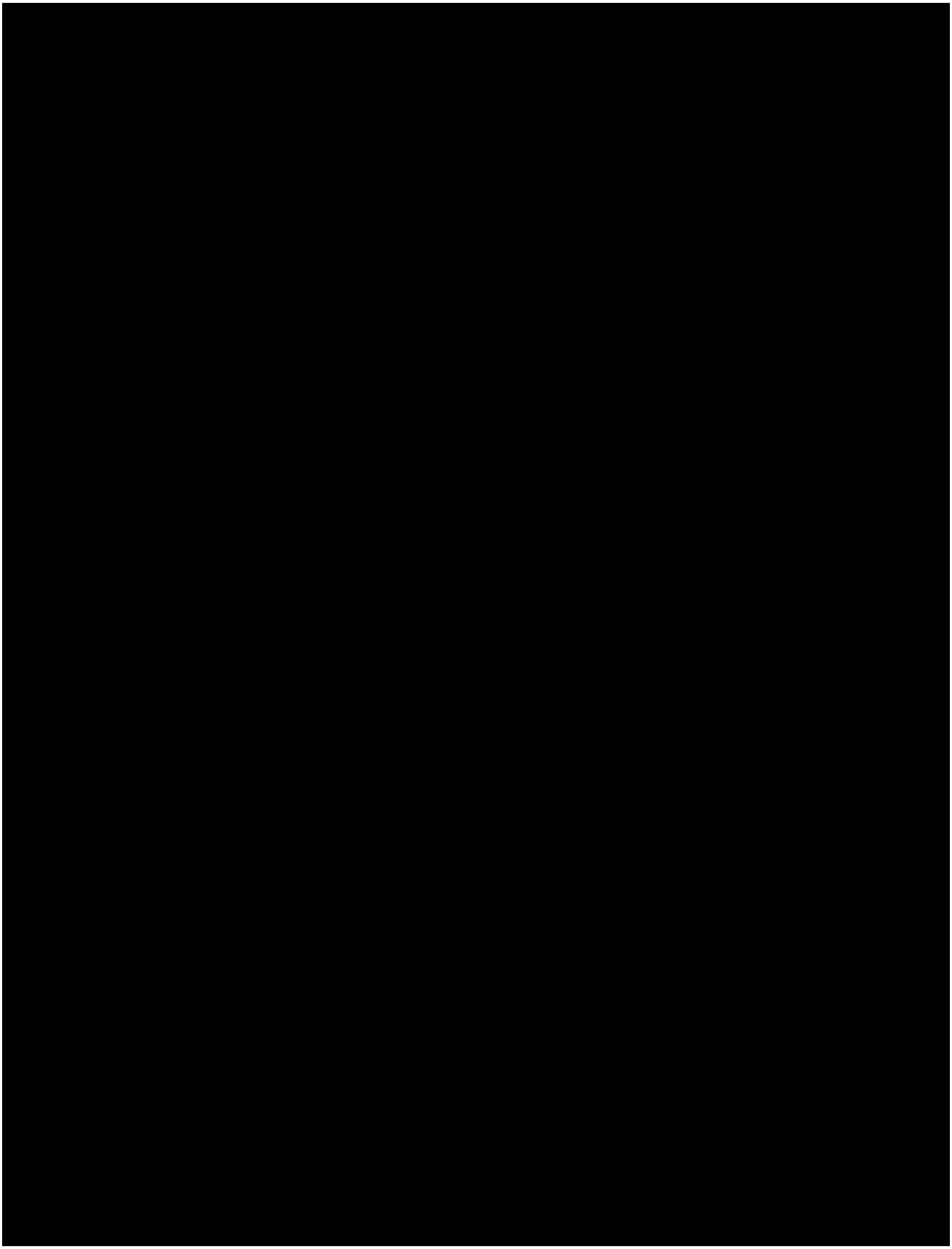


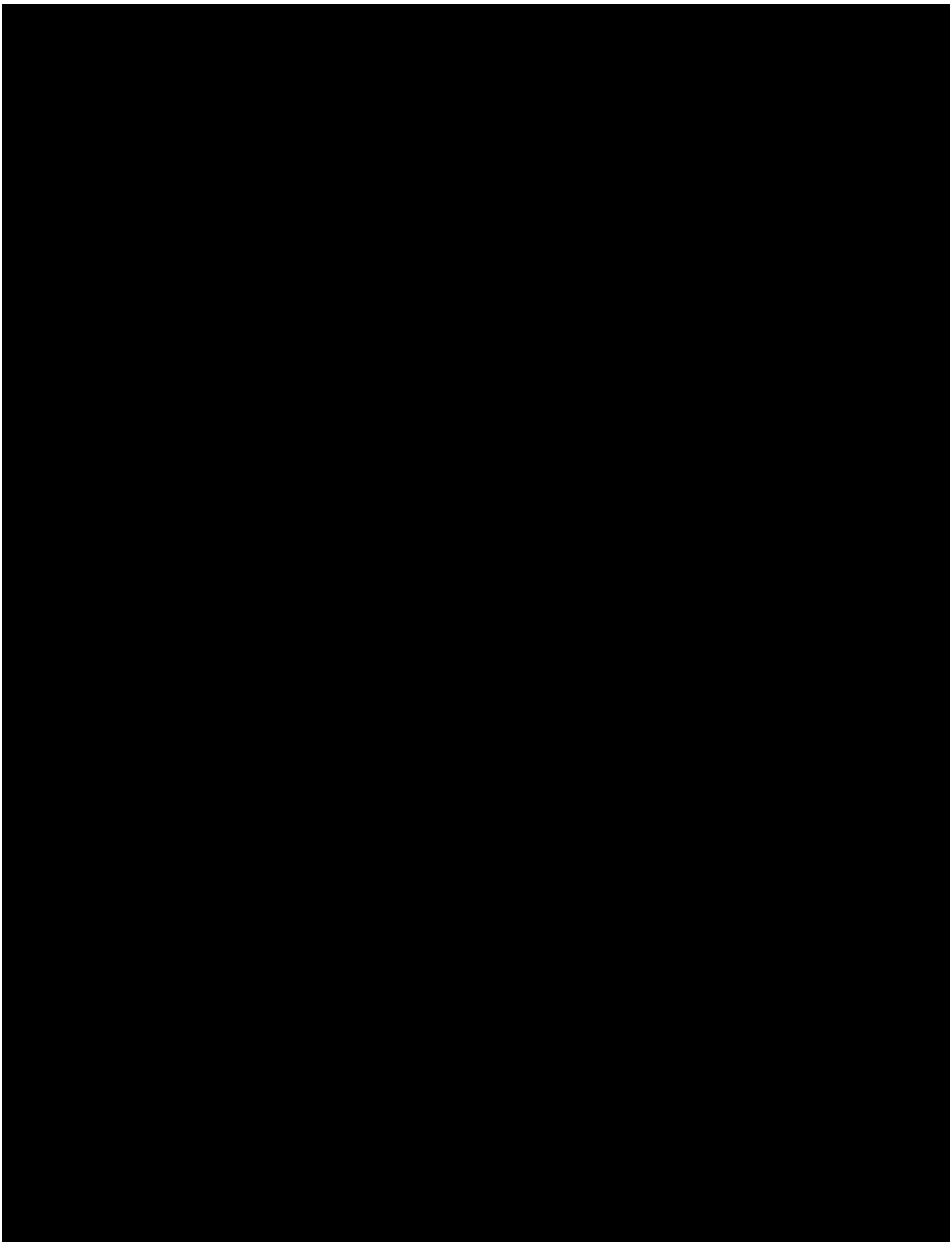


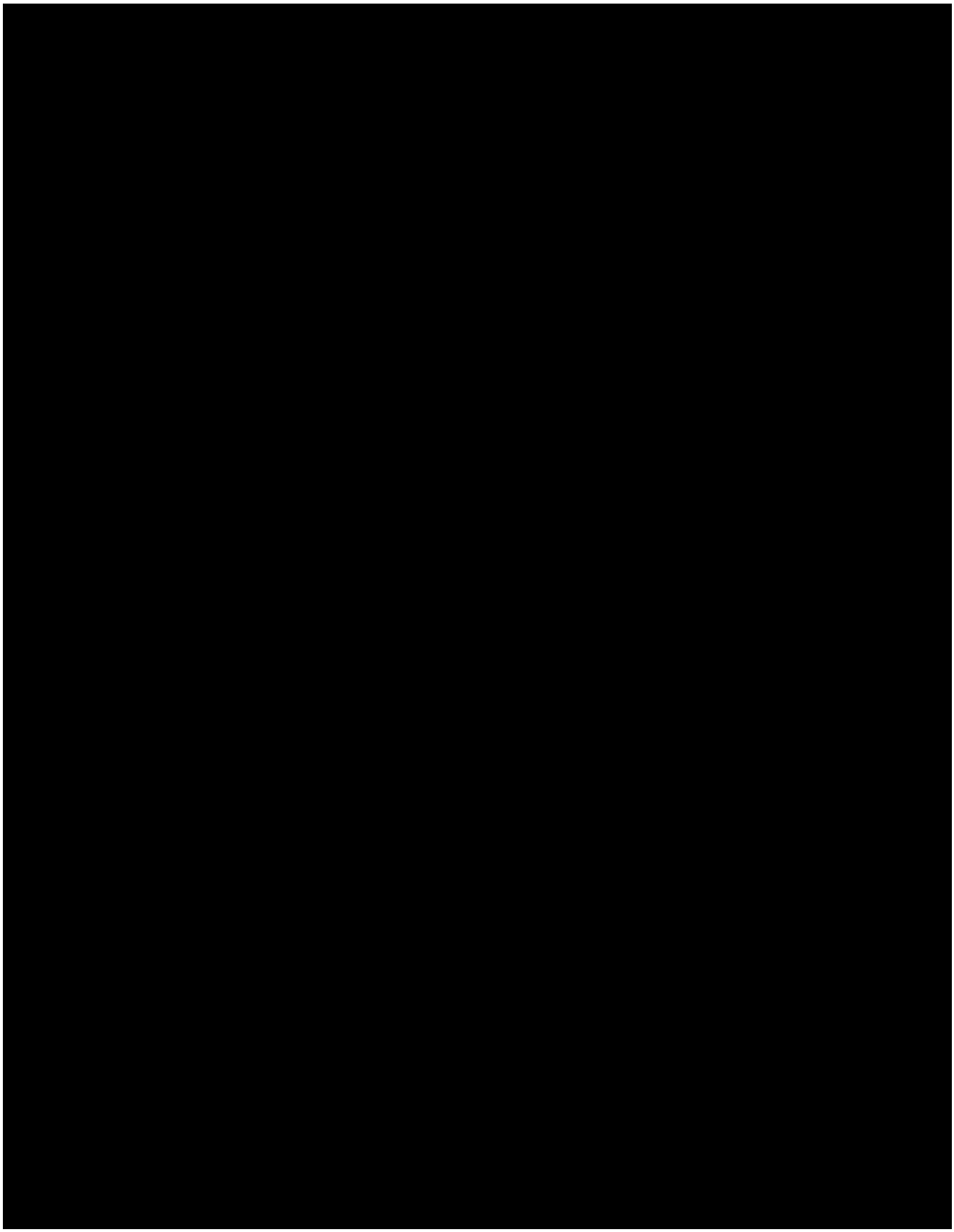


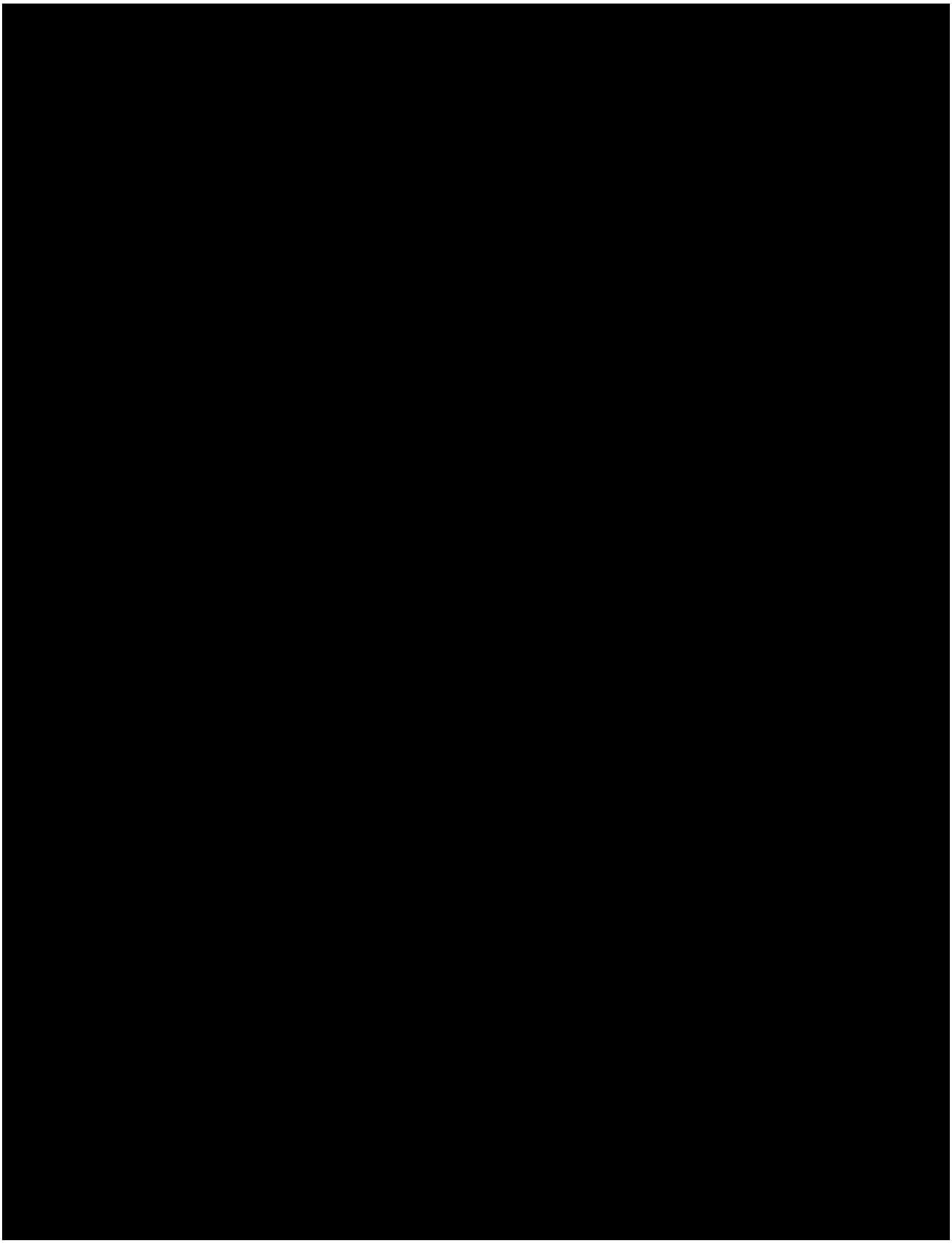


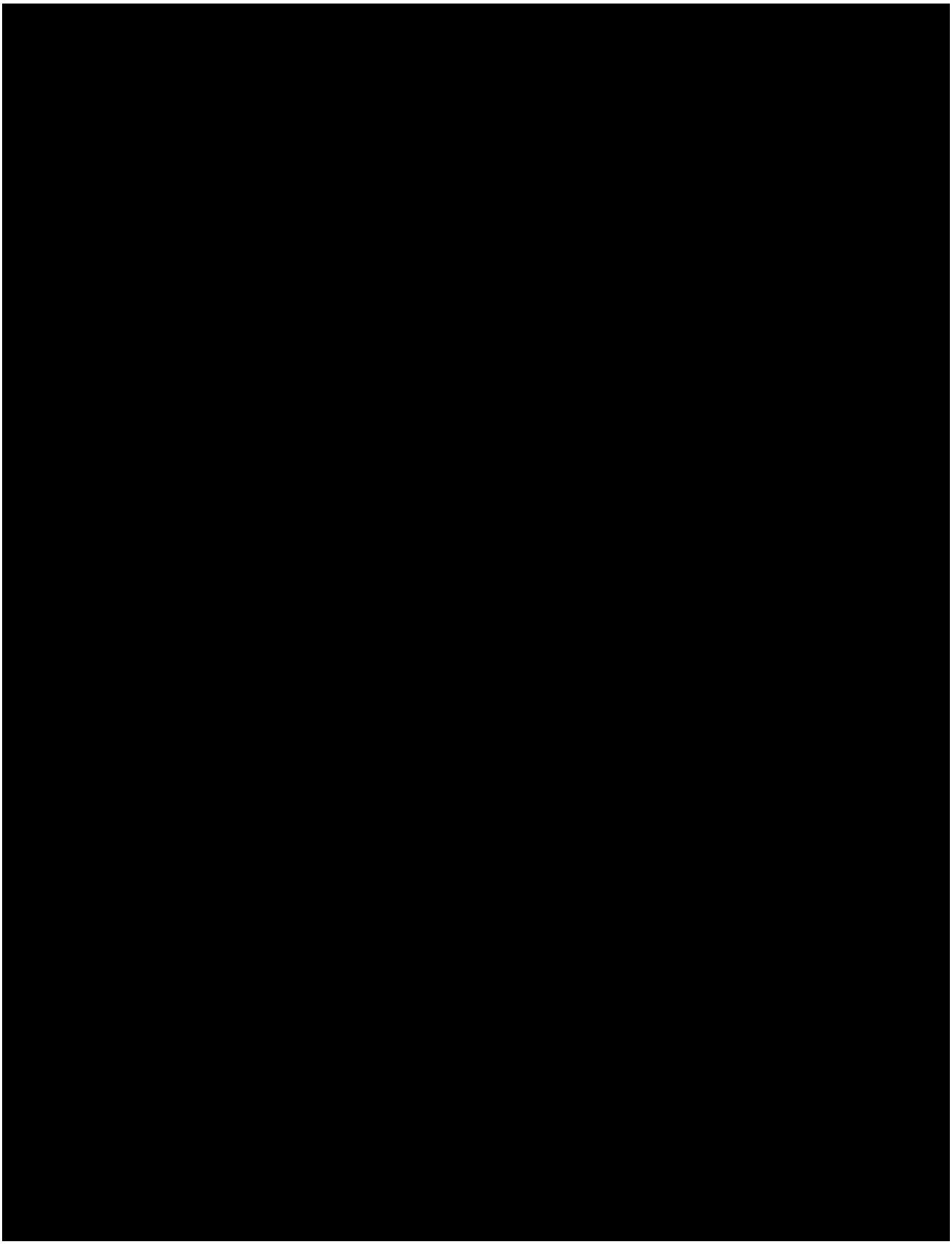


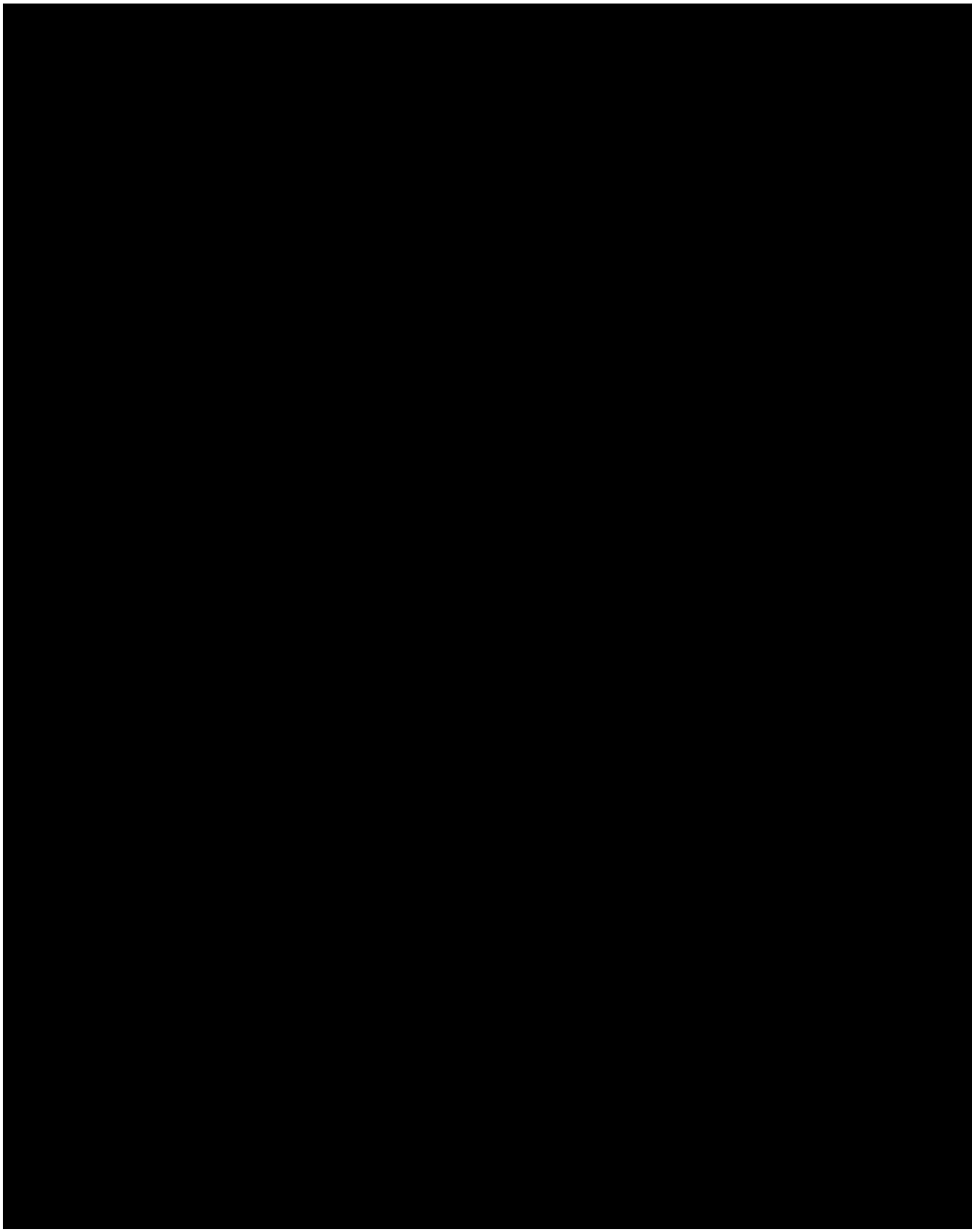












11. STUDY ASSESSMENTS

11.1. Demographic and Other Pretreatment Assessments: Part 1 and/or Part 2

After written informed consent is obtained, demographic data and a complete medical and medication history will be collected at the Screening visit. A complete physical examination, including measurements of height and body weight will be performed. Medical history will be updated until the first dose of study drug. All AEs will be recorded from the time of informed consent and throughout the study, regardless of apparent causality from use of the study drug. Medications taken before the first dose of study drug will be recorded as prior medications.

11.2. Assessments of Efficacy

In Part 1, subjects meeting all eligibility criteria and with suspicion of significant liver fibrosis (through clinical, hepatic fibrosis indices, and/or liver stiffness assessment) will have a liver biopsy read by an independent central pathologist during the Screening period. In randomized subjects, a second post-treatment liver biopsy will be collected within ± 2 weeks of the Month 12 visit.

In Part 2, newly enrolled subjects will undergo a liver biopsy at Screening for assessment of eligibility and a second post-treatment liver biopsy will be collected within ± 2 weeks of the

Month 12 visit. All subjects (newly randomized subjects with a liver biopsy diagnosis of NASH and Stage 3 liver fibrosis (by NASH CRN system) and those who continue from Part 1) will undergo a liver biopsy at Month 60 (within ± 2 weeks) after first dose of study drug.

At the end of study, if a subject has received study drug for at least 6 months and has not had the Month 60 biopsy, then a biopsy should be taken within 30 days of the end of study, if feasible.

Liver biopsies will be performed per standard of care (eg, taking into account the subject's health status, coagulation profile, and use of concomitant medications). Subjects who discontinue study drug are encouraged to continue with all other evaluations as scheduled in this protocol, including biopsies and other invasive procedures at the scheduled visits. If a subject discontinues study participation early and has received study drug for at least 6 months in Part 1 or Part 2, then a biopsy should be taken within 30 days of discontinuation, if feasible. All liver biopsies will be evaluated by an independent central pathologist; whenever possible, the same pathologist will evaluate all biopsies from an individual subject. The independent central pathologists will be blinded to individual treatment assignment.

Liver biopsy at Screening and Months 12 and 60 will be used to determine improvement in histologic fibrosis stage (NASH CRN – the system used to assess the primary efficacy endpoint – and Ishak systems).

NASH CRN Staging System

The NASH CRN adopted the staging system validated by Kleiner.[28] The authors evaluated a scoring system comprising 14 histological features that addressed the full spectrum of lesions of NAFLD. Five features were evaluated semi-quantitatively (steatosis [0-3], location [0-3], lobular inflammation [0-3], hepatocellular ballooning [0-2], and fibrosis stage [0-4]) and 9 additional features were recorded as present or absent. As a result of this evaluation, the NASH CRN staging system for evaluating histological changes after therapeutic intervention trials adopted a defined and validated semi-quantitative scoring system, NAS, based on the unweighted sum of steatosis, lobular inflammation, and hepatocellular ballooning scores. The system is simple and requires only routine histochemical stains (hematoxylin and eosin and Masson trichrome stains). This strong scoring system and NAS for NAFLD and NASH was shown to have reasonable inter-rater reproducibility in both adults and children with any degree of NAFLD. A NAS of > 5 correlated with a diagnosis of NASH, and biopsies with scores of < 3 were diagnosed as not NASH. The primary purpose of the NAS is to assess overall histological change; it is not intended that numeric values replace the pathologist's diagnostic determination of steatohepatitis.

The evaluation of fibrosis stage associated with NASH will be based on the NASH CRN Fibrosis Staging System, as follows:[28]

Fibrosis	Stage
None	0
Perisinusoidal or periportal	1
Mild, zone 3, perisinusoidal	1A
Moderate, zone 3, perisinusoidal	1B
Portal/periportal	1C
Perisinusoidal and portal/periportal	2
Bridging fibrosis	3
Cirrhosis	4

Ishak Staging System

The morphological features that are important in undertaking grading and staging in chronic hepatitis are described by Ishak.[29] The Ishak fibrosis stage will be based on the following scoring system:[29]

Architectural Changes, Fibrosis and Cirrhosis	Score
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3
Fibrous expansion of portal areas with marked bridging [portal to portal (P-P) as well as portal to central (P-C)]	4
Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6

Serum hepatic fibrosis indices

Serum hepatic fibrosis indices (including FIB-4, APRI, and NFS) will be determined at Screening, Baseline, and Months 6 and 12 in Part 1, and at Screening, Baseline, Months 6 and 12, and every 12 months thereafter in Part 2.

APRI is calculated using the formula:[30]

$$\text{APRI} = (\text{AST level [/ULN]} / \text{platelet counts } [10^9/\text{L}]) \times 100$$

An APRI index of ≤ 0.50 indicates the absence of significant fibrosis and an index of > 1.50 indicates the presence of significant fibrosis.

NFS is a validated simple scoring system consisting of routinely measured and readily available clinical and laboratory data to categorize NAFLD patients with and without advanced fibrosis:[32]

NFS = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/L) – 0.66 × albumin (g/dL).FIB-4 is a noninvasive hepatic fibrosis index score combining standard biochemical values, platelets, ALT, AST, and age that is calculated using the formula:[31]

$$\text{FIB-4} = (\text{Age [years]} \times \text{AST [U/L]}) / (\text{platelets } [10^9/\text{L}] \times (\text{ALT [U/L]})^{1/2})$$

A FIB-4 index of < 1.45 indicates no or moderate fibrosis and an index of > 3.25 indicates extensive fibrosis/cirrhosis.

The Enhanced Liver Fibrosis (ELF™) Test is a blood test that provides an ELF Score that delivers information on liver fibrosis severity and will be assessed in this study. The ELF Score is determined by combining in an algorithm, quantitative measurements of by-products of the fibrotic process (hyaluronic acid [HA]), amino-terminal propeptide of type III procollagen [PIIINP]), tissue inhibitor of metalloproteinase 1 [TIMP-1]).

The ELF Score will be determined at Baseline, Month 6, Month 12, and every 12 months thereafter.

The authors analyzed routine demographic, clinical, and laboratory variables to predict presence or absence of advanced fibrosis. Age, hyperglycemia, BMI, platelet count, serum albumin, and AST/ALT ratio were found to be independent indicators of advanced liver fibrosis, so these 6 variables were included in the NFS scoring system. A low cut-off score of -1.455 indicates the absence of advanced fibrosis and a high cut-off score of 0.676 indicates the presence of advanced fibrosis.

At sites where available, liver stiffness will be assessed in fasting subjects by ultrasound TE at Baseline (if not performed within 6 months prior to the first day of Screening), at Months 6 and 12 in Part 1, and annually in Part 2. The Screening value (if performed by TE) will be used as the Baseline value. The visit window will be ± 2 weeks for all on-treatment TE assessments.

11.3. Assessments of Safety

AEs will be assessed at each visit.

11.3.1. Adverse Events and Serious Adverse Events

11.3.1.1. Definitions

11.3.1.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject 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.

11.3.1.1.2. Treatment-Emergent Adverse Events

An event will be considered a TEAE if:

- The event began on or after the date of the first dose of study drug; or
- An exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition on or after the date of the first dose of study drug

An AE that occurs more than 30 days after the last dose of study drug will not be counted as a TEAE.

11.3.1.1.3. Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as any adverse event caused by the use of a pharmaceutical product. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the pharmaceutical product caused the event.

11.3.1.1.4. Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the study drug caused the adverse event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study drug and adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means an adverse event caused by a study drug.

11.3.1.1.5. Unexpected Adverse Event or Reaction

An adverse event or suspected adverse drug reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

11.3.1.1.6. Events Related to Disease Under Study

Worsening of a pre-existing illness other than the disease under study will be assessed as an AE. If such an AE meets the definition of an SAE (see Section 11.3.1.1.10), it must be reported as such (see Section 11.3.1.5).

11.3.1.1.7. Clinically Significant Laboratory Abnormalities

Any laboratory abnormalities deemed clinically significant by the investigator must be reported as an AE. A clinically significant abnormality is a confirmed abnormality (by repeat testing) that is changed sufficiently from Baseline so that in the judgment of the investigator a change in management is warranted. This alteration may include: monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment. See Section 11.3.6 for details regarding the management and monitoring of laboratory abnormalities of interest. See Section 11.3.1.2 for details regarding recording of adverse events.

11.3.1.1.8. Surgical Procedures

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of the study drug. In the latter case, the condition should be reported as medical history.

11.3.1.1.9. Overdose

An overdose is defined as a subject's report of taking more than 1 tablet of study drug (ie, more than 1 tablet per day of blinded CVC or placebo). Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For reporting purposes, overdose will be considered an SAE only if any of the seriousness criteria are met (see definition in Section 11.3.1.1.10).

11.3.1.1.10. Serious Adverse Event or Serious Adverse Reaction

An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
    - An AE or suspected AE is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at

immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization (ie, admission, overnight stay) or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events
    - An important medical event is one that, when based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE. (Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

11.3.1.1.11. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and to understand it.

Elevations in biochemistry that are associated with liver injury have been identified as potentially important risks and are considered AESI for the study drug in this protocol. If subjects meet biochemical criteria for suspected DILI, as defined in Section 11.3.6.4, the event should be reported to Global Patient Safety and Epidemiology (GPSE) within 24 hours on the AESI form (see Section 1). In addition, the AESI form should be completed and sent to GPSE within 24 hours of permanent study drug discontinuation for confirmed ALP, ALT, AST, and/or bilirubin elevations. AESI will be adjudicated by a hepatologist with expertise in DILI and reviewed by the DSMB.

11.3.1.2. Adverse Event and Clinically Significant Laboratory Abnormality Recording

Treatment-emergent adverse events and laboratory test abnormalities considered to be clinically significant should be recorded as AEs in the eCRF.

The AE or clinically significant laboratory abnormality should be reported in standard medical terminology. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded.

If the laboratory abnormalities are part of a clinical constellation of signs and/or symptoms that comprise a medical diagnosis, then the terminology for that medical diagnosis should be used in the AE record.

AEs and clinically significant laboratory abnormalities that are reported as AEs fall into the categories of "non-serious" and "serious." From the time of informed consent and throughout the study, all AEs and clinically significant laboratory abnormalities must be recorded in the eCRF, regardless of apparent causality from use of the study drug.

The following information should be captured for all AEs and clinically significant laboratory abnormalities: date of onset and end date or outcome (eg, ongoing), severity of the event, seriousness of the event, investigator's opinion of the relationship to investigational product (CVC), action taken with regard to any of the study drugs and treatment required for the AE, cause of the event (if known), and information regarding the resolution/outcome.

AEs classified as serious must be recorded on the appropriate SAE reporting tool and reported to the sponsor using expeditious handling to comply with regulatory requirements (see Section 11.3.1.5).

11.3.1.3. Adverse Event Classification

The intensity of an AE or clinically significant laboratory abnormality will be graded according to the scale below in addition to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 Table for Grading the Severity of Adult Adverse Events (see Appendix 20.2). The clinical significance of the AE is determined by the investigator. The investigator is encouraged to consult with the medical monitor. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

- **Grade 1 (Mild)**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2 (Moderate)**: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- **Grade 3 (Severe)**: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- **Grade 4 (Life-Threatening)**: Life-threatening consequences; urgent intervention indicated
- **Grade 5 (Death)**: Death related to AE

When the intensity of an AE or clinically significant laboratory abnormality changes over time for a reporting period (eg, between visits), each change in intensity will be reported as an AE until the event resolves. For example, 2 separate AEs will be reported if a subject

experiences Grade 1 diarrhea for 3 days, meeting the definition of an AE, and then after 3 days the event increases to a Grade 3 intensity that lasts for 2 days and then resolves. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the AE definition and a stop date equal to the day that the event increased in intensity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date on the day that the event changed intensity again or resolved. For analysis purposes, this will be considered one AE for this subject and the maximum intensity will be recorded.

The relationship or association of the AE to a study drug (CVC or placebo) should be assessed using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication)

- **Yes:** A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the study drug. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon re-challenge.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or liver biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure

- **Yes:** The adverse event occurred as a result of protocol-mandated procedures such as venipuncture or liver biopsy

11.3.1.4. Adverse Event Coding

AE verbatim terms provided by the investigator will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0 or later.

11.3.1.5. Reporting of Serious Adverse Events

The sponsor is required to expedite to regulatory authorities reports of SAEs, serious ADRs, or suspected unexpected serious adverse reactions (SUSARs) in line with relevant legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Commission Clinical Trials Directive (2001/20/EC), and other country specific legislation or

regulations. Expectedness of SAEs will be determined by the sponsor using reference safety information specified in the Investigator Brochure.

Any SAE, serious ADR or SUSAR that occurs during the study from the time of signing the ICF to within 30 days following discontinuation of study drug, regardless of relationship to the study drug, must be reported within 24 hours to the contact below:

Send completed Safety Report Forms to Global Patient Safety and Epidemiology, Allergan plc (see Section 1)

The required SAE information must be completed on the SAE Form. The sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports. For questions on SAE reporting, please contact the medical monitor (see Section 1 for contact information).

A copy of the submitted SAE form must be retained on file by the investigator. The investigator must submit the SAE to the IRB/IEC according to local requirements and retain documentation of these submissions in the site study file.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE Form.

If the investigator detects an SAE in a study subject after the end of the period of observation, and considers the event possibly related to prior study drug, he/she should contact the medical monitor to determine how the event should be documented and reported.

In case of emergency, contact the medical monitor (see Section 1 for contact information).

All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the IRB/IEC as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

In accordance with the European Union (EU) Clinical Trials Directive (2001/20/EC), the sponsor or specified designee will notify worldwide regulatory authorities and the relevant Ethics Committees in concerned Member States of applicable SUSARs as individual notifications or through a periodic line listing.

11.3.1.6. Follow-up of AEs and SAEs

AEs (including SAEs) will be collected from the time of informed consent, throughout the treatment period, until 30 days after the last dose of study drug is administered.

All subjects who have AEs, whether considered associated with the use of the investigational product or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found, or the investigator

considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied if and when available. **In Parts 1 and 2, a plasma sample for PK should be collected, preferably within 24 to 48 hours of last intake of study drug, in any subject who develops an adverse event of hepatic injury or decompensation or if early treatment discontinuation was due to an AE. The date and time of the PK draw and the last dose of study drug must be recorded in the eCRF.**

11.3.1.7. Pregnancy

If a female subject becomes pregnant during the study, the subject must be instructed to discontinue study drug and inform the investigator immediately. The investigator should report all pregnancies occurring in a subject or partner of a subject participating in the study that occur up to 3 months following the last dose of study drug to Allergan Global Patient Safety and Epidemiology within 24 hours of becoming aware of the pregnancy. The investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE. Elective abortion procedures, without complications, should not be considered as AEs.

All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Allergan Global Patient Safety and Epidemiology.

[redacted]

11.3.1.8. Special Situation Reports

Special situation reports include reports of medication error, abuse, misuse, or overdose, and reports of adverse reactions associated with product complaints.

- Medication error is any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient, or consumer. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors. Cases of subjects missing doses of investigational product are not considered reportable as medication error.

- Abuse is defined as persistent, sporadic or intentional excessive use of a medicinal product by a patient accompanied by harmful, physical, and/or psychological effects.

- Misuse is defined as any use of a medicinal product in a way that is not in accordance with the protocol instructions or the local prescribing information and may be accompanied by harmful physical and/or psychological effects.

- An overdose refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the authorized product information (protocol). Clinical judgment should always be applied. In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s) or the investigator has reason to suspect that the subject has taken the additional dose(s).

- Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs (using the criteria for AEs and SAEs as described in Section 11.3.1) at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

11.3.1.9. Unblinding of Study Drug

Emergency Unblinding: In emergency situations, the investigator may need to break the blind if he/she finds it is in the best interest of the study subject. In the event that immediate knowledge of the treatment received (CVC versus placebo) is necessary for the management of the subject, the investigator may request unblinded treatment information using IxRS. The medical monitor should be notified promptly about the unblinding.

The event, the date, the time, the person who made the request, and the reason for unblinding will be recorded in the source documents. The identity and study responsibility of the individual(s) who were made aware of the unblinded treatment assignment must also be documented.

It is mandatory that research staff who were involved in the unblinding and who had access to the unblinded treatment assignment maintain the confidentiality of this information. Subjects who are prematurely unblinded should return for an Early Discontinuation and follow-up visit.

11.3.2. Laboratory Assessments

11.3.2.1. Measurement of Laboratory Assessments

A central laboratory will perform clinical safety laboratory tests. Urine pregnancy tests will be performed at the site using a dipstick method. Central laboratory values for INR that are > 1.5 should be repeated in the local laboratory and the central laboratory.

A complete list of all laboratory tests is provided in Appendix 20.5.

Refer to the manual provided by the sponsor for details on the laboratories for this study and for country-specific laboratory requirements.

Samples for hematology and serum chemistry will be prepared using standard procedures. Refer to the laboratory manual provided by the sponsor for further details and specifications for sample handling, processing, and shipment.

11.3.2.2. Clinically Significant Laboratory Abnormalities

Any laboratory test showing abnormal results (including those recorded as AEs) that are believed to be possibly/probably related to study drug treatment will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved (if baseline was within normal range), returns to Baseline range (if baseline was abnormal), or is otherwise explained. Whenever possible, the etiology of the abnormal findings will be documented on the eCRF. See Section 11.3.1.1.7 for a definition of clinically significant laboratory abnormality.

11.3.3. Vital Signs

Vital sign measurements (systolic and diastolic blood pressure, temperature, pulse rate, and respiration rate) will be taken at each visit. For subjects who discontinue study drug early, vital signs will be measured at the Early Discontinuation visit within 48 hours of stopping study drug unless the subject remains on study post-treatment termination. Vital signs will be performed with the subject in the sitting position after 5 minutes of rest and before any blood draws.

11.3.4. Electrocardiogram

A 12-lead ECG will be taken at Baseline and at Month 12 in Part 1, and at Baseline and annually throughout the study in Part 2. ECGs will be performed with the subject in the supine position after 5 minutes of rest and before any blood draws.

11.3.5. Physical Examination

A complete physical examination will be performed at the Screening visit and the Baseline/Day 1 visit in Part 1 and Part 2. A symptom-directed physical examination will be performed, as needed, at all On-treatment Visits, at the Early Discontinuation visit within 48 hours of stopping study drug, and at the Follow-up visit. The complete physical examination will include (but not limited to) the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver and spleen); extremities; lymph nodes; and a brief neurological exam. Abbreviated symptom-directed physical examinations will target signs and symptoms; any abnormal findings that are reported as AEs will be recorded in the eCRF.

11.3.6. Toxicity Management

Clinical events and clinically significant laboratory abnormalities will be graded according NCI CTCAE version 4.03 (Appendix 20.2).

11.3.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator and manage according to local practice.

11.3.6.2. Grade 3 Laboratory Abnormality or Clinical Event

For detailed management of subjects with ALT, AST, alkaline phosphatase (ALP), or bilirubin elevations, see Section 11.3.6.4.

For Grade 3 laboratory abnormalities, a confirmatory measurement should be obtained within 48 to 72 hours after the laboratory results become available.

[redacted]

to resume the normal study visit schedule must be agreed upon between the investigator and the medical monitor.

11.3.6.3. Grade 4 Laboratory Abnormality or Clinical Event

For detailed management of subjects with ALT, AST, ALP, or bilirubin elevations, see Section 11.3.6.4.

For Grade 4 laboratory abnormalities, a confirmatory measurement should be obtained within 48 to 72 hours after the laboratory results become available.

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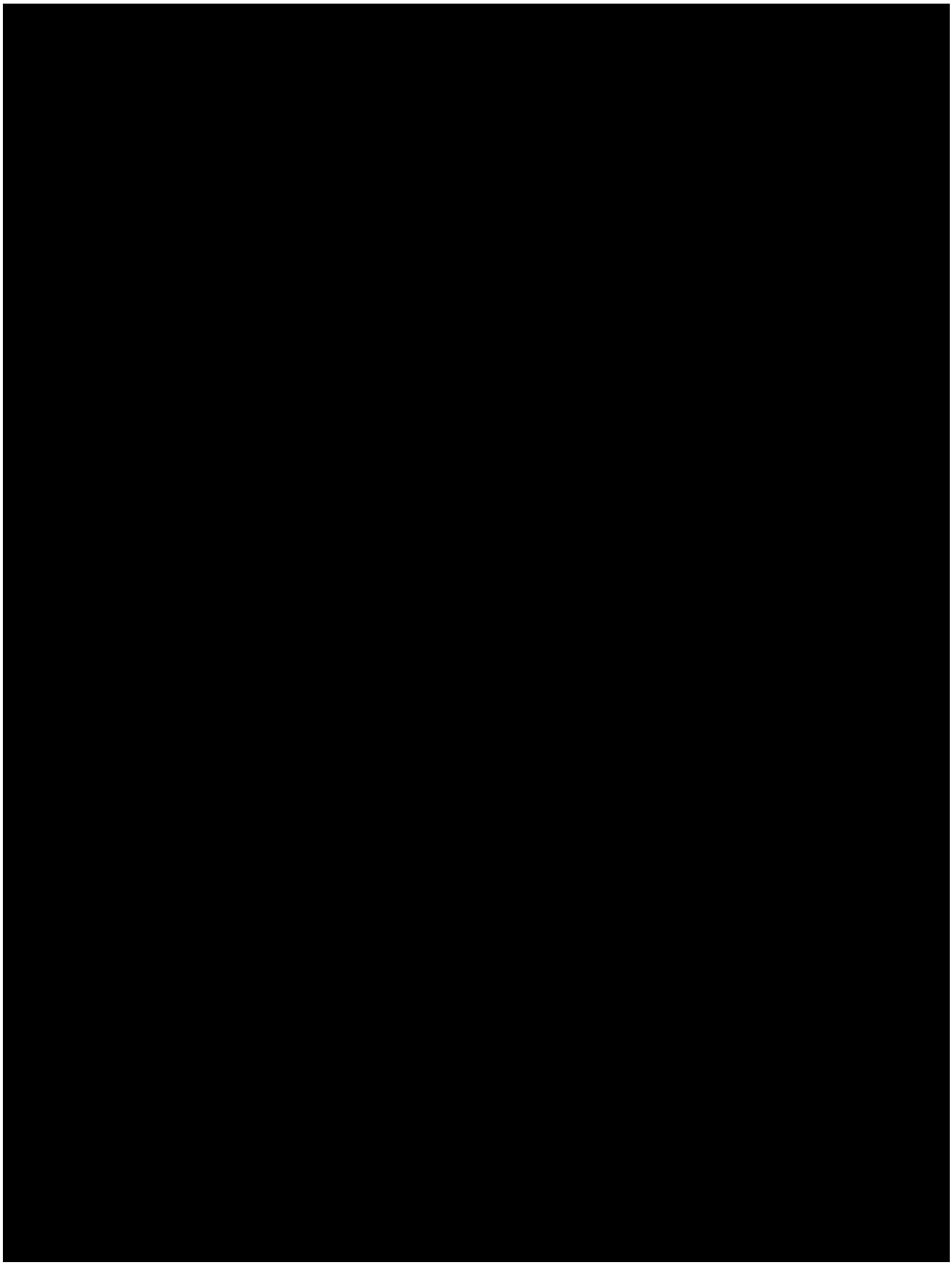
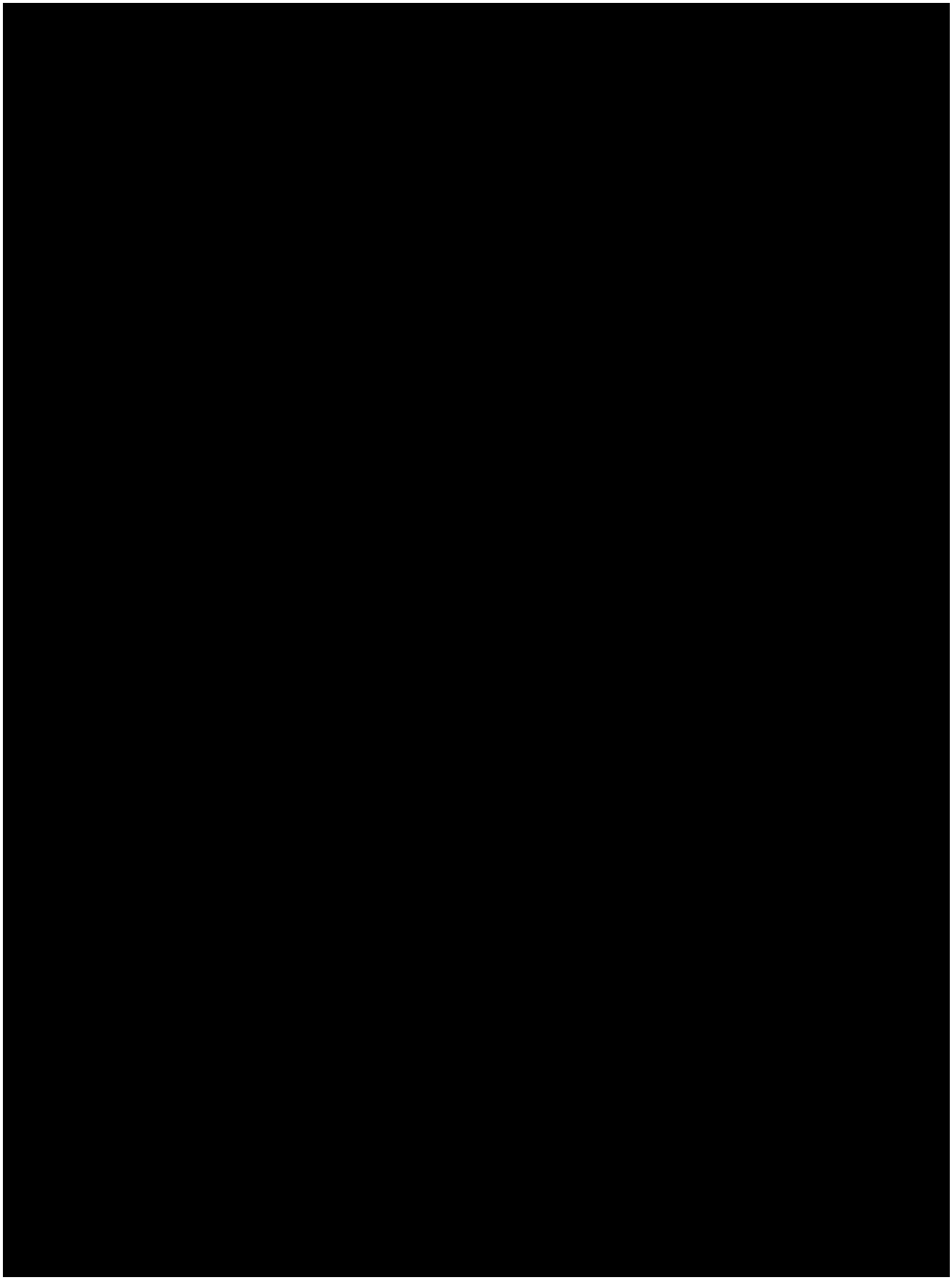
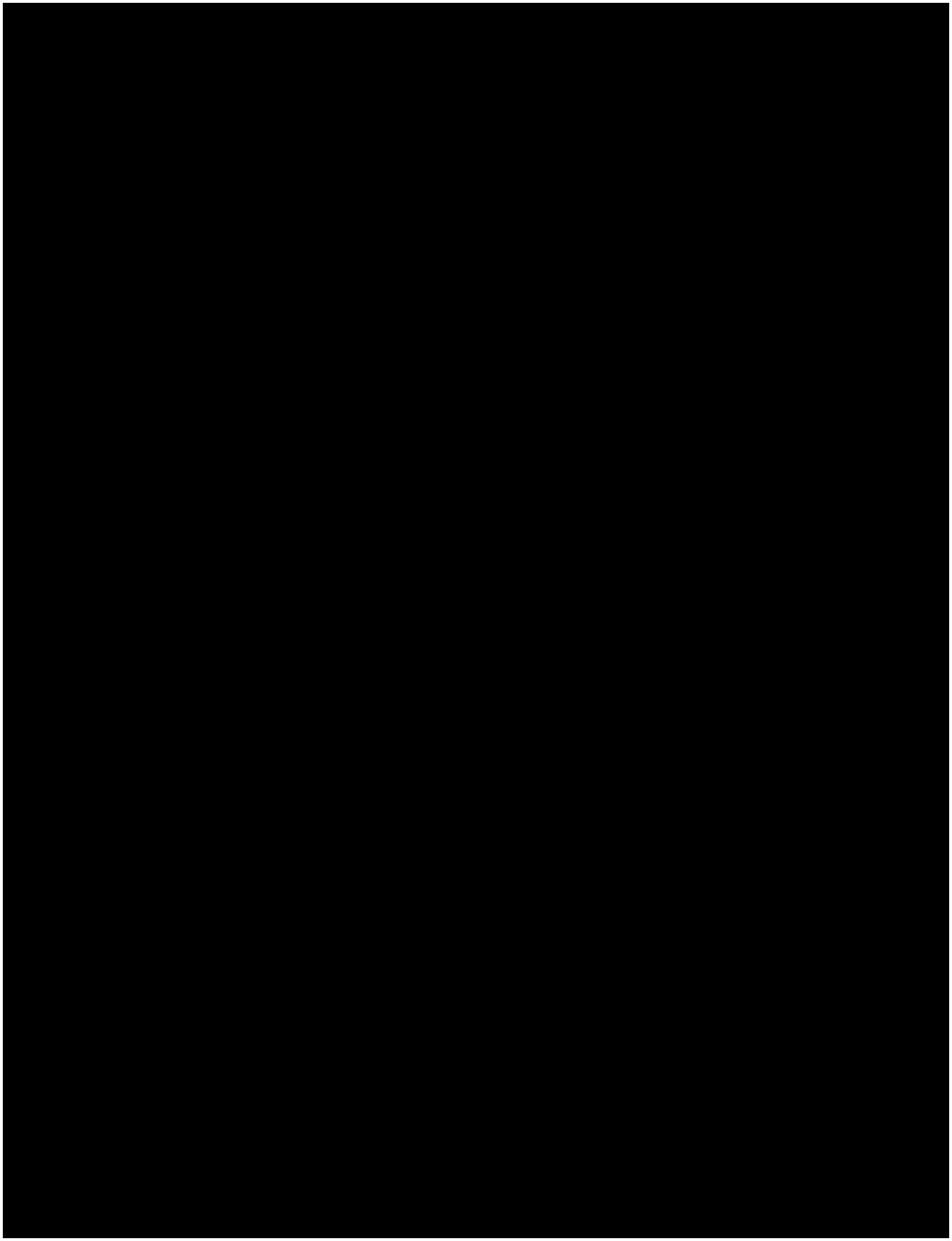
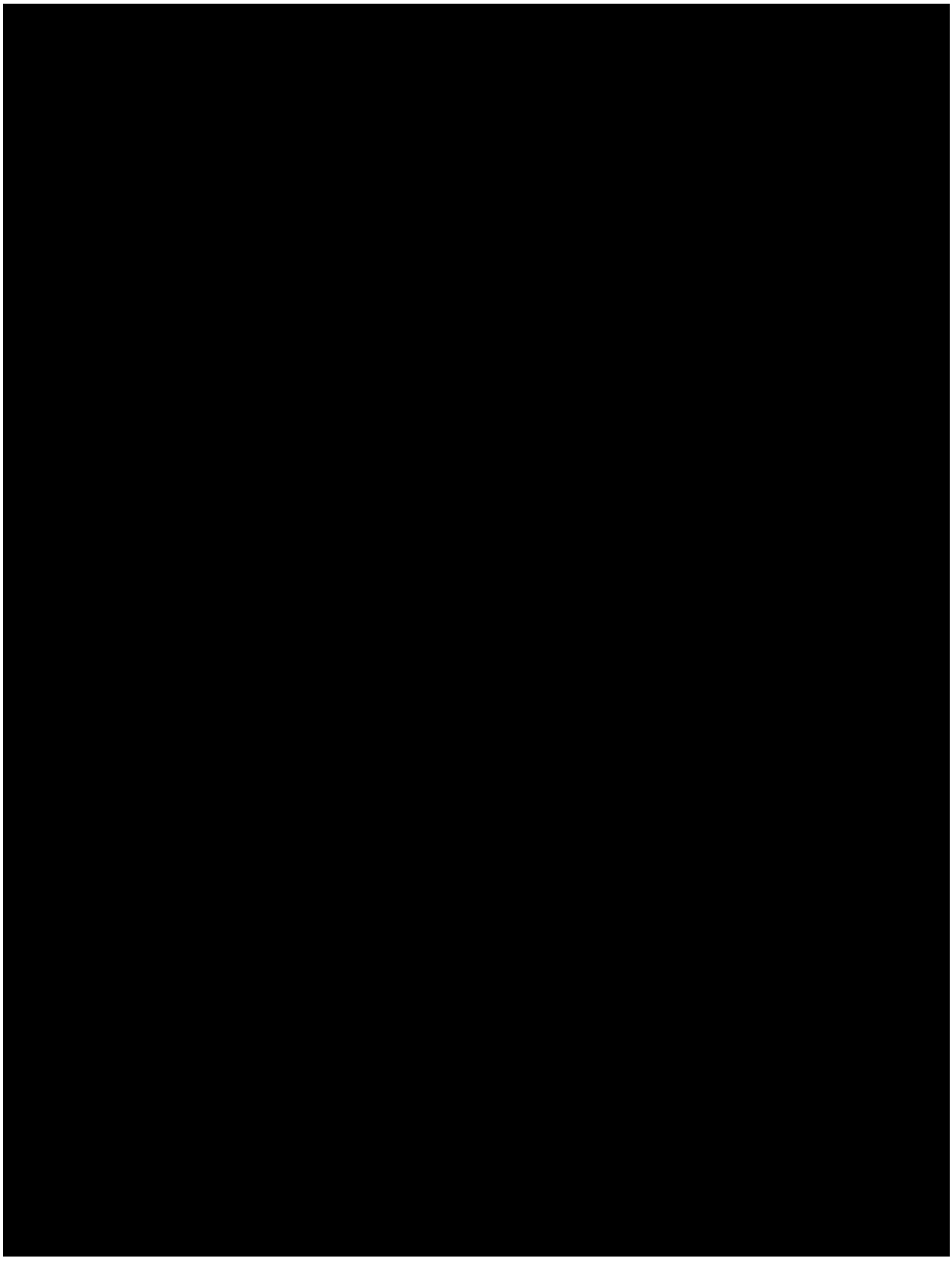
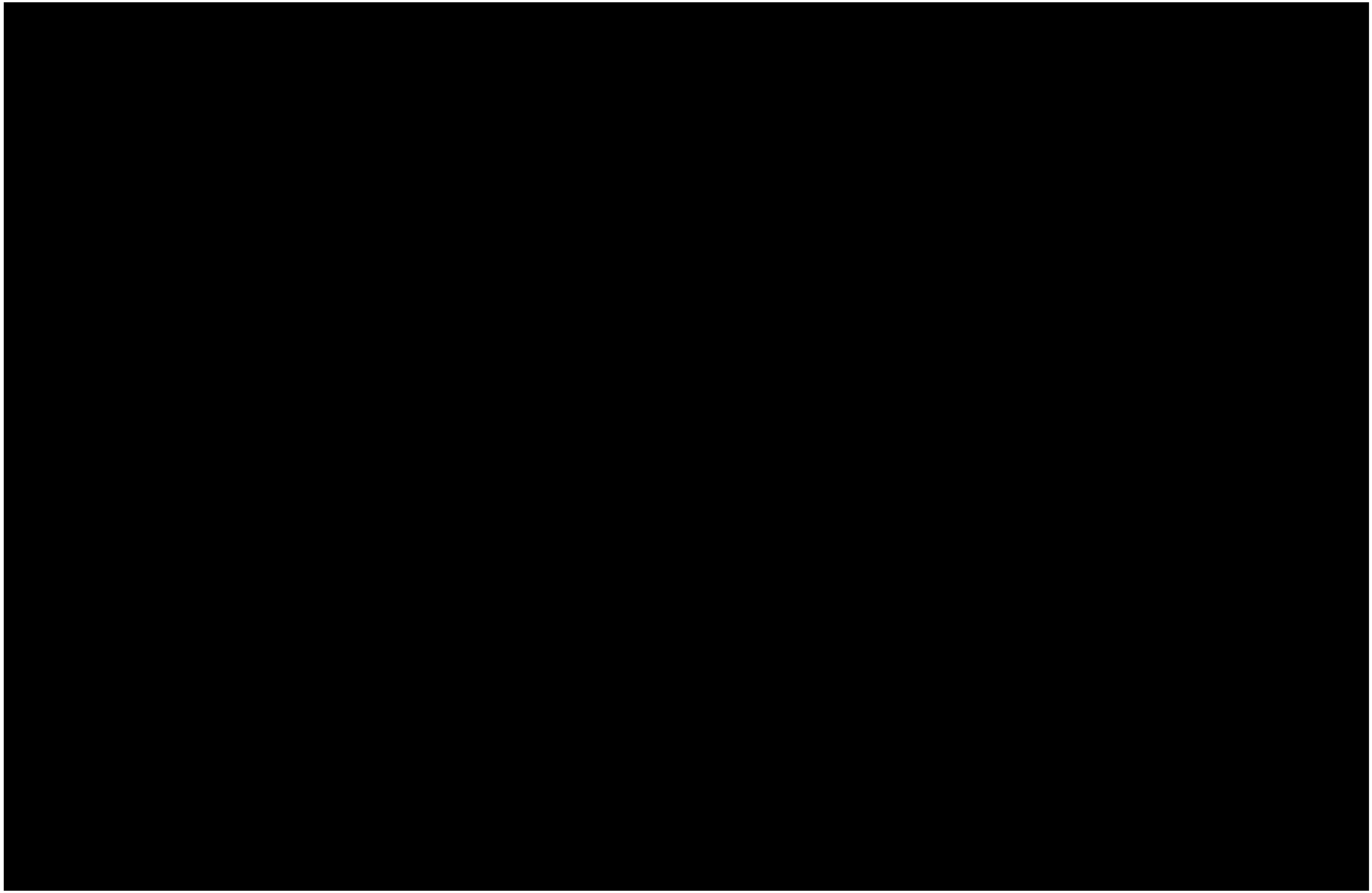
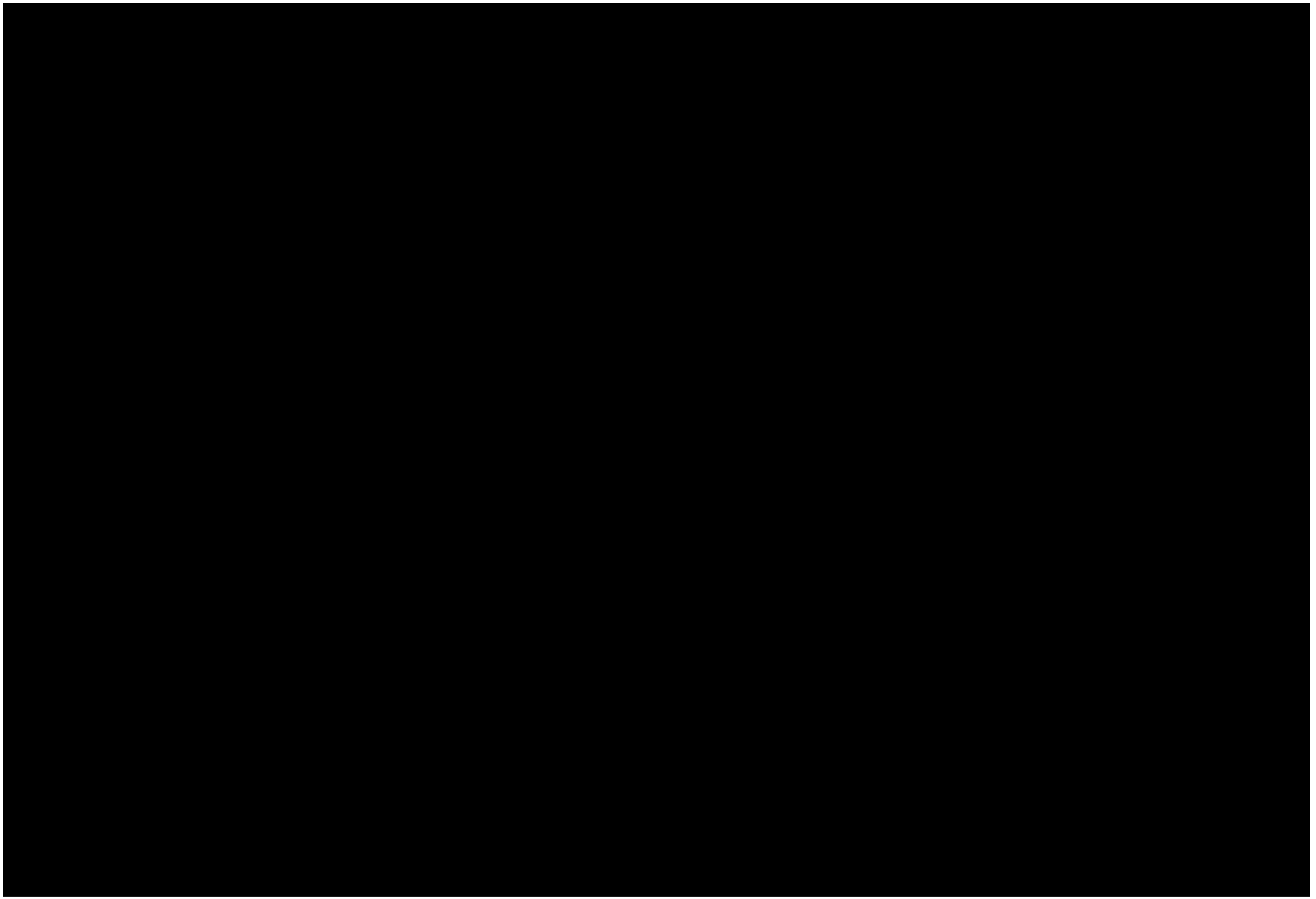


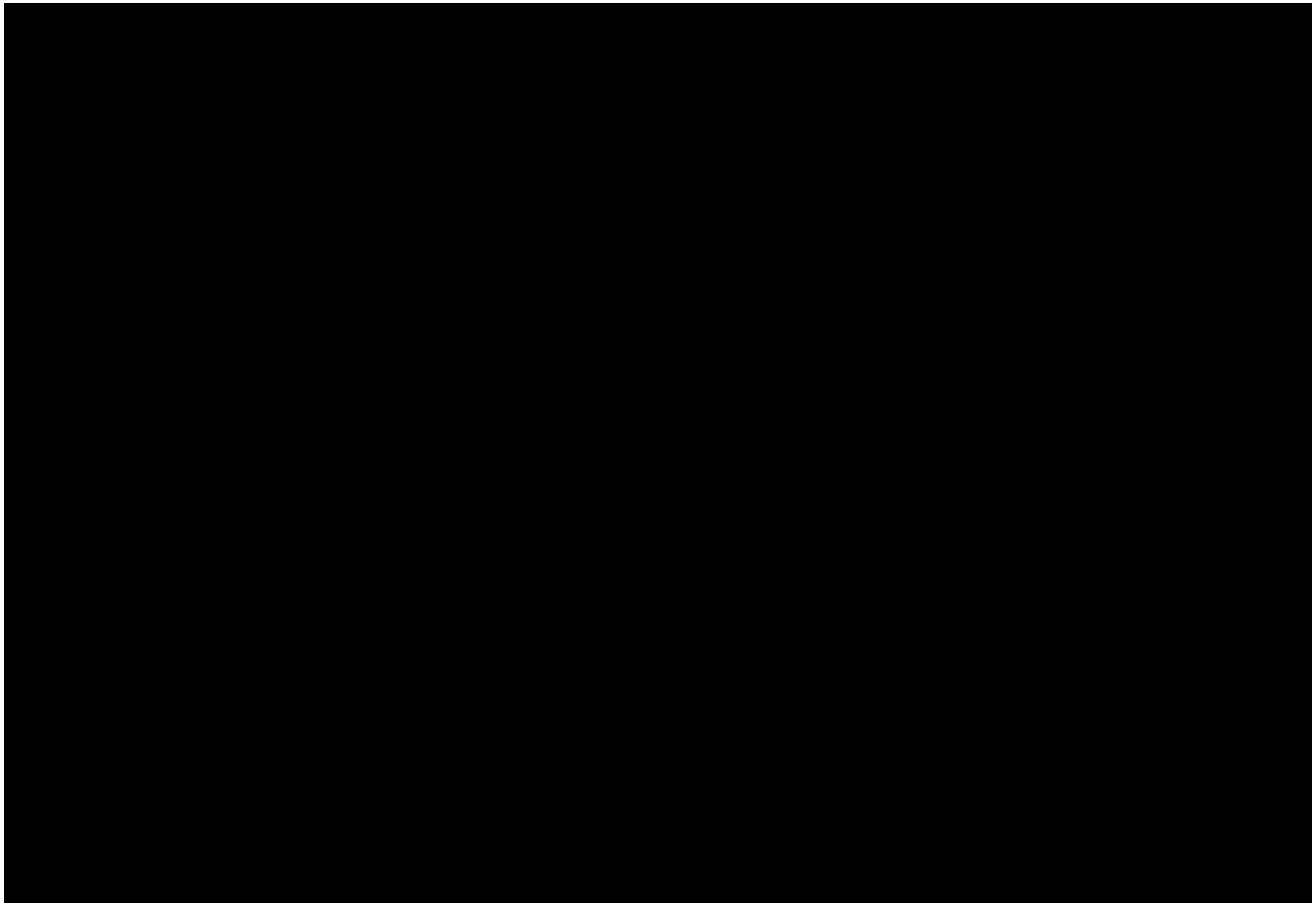












11.4. Assessments of Pharmacokinetics

In Part 1, all subjects who have consented to PK assessment will hold their daily dose on the day of clinic visits on Months 3, 6, and 12. Subjects will bring their study drug bottle to the clinic and take one dose of the study drug under witnessed dosing. One predose plasma sample will be collected and one sample will be collected between 1 to 2 hours after dosing (actual sample collection time and dosing time will be recorded) for population PK analysis at Months 3 and 12 in Part 1. If the subject takes the daily dose before the predose sample is collected, 2 PK samples will be drawn at least 1 hour apart instead and actual sample collection time will be recorded in addition to the dosing time.

Also, in all subjects who have consented to PK assessment, one sample will be collected between 2 to 6 hours after dosing (sample collection time and actual dosing time will be recorded) for population PK analysis at Month 6 in Part 1.

For all subjects enrolled in the study, at the Early Discontinuation visit (if applicable) in Parts 1 and 2, a PK sample should be collected, preferably within 24 to 48 hours of last intake of study drug, for any subjects who discontinue treatment due to an AE. **The date and time of the PK draw and the last dose of study drug must be recorded in the eCRF**.

Refer to the laboratory manual for further details and specifications for sample handling, processing, and shipment.

11.6. Assessments of Drug Accountability and Medication Adherence

Drug accountability through the assessment of tablet counts will be performed by clinic staff at each on-treatment evaluation visit.

Subjects will be instructed to bring back their bottles of study drug (used and unused) with them to every site visit. The investigator, or designee, will count all returned study drug to assess and estimate adherence. Subjects will receive sufficient number of study drug bottles and be reminded to take study drug once daily with food.

If the study drug adherence drops below 80% at any given time during the Treatment Period, the investigator, or designee, should discuss adherence with subject and counsel the subject appropriately. Nonadherence includes missed doses in addition to taking the wrong dose. The investigator must encourage adherence with the study drug and with the study procedures at all times.

11.7. Pharmacogenetic Sampling

Pharmacogenetic sampling is to be conducted only at study centers where the IRB has approved the pharmacogenetic portion of the study. Participation in the pharmacogenetics portion of the study is optional and will require a separate ICF. [redacted]

A subject who initially consents can withdraw that consent at any time and have his or her pharmacogenetic sample destroyed, including any by-products of the sample whenever possible. If a subject withdraws consent, their physical sample will be destroyed and no new health information identifying the subject will be gathered after that date. However, once the genetic data is anonymized and placed into the pharmacogenetic biorepository database, the information cannot be withdrawn.

12. STATISTICS

12.1. General Considerations

Continuous data will be described with sample size, mean, standard deviation, median, minimum and maximum. Categorical data will be described with counts and percentages in each category. Two-sided p-values for all hypothesis tests will be reported and will be interpreted in accordance with the multiple comparisons procedure described in Section 12.1.5.

Subjects will be enrolled in 2 parts, Part 1 and Part 2. Only subjects randomized for Part 1 will contribute to the Part 1 analyses, and all randomized subjects will contribute to the Part 2 analyses. Subjects randomized for Part 1 will be determined at time of enrollment: when a sufficient number has been randomized for the Part 1 analysis, subsequent subjects will be randomized only for the Part 2 analysis. When subjects who contribute to Part 1 have completed their 12-month biopsy (or have been followed for a sufficient time to confirm that such a biopsy will not be obtained), the Part 1 analysis will commence. The Part 1 analysis will summarize subject disposition, protocol deviations, study drug exposure, concomitant medications, demographics and baseline characteristics, and safety for 2 sets of subjects: those who were randomized for Part 1 efficacy, including data up to the Month 12 visit, and all subjects randomized, including all available data in the database at the time of database lock. At the completion of the entire study, analyses will be provided for all subjects whether randomized for Part 1 or for Part 2 only, including all available data in the database.

The significance level of both 0.00125 (2-sided) and 0.05 (2-sided) will be applied for hypothesis testing, with the former to manifest strong evidence from a single confirmatory study and the latter for study success.

12.1.1. Analysis Sets

The following sets of subjects will be analyzed to evaluate the effect of CVC compared to placebo in subjects with NASH:

Intent-to-treat (ITT) analysis set: All subjects randomly assigned to a treatment group will be included in ITT analysis set. Subjects will be included with the randomly assigned treatment, if they receive treatment other than that to which they are randomly assigned. This will be a supportive analysis set for selected efficacy analyses. Subjects with missing Screening biopsy data should not be randomized in the study, hence will not be included in the ITT analysis set, should such subjects exist.

Modified intent-to-treat (mITT) analysis set: All subjects in the ITT analysis set who receive at least one dose of study drug will be included in the mITT analysis set. Subjects will be included with the randomly assigned treatment, if they receive treatment other than that to which they are randomly assigned. This will be the primary analysis set for the efficacy analyses.

Month 12 per protocol (PP1) analysis set: All subjects randomly assigned to a treatment group who have an evaluable biopsy at Screening and another after at least 6 months but before 15 months of follow-up, receive at least 6 months of assigned study drug and have no significant protocol deviations that potentially influence the primary efficacy assessment will be included in the PP1 analysis set. This will be a supportive analysis set for selected efficacy analyses of Part 1 and Part 2. Subjects will be included with the randomly assigned treatment; this will also be the treatment subjects actually received since subjects who receive treatment other than that to which they are randomly assigned will be excluded from PP1. The list of significant protocol deviations will be reviewed by the study team on an ongoing basis and the set of subjects excluded from the PP1analysis set will be identified prior to locking and unblinding the study database.

Month 60 per protocol (PP2) analysis set: All subjects randomly assigned to a treatment group who have an evaluable biopsy at Screening, have no significant protocol deviations that potentially influence the primary efficacy assessment, and either:

- Have an adjudicated event that is a component of the primary composite endpoint within 24 months after randomization

  OR

- Have at least 24 months of follow-up for clinical events **AND** one of the following:

  - Have an adjudicated event that is a component of the primary composite endpoint within 6 months of last intake of study drug,

    OR

  - Have a biopsy at least 24 months after randomization and within 6 months of last intake of study drug,

This will be a supportive analysis set for selected efficacy analyses of Part 2. Subjects will be included with the randomly assigned treatment; this will also be the treatment subjects actually received since subjects who receive treatment other than that to which they are randomly assigned will be excluded from PP2. The list of significant protocol deviations will be reviewed by the study team on an ongoing basis and the set of subjects excluded from the PP2 analysis set will be identified prior to locking and unblinding the study database.

Safety analysis set: All subjects randomly assigned to a treatment group who receive at least one dose of study drug will be included in the safety analysis set. Subjects will be included with the treatment group according to treatment actually received, if they receive treatment other than that to which they are randomly assigned. Subjects who inadvertently receive both treatments will be included with the CVC group. This will be the primary analysis set for the safety analyses.

Pharmacokinetic analysis set: All subjects who are randomized and receive at least one dose of study drug and have at least one post-dose PK sample will be included in the PK analysis set.

12.1.2. Data and Safety Monitoring Board

An independent DSMB will be formed to review ongoing data from this study. The DSMB will be composed of members who have medical expertise in liver disease and at least one statistician. The DSMB will be empowered to recommend changes to the protocol to ensure the safety of subjects in the study, but will not be empowered to recommend stopping or changing the study due to accumulating efficacy data, other than at the planned futility analysis in Part 2 of the study.

Safety data will be reviewed by the DSMB. The first review will occur after the first subject has been followed for at least 6 months. Subsequent reviews will be at least quarterly, at a schedule agreed by the sponsor and the members of the board per the DSMB charter. This data review will not result in any adjustments to alpha because there will not be a chance to stop the study early for a conclusion of efficacy.

For Part 2 of the study, one unblinded assessment of futility will be considered by the DSMB. This will occur after the last randomized subject has been followed for at least 2 years and at least half of the expected events have been observed. If the conditional power exceeds 5%, the study will continue. The study will be stopped only for a conclusion of futility. This data review will not result in any adjustments to alpha because there will not be a chance to stop the study early for a conclusion of efficacy.

No investigator or subject will be unblinded to support DSMB review. No one involved in data review or subject care will be unblinded.

12.1.3. Adjudication Committee

An independent adjudication committee will be formed to review all events that would potentially be components of the primary composite endpoint for the study. Only events confirmed by the adjudication committee will be included in the analysis of the primary endpoint of Part 2; the time to onset will be determined as the date on which the event occurred according to the adjudication committee.

12.1.4. Handling of Missing Data

Data will be analyzed as recorded. Results will be used in the analysis as obtained, without regard for any visit windows. Subjects with missing baseline biopsy data should not be randomized in the study; in the unlikely event that any such subject is incorrectly randomized into the study, the subject will be excluded from analyses (including ITT) due to lack of data for stratification. Such subjects will be listed.

For the primary efficacy analysis in Part 1 using the mITT analysis set, any available liver biopsy after randomization will be used for the Month 12 biopsy, no matter when it was

obtained relative to the first dose of study drug. Subjects with multiple liver biopsies will have the evaluable biopsy closest to the Month 12 visit included in the analysis. Subjects who do not have an evaluable liver biopsy at both Screening and Month 12 will be included in the analyses as non-responders. Summaries of subjects who do and who do not have evaluable liver biopsies at Month 12 will be provided to assess whether demographics, baseline data or safety data are predictive of missingness. Sensitivity analyses for the primary efficacy endpoint will be performed, accounting for both missing at random and missing not at random scenarios.

For the primary efficacy analysis in Part 2 using the mITT analysis set, any available liver biopsy after baseline will be used for assessment of components of the clinical endpoint that require a biopsy, no matter when obtained. Subjects with multiple liver biopsies will be included as an event if any (one or more) biopsy meets the definition of the primary endpoint, as determined by the adjudication committee. Subjects who do not have an evaluable liver biopsy at both Screening and postbaseline will be included in the analysis as nonevents for any components of the primary endpoint requiring biopsies but may be included as events if they meet criteria for another component of the primary endpoint. Subjects with partial follow-up data will be included as an event if they meet the criteria for any component of the primary efficacy endpoint, and as a nonevent if they do not meet the criteria for any component. A sensitivity analysis assuming data are missing not at random will be reported.[33] An additional sensitivity analysis imputing an event at the time of censoring will also be reported, although it is anticipated that this analysis will not be informative unless many subjects discontinue due to unobserved NASH progression, which cannot be known.

12.1.5. Multiple Comparisons

Alpha splitting will be applied for multiplicity adjustment.

12.2. Subject Disposition, Demographics, and Treatment Adherence

Subject disposition will be presented for all subjects. The number of subjects who were screened, randomized, started study drug, completed the study, discontinued study drug early, and discontinued from the study early will be provided for Part 1 and for Part 2. The reasons for early discontinuation of study drug and of study will be presented for each part.

Demographic data (age, gender, ethnicity and race) and baseline characteristics will be listed and summarized by randomized treatment group and overall for the ITT Analysis Set.

Adherence to planned study drug dosing will be estimated by drug accountability.

12.3. Efficacy

12.3.1. Efficacy Endpoints

12.3.1.1. Part 1

Primary Efficacy Endpoint (Part 1)

- Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver histology at Month 12 relative to the Screening biopsy

Key Secondary Efficacy Endpoint (Part 1)

- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver histology at Month 12 relative to the screening biopsy

Secondary Efficacy Endpoints (Part 1)

- Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis, at Month 12 relative to the Screening biopsy

- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on steatohepatitis, at Month 12 relative to the Screening biopsy

- Change from baseline to Month 12 in ELF.

12.3.1.2. Part 2

Primary Efficacy Endpoint (Part 2)

- Time to first occurrence of any of the following adjudicated events:
  - Death (all cause)
  - Histopathologic progression to cirrhosis (defined by NASH CRN Fibrosis Stage 4)
  - Liver transplant
  - MELD score ≥15
  - Ascites (requiring intervention, ie, large volume paracentesis ≥ 1L or initiation of a diuretic)
  - Hospitalization (as defined by a stay of ≥ 24 hours) for onset of: variceal bleed, hepatic encephalopathy (defined by a West Haven Stage of ≥2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis with positive ascitic fluid bacterial culture)

  Each component of this endpoint will be considered by the independent adjudication committee, and only events confirmed by the committee will be included in the primary analysis.

  If any of the above events occur in Part 1, they will be included in this primary efficacy endpoint for Part 2.

Secondary Efficacy Endpoints (Part 2)

- Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver biopsy at Month 12 relative to the Screening biopsy – (subjects newly randomized in Part 2)

- Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis, on liver biopsy at Month 12 relative to the Screening biopsy – (subjects newly randomized in Part 2)

- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver biopsy at Month 12 relative to the screening biopsy – (subjects newly randomized in Part 2)

- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) regardless of effect on steatohepatitis on liver biopsy at Month 12 relative to the screening biopsy – (subjects newly randomized in Part 2)

- Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver biopsy at Month 60 relative to the Screening biopsy – (all subjects)

- Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on steatohepatitis, on liver biopsy at Month 60 relative to the Screening biopsy – (all subjects)

- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver biopsy at Month 60 relative to the screening biopsy – (all subjects)

- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on steatohepatitis on liver biopsy at Month 60 relative to the screening biopsy – (all subjects)

- Proportion of subjects with improvement in fibrosis by at least 1 stage (Ishak system), regardless of effect on steatohepatitis, on liver biopsy at Month 12 relative to the Screening biopsy – (subjects newly randomized in Part 2)

- Proportion of subjects with complete resolution of steatohepatitis (defined as histopathologic interpretation of no fatty liver disease or simple or isolated steatosis with no steatohepatitis) AND no worsening of liver fibrosis (defined as progression of NASH CRN fibrosis stage) at Month 60 relative to the Screening biopsy – (all subjects)

- Proportion of subjects with improvement in fibrosis by at least 1 stage (Ishak system), regardless of effect on steatohepatitis, on liver biopsy at Month 60 relative to the Screening biopsy – (all subjects)

- Proportion of subjects with histopathologic progression to cirrhosis (defined by NASH CRN Fibrosis Stage 4) at Month 60– (all subjects)

- Change from baseline in noninvasive assessments of liver fibrosis (including FIB-4, APRI, NFS, ELF and liver stiffness through TE) over time – (all subjects)

12.3.2. Methods of Analysis for Efficacy Endpoints

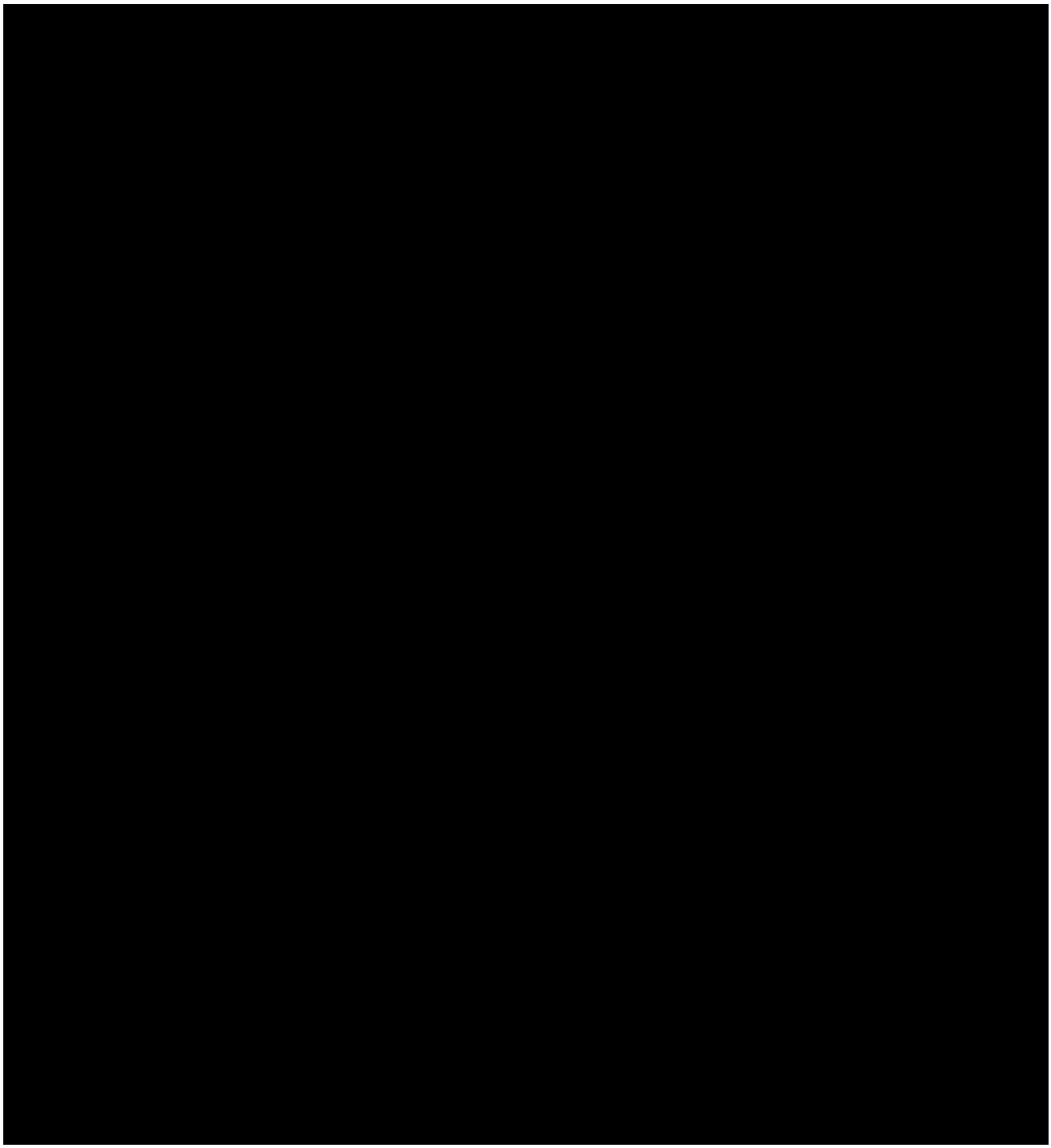
12.3.2.1. Part 1

The primary analysis of Part 1 will occur when approximately 1200 randomized subjects have been followed for at least 12 months. Subjects who will contribute to the primary analysis of Part 1 will be identified before unblinding of any subjects for Part 1 analysis; subjects who will not contribute to the primary analysis of Part 1 will be identified by date of randomization and will be determined before randomization. Individual subjects' treatment group assignments will not be disseminated to the sites until the end of Part 2 to allow for continued blinded assessment during Part 2.

For the primary efficacy analysis in Part 1, using the mITT analysis set, any available liver biopsy after baseline will be used as the Month 12 biopsy, no matter when it was obtained relative to the first dose of study drug. Subjects who do not have an evaluable liver biopsy at both Screening and Month 12 will be included in the analyses as nonresponders. Subjects with multiple liver biopsies will have the evaluable biopsy closest to the Month 12 visit included in the analysis.

The proportion of subjects who meet the primary efficacy endpoint in Part 1, and each component, will be summarized by treatment group. Two-sided 95% confidence intervals for the proportion who meet the primary efficacy endpoint, calculated using Wilson's method for CI, will also be reported.

Part 1 testing hierarchy includes 2 tests, one for the primary endpoint and the other for the key secondary endpoint. The key secondary endpoint is tested only when the primary endpoint result is significant. The surrogate endpoint will be tested at 0.0012 (2-sided) level



12.3.2.2. Part 2

The primary analysis for Part 2 will occur when adjudicated events have been accrued in 367 unique subjects across Part 1 and Part 2. Because many events may be observed from the Month 60 liver biopsy, and given that all reported events will need to undergo independent adjudication prior to being included or excluded from the analysis, it is possible that more than or fewer than 367 events will be included in the analysis. All subjects and events in the

database at the time of Part 2 database lock and unblinding, and only those events, will be included in the primary analysis of Part 2. If multiple events are observed in a single subject, only the first observed event will be used in the analysis.

For the primary efficacy analysis in Part 2 using the mITT analysis set, any available liver biopsy after baseline will be used for assessment of components of the clinical endpoint that require a biopsy, no matter when obtained. Subjects who do not have an evaluable liver biopsy at both Screening and postbaseline will be included in the analyses as having an event only if they meet a component that does not require a biopsy; otherwise they will be included as not having an event and censored at the last visit. Subjects with multiple liver biopsies will be included as an event if any (one or more) biopsy meets the definition of the primary endpoint, as determined by the adjudication committee.

The proportion of subjects who meet the primary efficacy endpoint in Part 2, and each component, will be summarized by treatment group. Two-sided 95% CIs for the proportion who meet the primary efficacy endpoint, calculated using Wilson's method for CI, will also be reported. Time-to-event analyses will be performed using the Kaplan-Meier product-limit method with tabular and graphical presentation for the cumulative probability of event rate by treatment group. Subjects will be censored for analysis at the last recorded study visit.

Analysis of the primary endpoint of Part 2 will use the logrank test, stratified by randomization strata (fibrosis stage [2 vs 3] and presence or absence of T2DM at Baseline, for a total of 4 strata), to compare the rates in the 2 randomized treatment arms. If multiple adjudicated events are observed in a single subject, only the first observed event will be used in the analysis. The analysis will use the mITT analysis set, with supportive analyses reported for the ITT and PP2 analysis sets. Subjects who do not have an adjudicated event will be censored for analysis at the last recorded study visit. The p-value for the test of no difference between treatment arms (hazard ratio=1) will be presented as well as the hazard ratio from a proportional hazards model (CVC divided by placebo) and corresponding 95% CI. To manifest strong evidence from a single confirmatory study, the hypothesis test of clinical endpoint will be performed at a significance level of 0.00125 (2-sided) if the test of the surrogate endpoint is successful and 0.00005 (2-sided) otherwise. For study success, the hypothesis test of clinical endpoint will be performed at a significance level of 0.05 (2-sided) if the test of the surrogate endpoint is successful and 0.002 (2-sided) otherwise.

Analysis of secondary efficacy endpoints of Part 2 will use similar methods to the primary endpoint analysis in Part 2. The primary endpoint in Part 1, improvement in fibrosis by at least one stage and no worsening of steatohepatitis at Month 12, will be reported for subjects not in the Part 1 analysis (subjects newly randomized in Part 2), and for all subjects in the study (Month 12 results from Part 1 and Part 2 combined). Results for the mITT and PP2 analysis sets will be reported for the secondary endpoints in Part 2. Binary endpoints will be analyzed with the CMH procedure, stratified by randomization strata. Continuous endpoints will be analyzed with analysis of covariance, with randomization strata included as covariates. Time to event endpoints will be analyzed with the stratified logrank test, stratified by randomization strata.

[redacted]

12.4. Safety

12.4.1. Safety Endpoints (Part 1 and Part 2)

- Clinical adverse events, including major adverse cardiovascular events (MACE) and new-onset T2DM
- Clinical laboratory tests (hematology, chemistry, and fasting metabolic parameters)
- Physical examination
- Vital signs
- 12 lead ECG

12.4.2. Methods of Analysis for Safety Endpoints (Part 1 and Part 2)

No statistical hypotheses are prespecified for safety endpoints. Analyses will be primarily descriptive, with any p-values post-hoc and any comparative conclusions requiring confirmation.

12.4.2.1. Adverse Events

AEs will be categorized by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system-organ classification. The occurrence of TEAEs will be summarized using MedDRA preferred terms, system organ classifications, and severity (see Sections 11.3.1.3 and 11.3.1.4). The occurrence of TEAEs will be summarized by treatment group for the safety analysis set using MedDRA preferred terms, system organ classifications, and severity.

All AEs (including nontreatment-emergent events) recorded on the eCRF will be listed for individual subjects showing both verbatim and preferred terms. The number of subjects with at least one TEAE, at least one severe TEAE, at least one serious TEAE, at least one TEAE judged by the investigator to be related to study drug, and with a TEAE leading to death will

be summarized by treatment group. Summaries TEAEs will also be presented by subgroups of age, sex, and race.

12.4.2.2. Clinical Laboratory Tests

Descriptive summaries of clinical laboratory results will be presented by study visit. The Baseline assessment will be the last value before randomization for each laboratory parameter. The change from baseline to each postbaseline assessment will be derived for each of the continuous laboratory parameters. Laboratory abnormalities will be graded according to NCI CTCAE version 4.03 (see Appendix 20.2). The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by treatment group and severity grade. Change from baseline in laboratory tests will be summarized for each treatment group.

12.4.2.3. Physical Examination and Vital Signs

Any abnormal findings that are considered clinically significant in the opinion of the investigator will be recorded as AEs or be captured as medical history, if already present at Screening.

Descriptive summaries of vital signs will be presented by study visit. A baseline value will be derived for each parameter as the last value prior to randomization. A change from baseline to each of the postbaseline assessments will be derived. Descriptive summaries of quantitative changes in vital signs will be presented by treatment group and study visit.

12.4.2.4. Electrocardiograms

Any abnormal findings that are considered clinically significant in the opinion of the investigator will be recorded as AEs or be captured as medical history, if already present at Screening.

ECG results will be reviewed for clinically notable abnormalities according to predefined criteria. Subjects exhibiting Grade 3 or 4 PR or QT interval corrected for heart rate (QTc) interval will be summarized. Abnormalities in Fridericia's corrected QT interval (QTcF) interval, Bazett's corrected QT interval (QTcB) interval, QRS, PR, and heart rate (HR) will be summarized.

12.4.2.5. Prior and Concomitant Medications

A prior medication is defined as a (nonstudy) medication taken at any time during 30 days before first study drug intake and stopped before the date of first dose of study drug.

Concomitant medications are those taken at any time during the study from first intake of study drug through the 30-day Follow-up visit after last study drug intake (or final visit, for subjects who do not complete a Follow-up visit). This includes medications ongoing at the time of first study drug intake and medications started after first study drug intake. A new concomitant medication will be a (nonstudy) medication started or for which the dose

increased between first study drug intake through the 30-day Follow-up visit after last study drug intake (or final visit, for subjects who do not complete a Follow-up visit).

A subsequent medication is defined as a (nonstudy) medication started after the date of the 30-day Follow-up visit after last study drug intake (or 30 days after last intake of study drug, if no 30-day Follow-up visit occurs).

Prior, concomitant, and subsequent medications will be coded based on the World Health Organization (WHO) preferred term and drug classification. The number and percent of subjects taking prior, concomitant and subsequent medications will be summarized by treatment group using preferred terms and drug classifications for the Safety Analysis Set. In addition, a summary of the number and percent of subjects taking new concomitant medications by treatment group will be presented.

12.5. Population Pharmacokinetics

12.5.1. Population Pharmacokinetic Endpoints

- Characterization of the population PK of CVC and possible metabolites in subjects with NASH
- Evaluation of covariates that impact the PK of CVC and possible metabolites (age, sex, weight, race, ethnicity, fibrosis stage, etc.)

[redacted]

12.5.2. Methods of Analysis for Population Pharmacokinetic Endpoints

A population PK analysis of CVC will be performed by using predose and post-dose PK samples collected at steady state throughout Part 1 of the study. Population PK modeling of measured plasma CVC concentrations will be conducted using nonlinear mixed effects modeling. An analysis of subject covariates will be conducted.

[redacted]

12.8. Sample Size and Power

12.8.1. Part 1

The sample size for the primary endpoint of Part 1 is based on the primary binary endpoint at the end of Month 12 comparing treatment with CVC versus placebo. The planned sample size of 1200 subjects (800 in treatment Arm A and 400 in treatment Arm B) for Part 1 of this study is expected to provide 84% power to demonstrate strong evidence with a single study (2-sided alpha level of 0.0012), assuming a 15% response rate for the placebo arm and a 25% response rate for CVC according to the results from the Phase 2b Study 652-2-203 (CENTAUR).

The planned 800 subjects in treatment Arm A and 400 subjects in treatment Arm B is expected to provide 97% power to demonstrate strong evidence with a single study (2-sided alpha level of 0.0012) in the key secondary endpoint, assuming a 2.2% response rate for the placebo arm and an 8.6% response rate for CVC according to the results from the Phase 2b Study 652-2-203 (CENTAUR).

PASS 8.0 was used to calculate the sample size.

These response rates reflect the primary analysis, in which subjects missing the postbaseline liver biopsy will be included as nonresponders. The anticipated proportion of subjects with missing Month 12 liver biopsies, as a result of either premature subject discontinuation or nonevaluable liver biopsy results (ie, biopsy sample deemed inadequate for evaluation of efficacy endpoints by an independent central pathologist), is estimated to be 15% of subjects at Month 12, compared to approximately 13% of missing post-treatment liver biopsies in the Phase 2b study.

12.8.2. Part 2

The sample size for the primary endpoint analysis in Part 2 is based on the estimated event-free survival rate of 80% for the placebo group and detection of a hazard ratio of 0.62 by the end of the study (corresponding to a median event-free survival time of approximately 15 years for placebo and 25 years for CVC). A total of 2000 subjects (2:1 randomization ratio between CVC and placebo) enrolled approximately uniformly over 2 years for an overall study duration of approximately 8 years (2 years of accrual period plus 5 to 6 years of follow-up) will lead to about 367 events, after accounting for an overall dropout rate of 20%. With these events, there will be 85% power to demonstrate strong evidence of superiority of CVC over placebo (at a 2-sided 0.00125 significance level, for a single registration study), and 99% power to test the superiority of CVC over placebo (at the 2-sided test 0.05 significance level for a registration study). EAST 6.4 is used for the calculation.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Sponsor Audits

During the study, individuals from the sponsor's quality assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the investigator's adherence to the protocol, applicable regulations, and the sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the investigator will be contacted by the sponsor to arrange a convenient time for this visit. The investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the eCRFs and other study-related documents.

13.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

14. ETHICS AND PROTECTION OF HUMAN SUBJECTS

14.1. Compliance Statement

The investigator agrees to conduct the study in compliance with the protocol, ICH E6 Good Clinical Practice (GCP) guidelines, and all local and national regulations.

The investigator must adhere to the protocol as described in this document and agree that deviations to the protocol, with the exception of medical emergencies, must be discussed and approved by the sponsor prior to seeking approval from the IRB/IEC. The investigator is responsible for enrolling subjects who have met the protocol inclusion and exclusion criteria or must have obtained prior documented approval from the sponsor prior to enrollment in the study. The IRB/IEC that granted original approval, or the IRB/IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB/IEC to the sponsor or contract research organization (CRO) and retain the original in the site study regulatory file.

14.2. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki (October 20**13**) as described in the ICH E6: GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The protocol and any information supplied to the subject to obtain informed consent, including written ICF(s), subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), must be reviewed and approved by a qualified IRB/IEC prior to enrollment of participants in the study. Prior to initiation of the study, the sponsor must receive documentation of the IRB/IEC approval, which specifically identifies the study/protocol, and a list of the committee members.

Amendments to the protocol and revisions to the informed consent must also be submitted to and, if required, approved by the IRB/IEC.

Investigators must submit progress reports to the IRB/IEC in accordance with the IRB/IEC requirements. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the sponsor.

When the sponsor provides the investigator with a safety report, the investigator must promptly forward a copy to the IRB/IEC.

After completion or termination of the study, the investigator must submit a final report to the IRB/IEC and to the sponsor.

The investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB/IEC.

The investigator is responsible for conducting the study in accordance with the protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

14.3. Informed Consent

Preparation of the consent form is the responsibility of the investigator and the sponsor or designee and must include all elements required by the ICH, GCP, and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

A template will be provided by the sponsor or designee. The sponsor or designee must review and approve all changes to site-specific ICFs.

The consent form must include a statement that the sponsor or designee and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The investigator must inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

14.4. Subject Confidentiality

Applicable data privacy laws and regulations must be adhered to. The investigator and the sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, Health Insurance Portability and Accountability Act [HIPAA] and the European Union Data Protection Directive 95/46/EC). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e g, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

14.5. Study Conduct

The study will be conducted in compliance with the Declaration of Helsinki (October 20**13**) and the ICH E6 Guideline for GCP. All national, state, and local laws of the pertinent regulatory authorities will be followed.

If it is necessary to amend either the protocol or the ICF, the investigator will be respons ible for ensuring that the IRB/IEC reviews and approves the amended documents. Amended ICFs must be obtained and used for obtaining consent from new subjects.

14.6. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination, and send a copy of the notification to the sponsor or CRO and retain one copy for the site study regulatory file.

15. DATA HANDLING AND RECORD KEEPING

15.1. Data Management Responsibilities

All eCRF data will be entered into a validated database. Laboratory data will be imported to the database electronically.

All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the sponsor or its designee. The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

15.2. Data Handling and Record Keeping

15.2.1. Data Collection and Retrieval

The investigative site will be provided with eCRFs in which to record all the protocol-specified data for each subject in this study. Entries made in the eCRF must be verifiable against source documents, or in certain circumstances as directed by the sponsor, entries will have been directly entered into the eCRF; in such cases, the entry in the eCRF will be considered as the source data. Data reported in the eCRF that are derived from source

documents should be consistent with the source documents or the discrepancies should be explained.

The investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each subject's eCRF, verifying that the information is true and correct.

Queries generated by Data Management will be sent to the study site for resolution. The investigator is responsible for the review and approval of all responses to eCRF queries.

15.2.2. Records Retention

The investigator must ensure that all records pertaining to the conduct of the clinical study, ICFs, drug accountability records, source documents, and other study documentation are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor must be contacted to arrange alternative record storage options.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

15.2.3. Study Monitoring and Access to Source Documents

Qualified representatives of the sponsor or its designees ("study monitors") will monitor the study according to a predetermined monitoring plan. Monitoring visits provide the sponsor with the opportunities to do the following:

- Evaluate the progress of the study
- Verify the accuracy and completeness of eCRFs
- Assure that all protocol requirements, applicable laws and/or regulations, and investigator's obligations are being fulfilled
- Resolve any inconsistencies in the study records

The investigator must allow the study monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The eCRFs and other documentation supporting the study must be kept up-to-date by the investigator and the research staff at the investigative site. These study materials (written notes and electronic medical records, if used) must be available for review by the study monitor, and/or other qualified representatives of the sponsor, at each monitoring visit.

The study monitor will periodically monitor the progress of the study by conducting on-site visits. The study monitor will review data remotely, possibly warranting more frequent communication and/or site visits with the investigator and the study site staff. Protocol deviations will also be identified and recorded. The study monitor will create action items in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner.

16. PUBLICATION POLICY

Neither the institute nor the principal investigator shall have the right to publish or present any materials made available or generated through the study except as specified herein.

The institute and the principal investigator shall be free to publish or present site-specific results of the project subject to the following conditions:

a. In the case of a study conducted at multiple institutions or study sites, institute and principal investigator agree that they will not submit a publication or make any presentation prior to the initial publication of the joint, multi-center results of the study, which shall be coordinated by sponsor

b. Institute and principal investigator agree that any authorized publication or presentation shall not reveal any of the sponsor's information without the expressed written consent of the sponsor

c. Institute and principal investigator shall send sponsor a copy of any such proposed publication for sponsor's review and comment ninety (90) days prior to submission for publication and shall not disclose to any third party prior to such submission any data, results, discoveries, or inventions arising from the clinical research study regardless of a determination of the ownership of rights to such material

d. Institute and principal investigator, upon sponsor's request, shall delete any of sponsor's information in the proposed publications; and shall not include raw data in such publications, except in the case of any information or data to the extent necessary to present the analysis in a manner consistent with generally accepted scientific and academic standards

e. Institute and principal investigator, upon sponsor's request, shall delay submission for any publication or presentation while the sponsor files applications for patents or other registrations of intellectual property rights

Any publication or presentation, including summaries or abstracts will appropriately reference the support received from the sponsor for the conduct of the Project. The parties agree that any authorized publication or presentation shall comply with applicable guidelines set forth by International Committee of Medical Journal Editors (ICMJE) and Good Publications Practice for Communicating Company Sponsored Medical Research (GPP2). Institute agrees that pursuant to any authorized publication or presentation, authors must disclose in their manuscripts, journal submissions, and elsewhere as appropriate or required, any potential conflicts of interest, including their financial or personal relationship with sponsor, and the names of any individuals who have provided editorial support for any manuscript or other publication.

Sponsor shall have the right to identify Institute as the site at which the study was conducted and to identify those individuals responsible for conducting the study, including principal investigator, and to provide any other information as necessary to post the study on www.clinicaltrials.gov or any other applicable public registries as required by applicable laws and regulations.

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18. SPONSOR'S SIGNATURE PAGE

Protocol Number: 3152-301-002

Protocol Title: AURORA: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis

Amendment Number: 4

Date: 29 April 2019

I have reviewed and approved the attached version, cited above, of 3152-301-002 Amendment 4.

[redacted]

April 25, 2019
Date

Senior Vice President
Liver Therapeutic Area Head
Allergan

19. INVESTIGATOR'S SIGNATURE PAGE

Protocol Number: 3152-301-002

Protocol Title: AURORA: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis

Amendment Number: 4

Date:

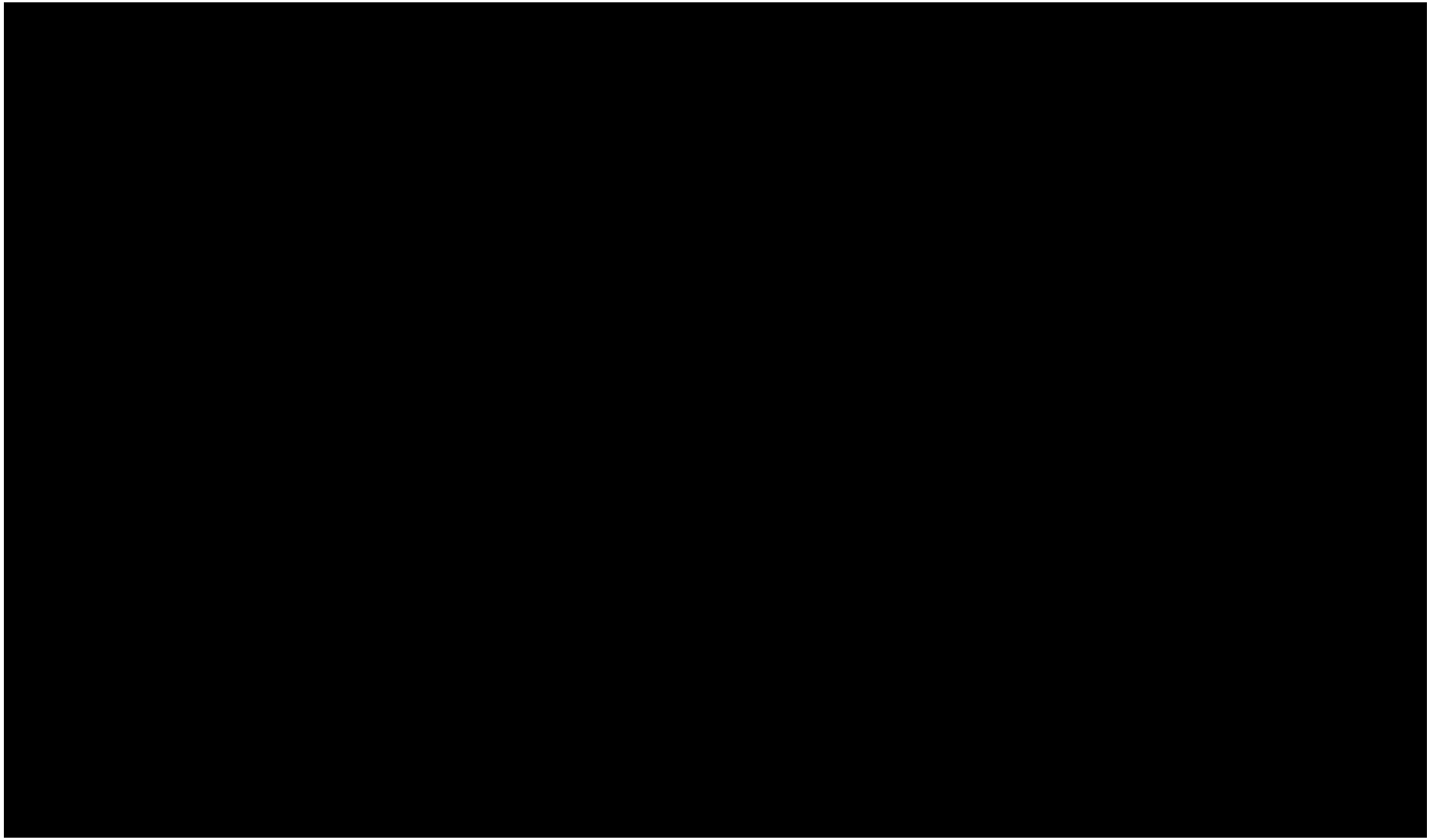
I have reviewed and approved the attached version, cited above, of 3152-301-002 Amendment 4.

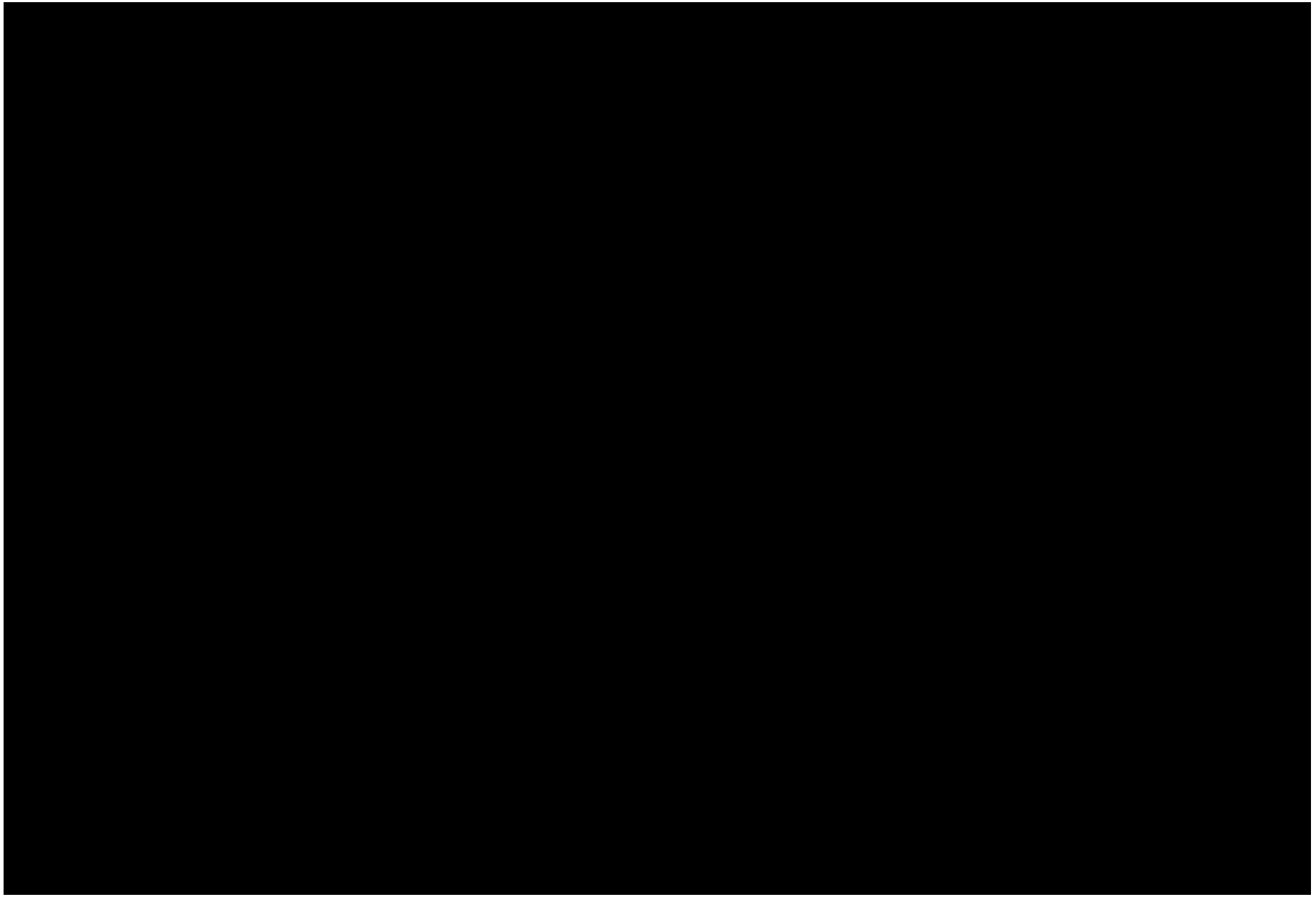
Principal Investigator Name (Print)	Signature
Date	Site Number

20. APPENDICES

20.1. Schedule of Assessments

Table 20–1 Schedule of Assessments: Part 1





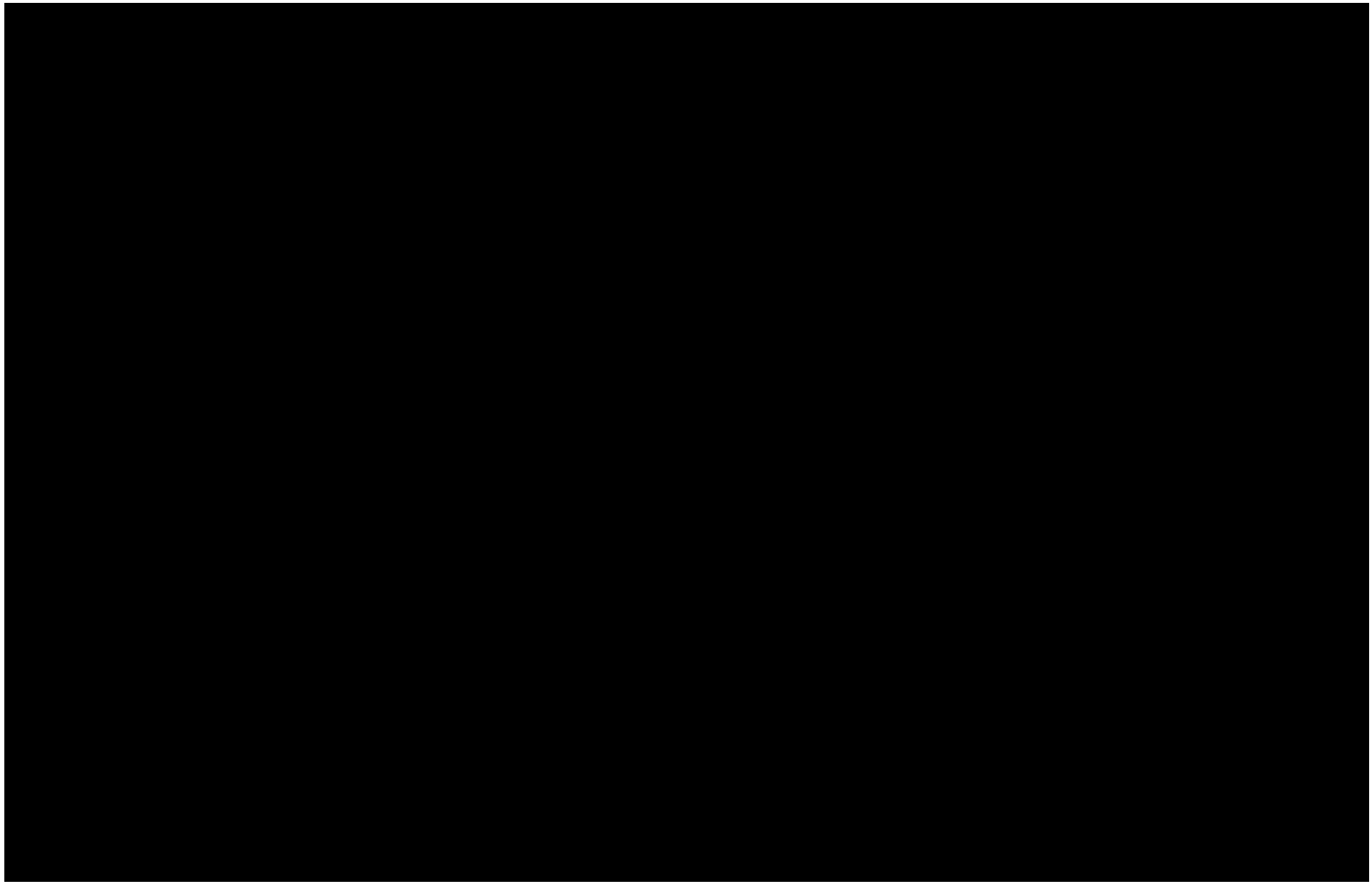
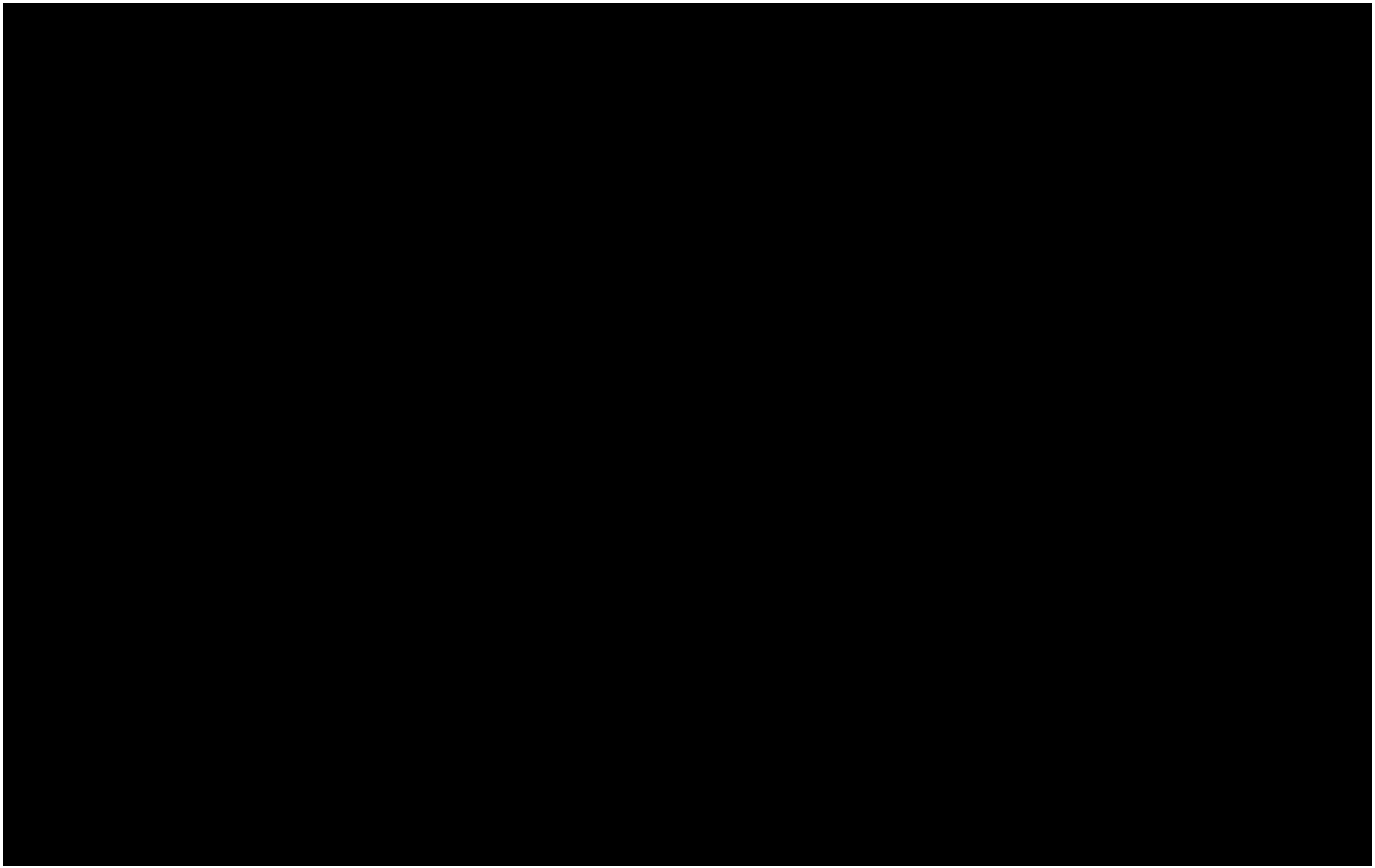
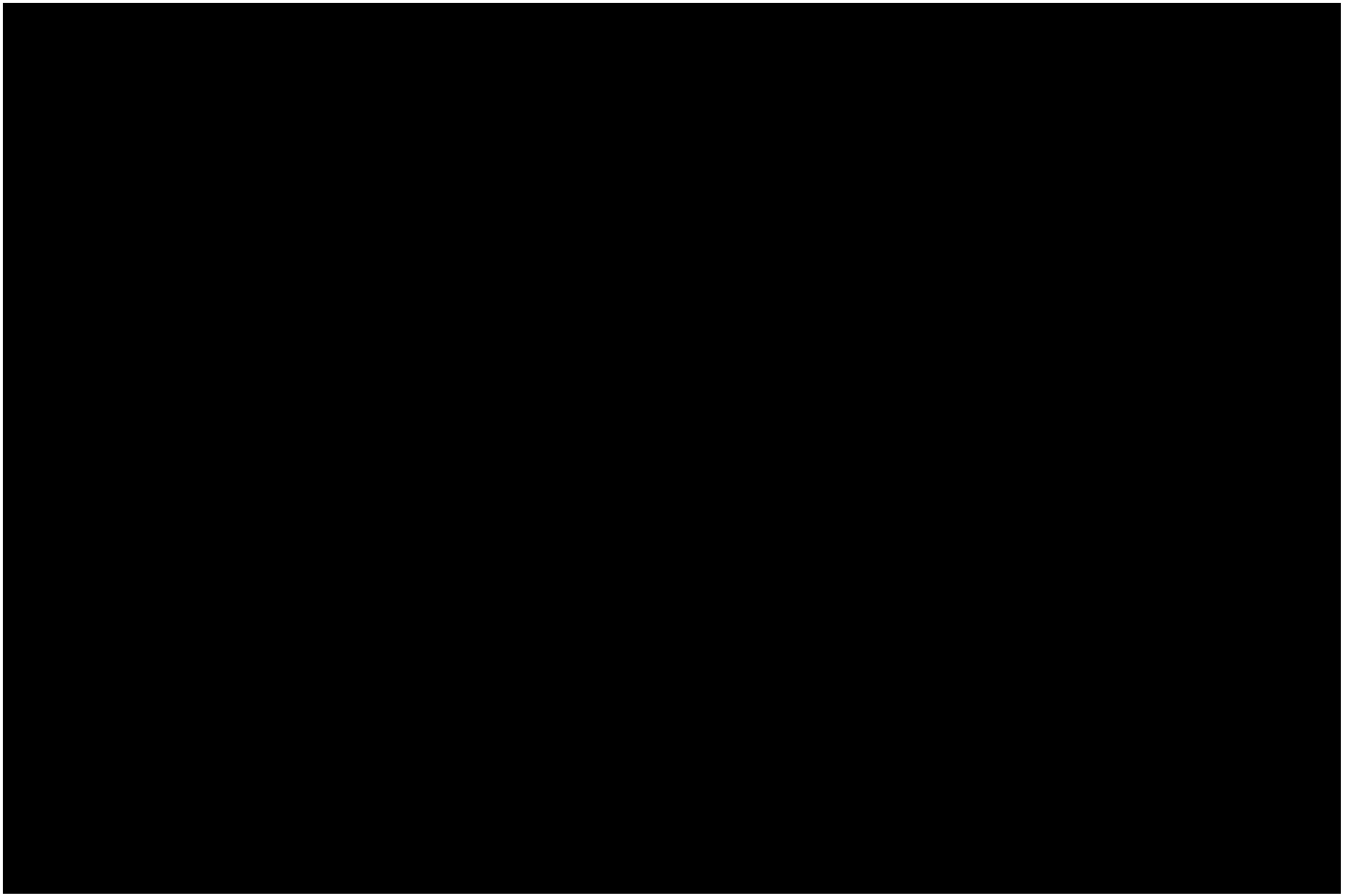
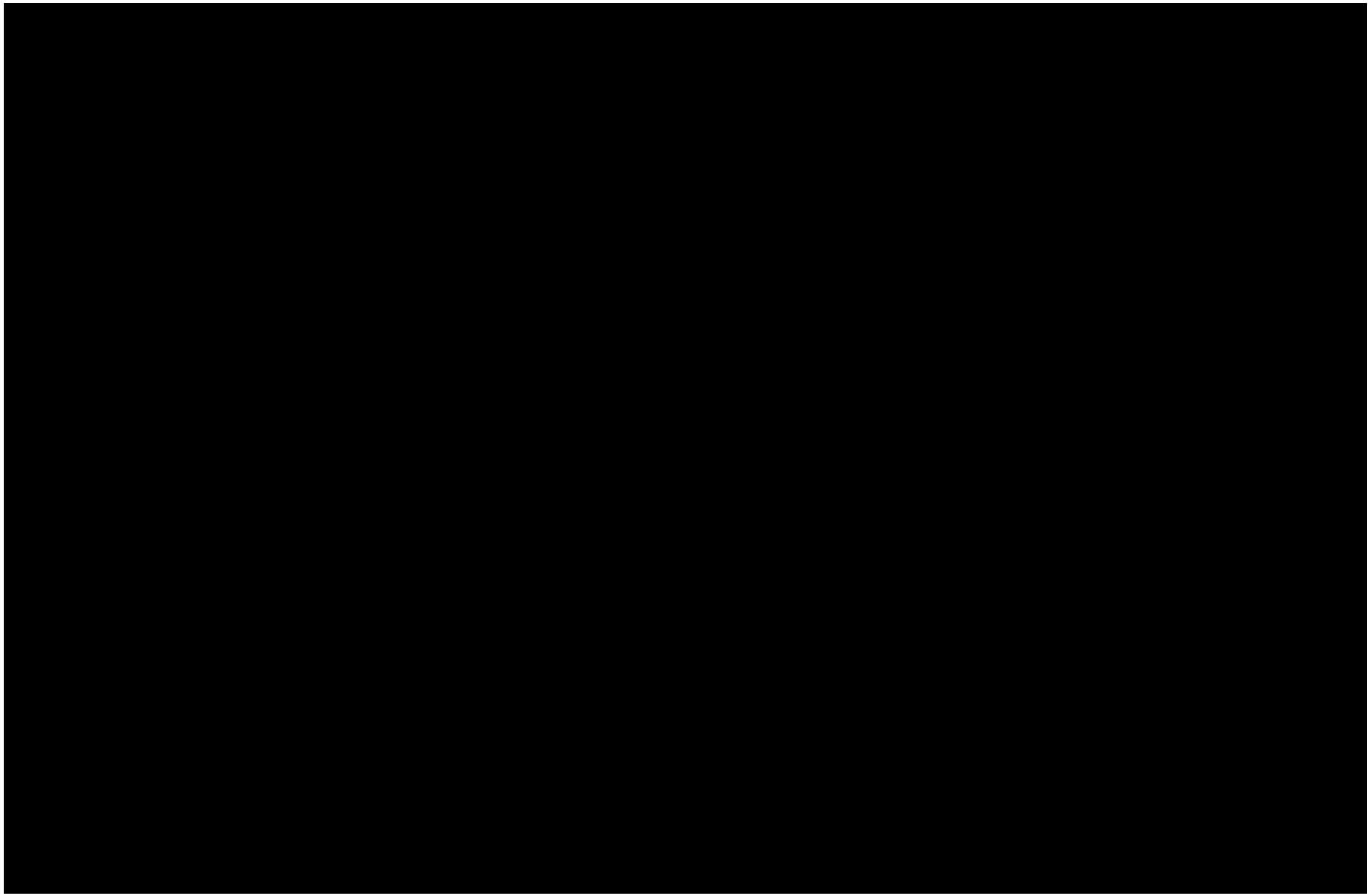
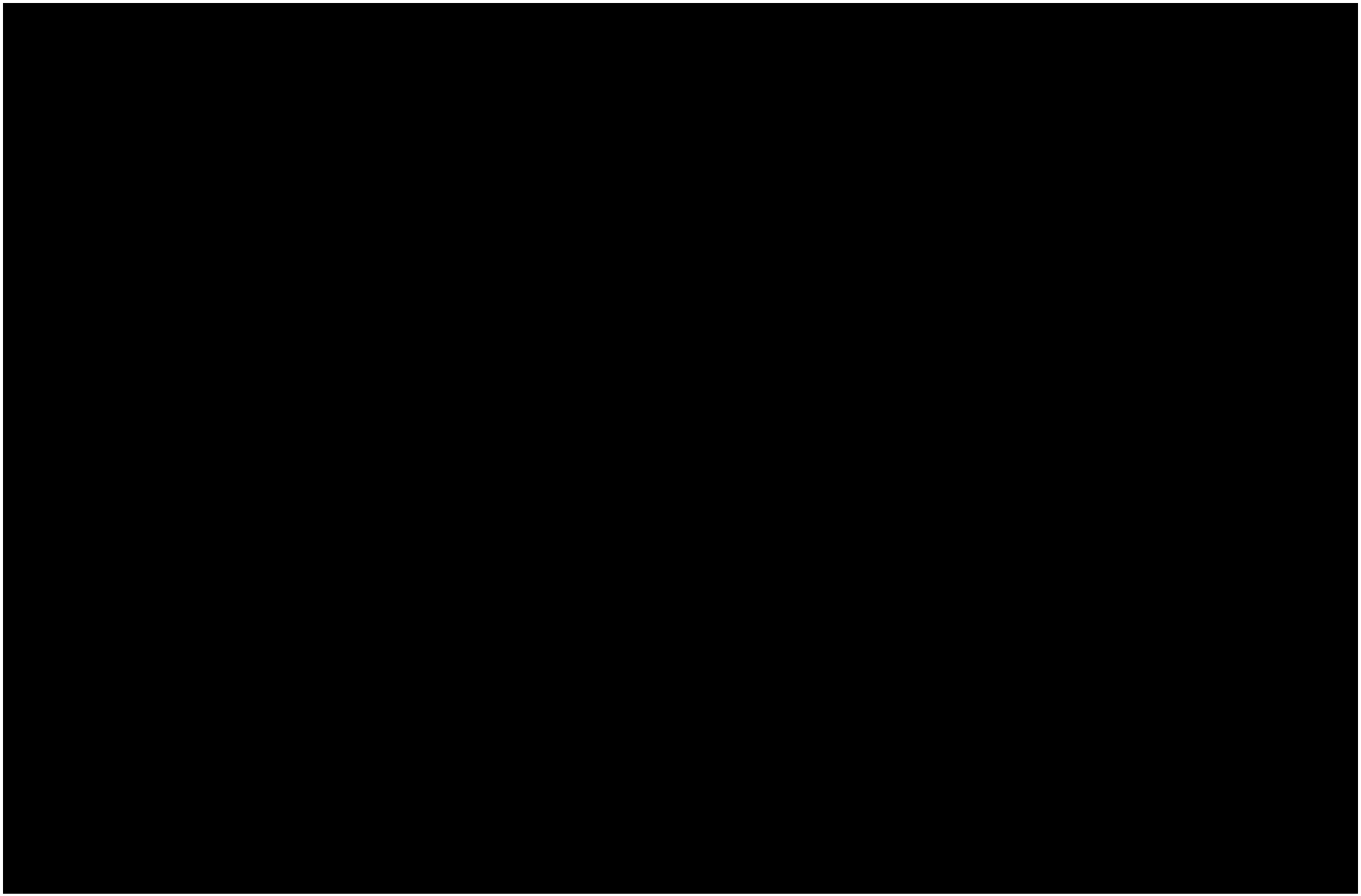


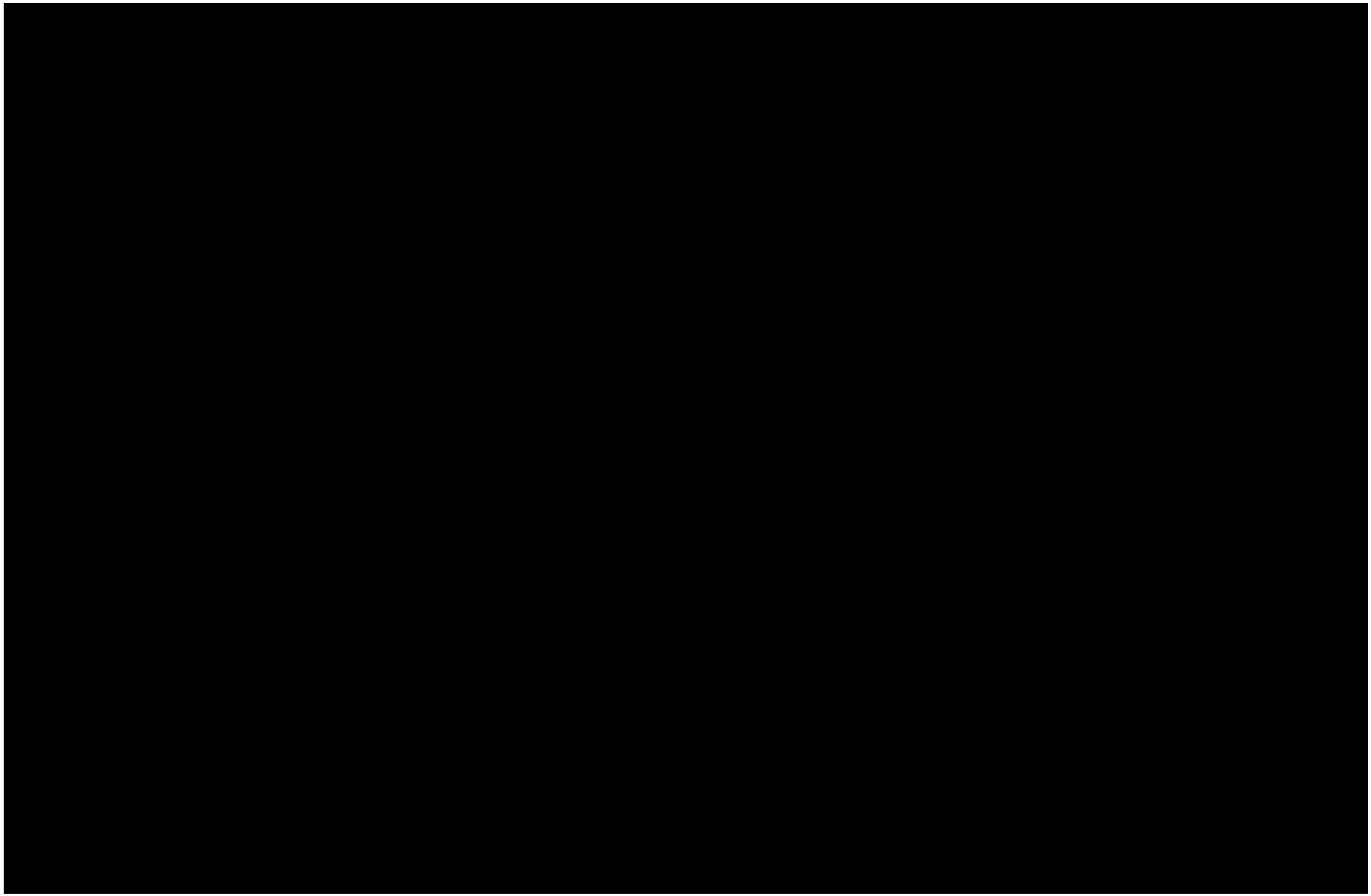
Table 20–2 Schedule of Assessments: Part 2

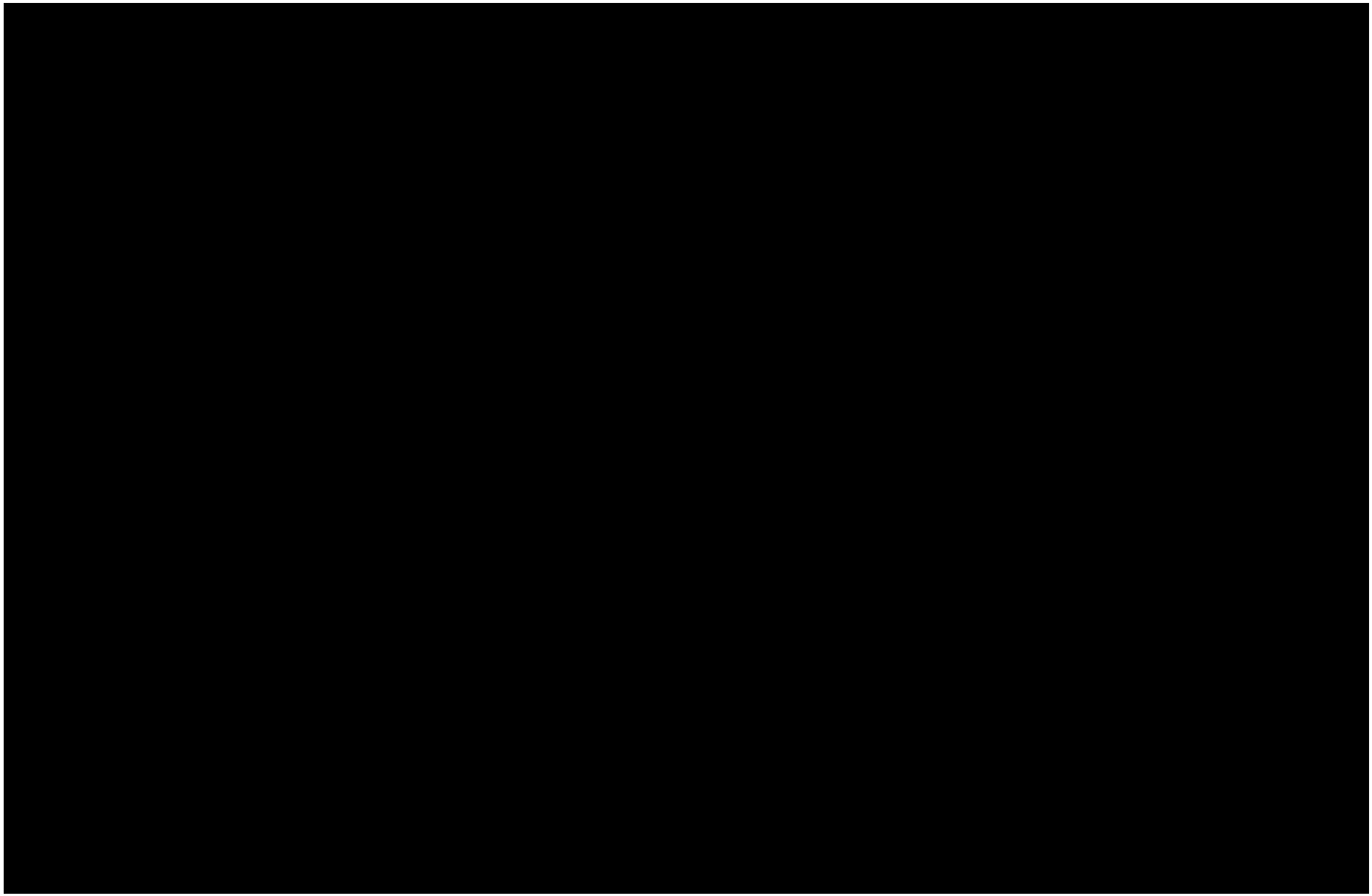


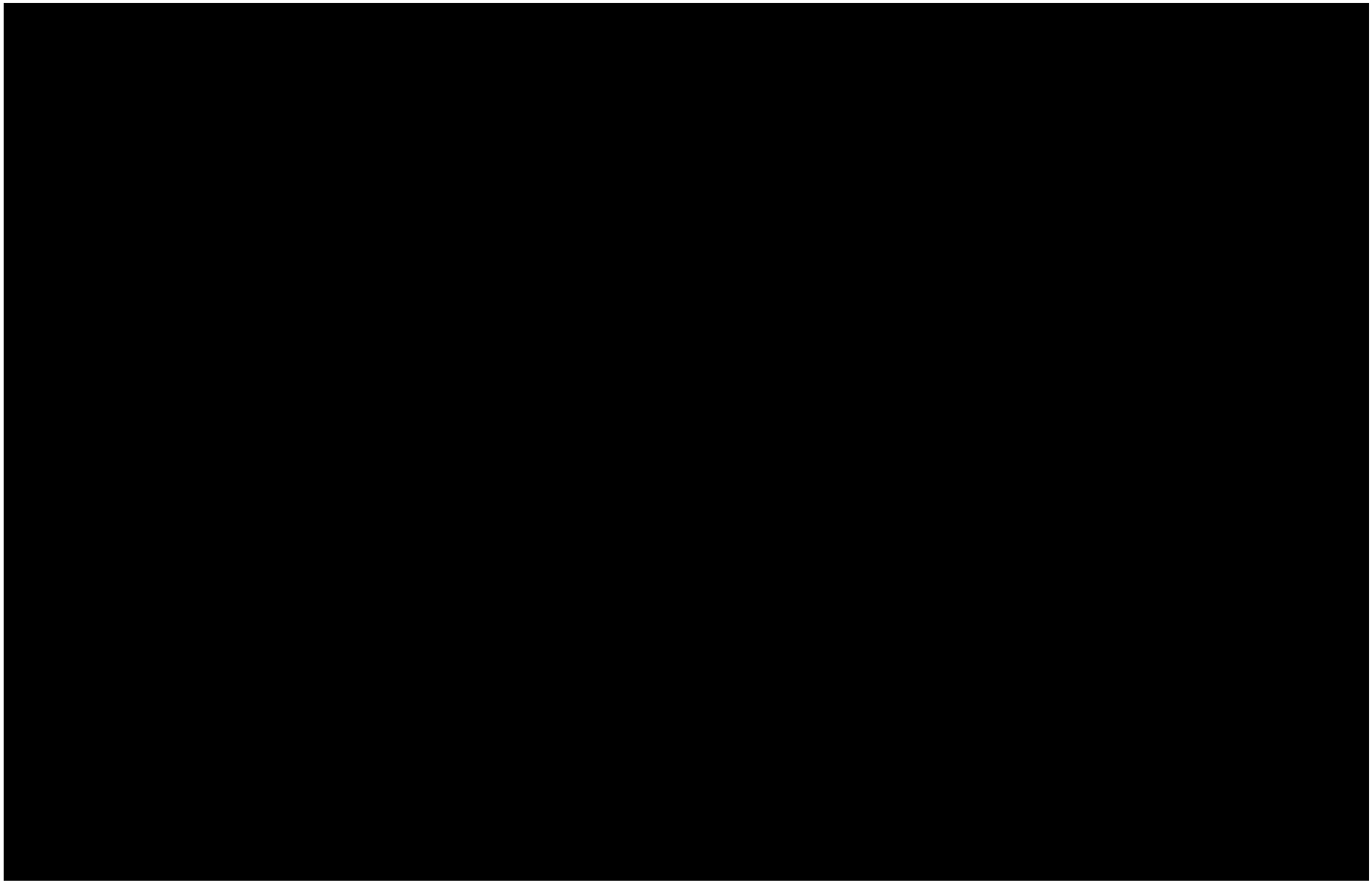












20.2. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Quick Reference

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) is a descriptive terminology which can be utilized for adverse event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

System Organ Class

System Organ Class (SOC), the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (eg, SOC investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (grade).

CTCAE Terms

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA lowest level term (LLT).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE.

ADL = activities of daily living

A semi-colon indicates ‘or’ within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for grade selection.

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

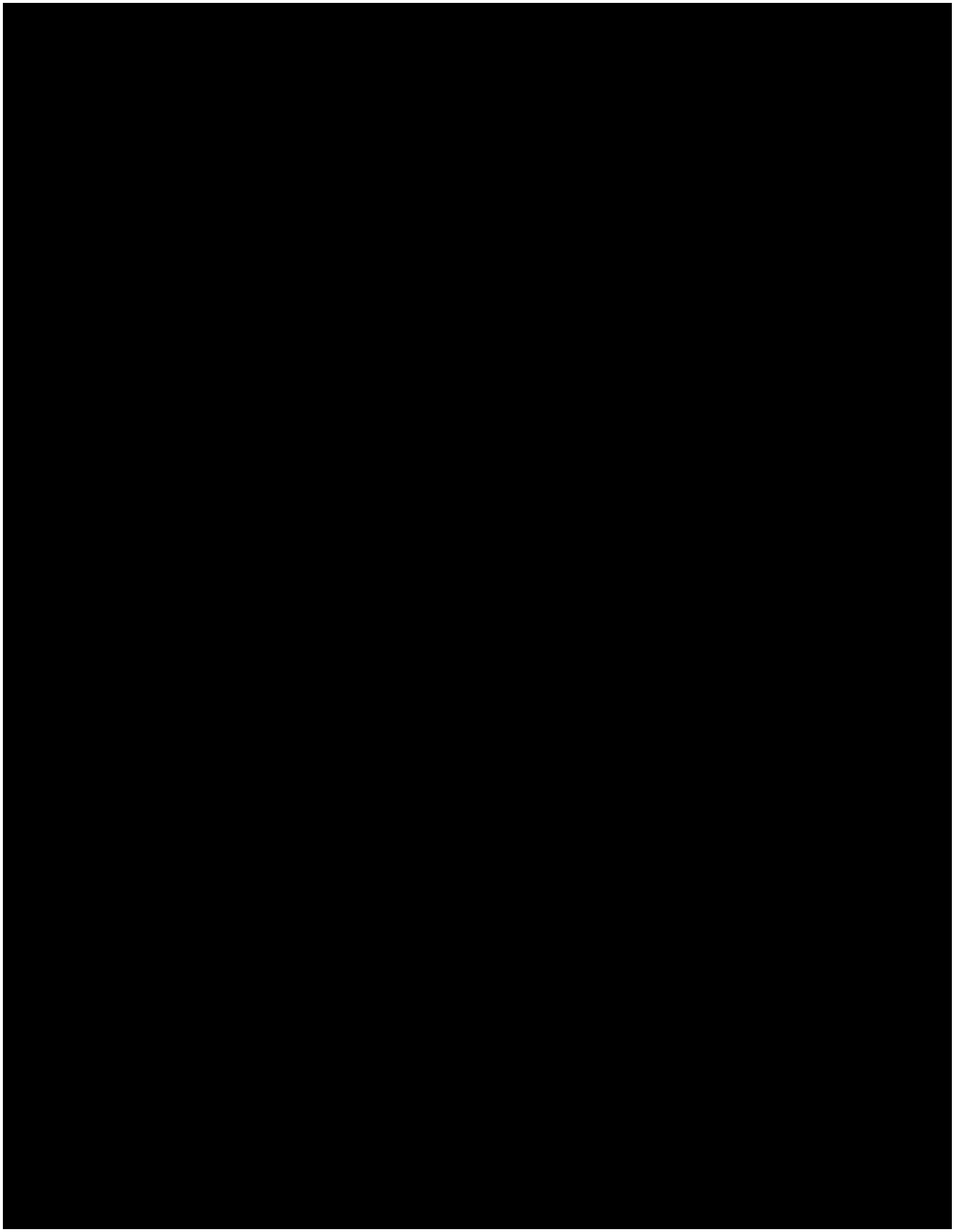
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

20.3. Information on Contraception Effectiveness

For Female Study Subjects of Child-Bearing Potential and For Male Study Subjects with Female Partners:

The following methods have been determined to achieve a failure rate < 1% per year, when used consistently and correctly, are considered highly effective birth control methods and are permitted under this protocol:



20.4. Disallowed Medications

Caution should always be exercised when administering concomitant medications based on the individual medication profile and clinical risk-benefit assessment.

The subject must not take the following disallowed medications at any time during the study, from Screening through the 30-day Follow-up visit.

Disallowed Medications				
Medicinal Product Class (WHO preferred term and drug classification)	**Examples of CYP3A4 Substrates with Narrow Therapeutic Index**	**Examples of Strong/Moderate CYP 3A4 Inducers**	**Examples of Strong CYP3A4 Inhibitors**	**Examples of Strong CYP2C8 Inhibitors**
Antibacterials		rifampin, nafcillin	clarithromycin, erythromycin, telithromycin	
Anticonvulsants		carbamazepin, phenytoin		
Antidepressants			nefazodone	
Antifungals			voriconazole, itraconazole, ketoconazole, posaconazole	
Antihistamines	astemizole			
Antipsychotics	pimozide			
Antivirals		efavirenz, etravirine	boceprevir, dasabuvir/ ombitasvir/paritaprevir /ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, ombitasvir/paritaprevir /ritonavir, ritonavir, saquinavir, telaprevir	
Ergot Alkaloids	dihydroergotamine, ergonovine, ergotamine, methylergonovine			
Immunosuppressants			cyclosporine, tacrolimus	
Lipid-lowering agents				gemfibrozil

Disallowed Medications				
Medicinal Product Class (WHO preferred term and drug classification)	**Examples of CYP3A4 Substrates with Narrow Therapeutic Index**	**Examples of Strong/Moderate CYP 3A4 Inducers**	**Examples of Strong CYP3A4 Inhibitors**	**Examples of Strong CYP2C8 Inhibitors**
Opioids	fentanyl, alfentanil **Exception**: fentanyl or alfentanil use is allowed for sedation on the day of Screening liver biopsy. However, for liver biopsies conducted at Months 12 and 60 **or for any procedure after intake of study drug.** Fentanyl is to be administered under medical supervision and all precautions should be in place, including availability of antidote, to prevent complication from its use. It is recommended that the initial dose be decreased by 50% and titrated to the desired effect.			
Sedative/hypnotics	midazolam, triazolam **Exception**: Midazolam use is allowed for sedation on the day of liver biopsy or for surgical outpatient procedures; however, for liver biopsies conducted at Months 12 and 60 **or for any procedure after intake of study drug,** the first dose should be decreased by 50% of the recommended dose and titrated according to the desired clinical response.			
Other	cisapride			

Disallowed Medications— BCRP Substrates	
WHO preferred term and drug classification	**Example of BCRP Substrates**
Anti-inflammatory drugs	sulfasalazine
Antimetabolite drugs	methotrexate
Antivirals	glecaprevir/pibrentasvir

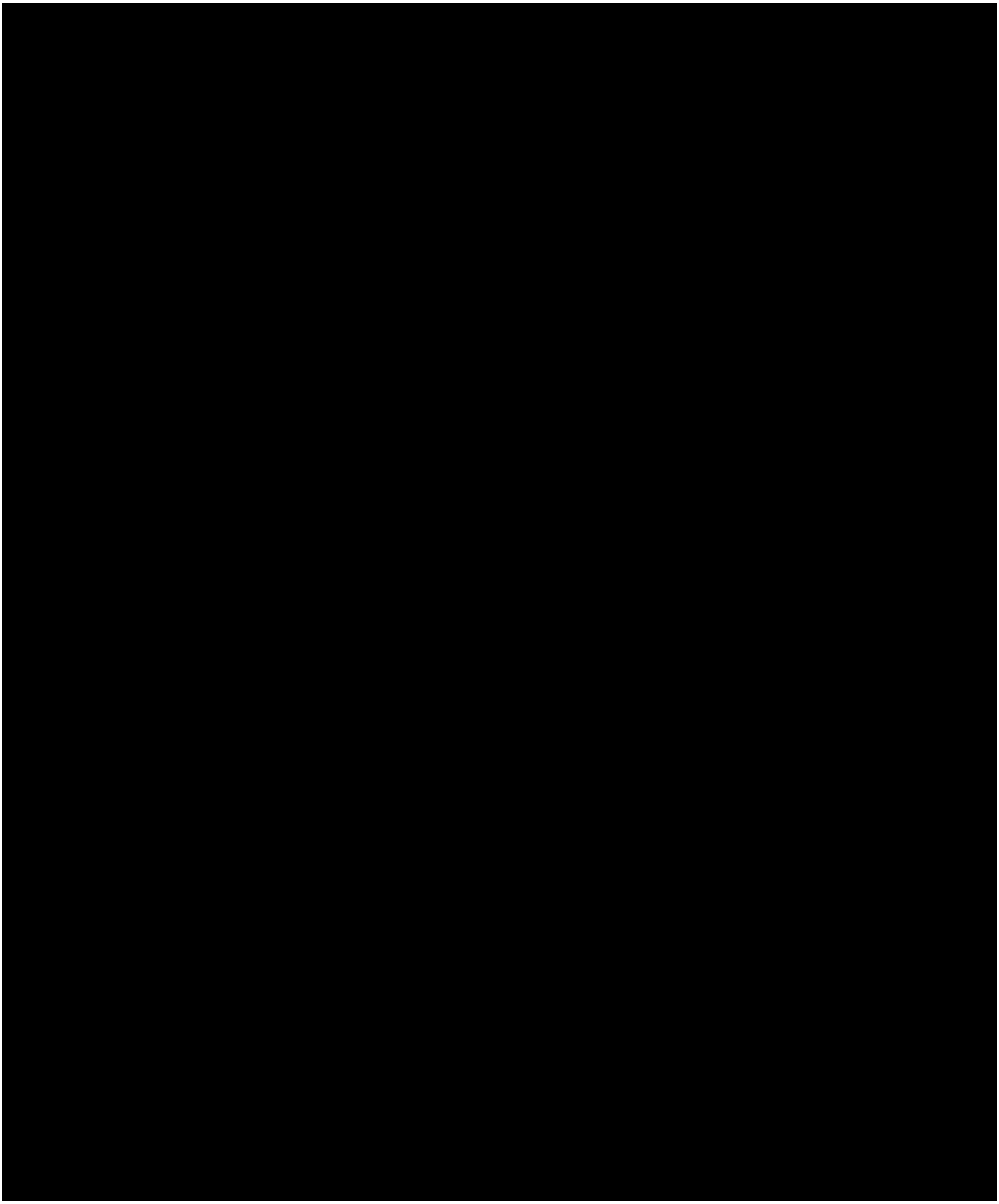
Disallowed Medications Due to Possible Confounding Effect on Efficacy	
WHO preferred term and drug classification	**Example of drugs/components that may have a confounding effect on efficacy**
Antidiabetics	pioglitazone
Fruits, vegetables, other foods, vitamins and supplements	high-dose (ie, > 400 IU/day) vitamin E
Other	obeticholic acid

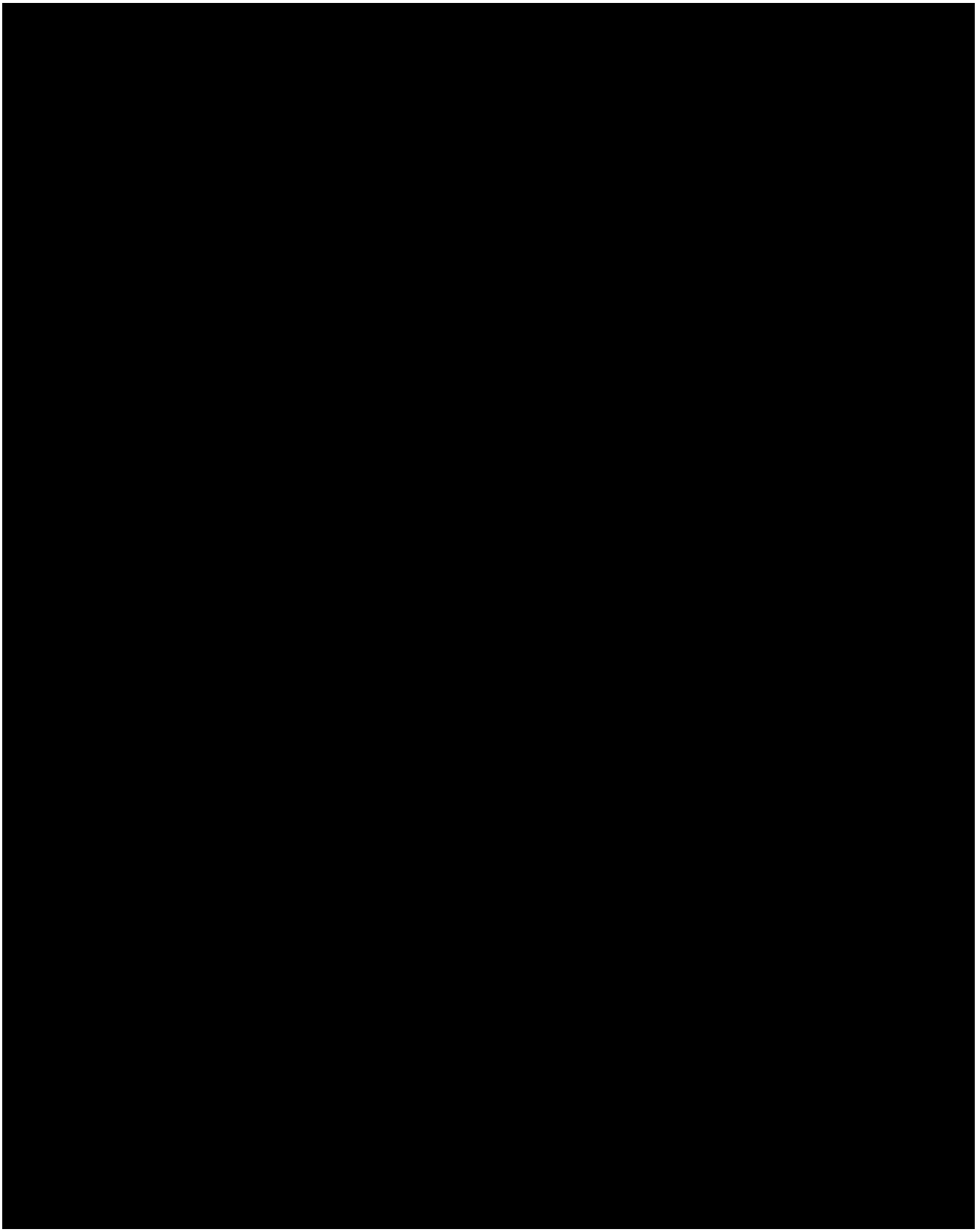
The following medications, if used, should be used with caution as CVC (mild CYP3A4 inhibitor and BCRP inhibitor) may increase exposure of these CYP3A4 and BCRP substrates or these medications may affect the exposure of CVC. If used, these medications should be used at the lowest possible dose and for the shortest duration possible considering individual subject risk-benefit considerations. Clinical monitoring and dose titration are recommended to achieve the desired clinical response. Other medications of a similar class should be considered if possible. Consult the individual medication prescribing information for additional guidance.

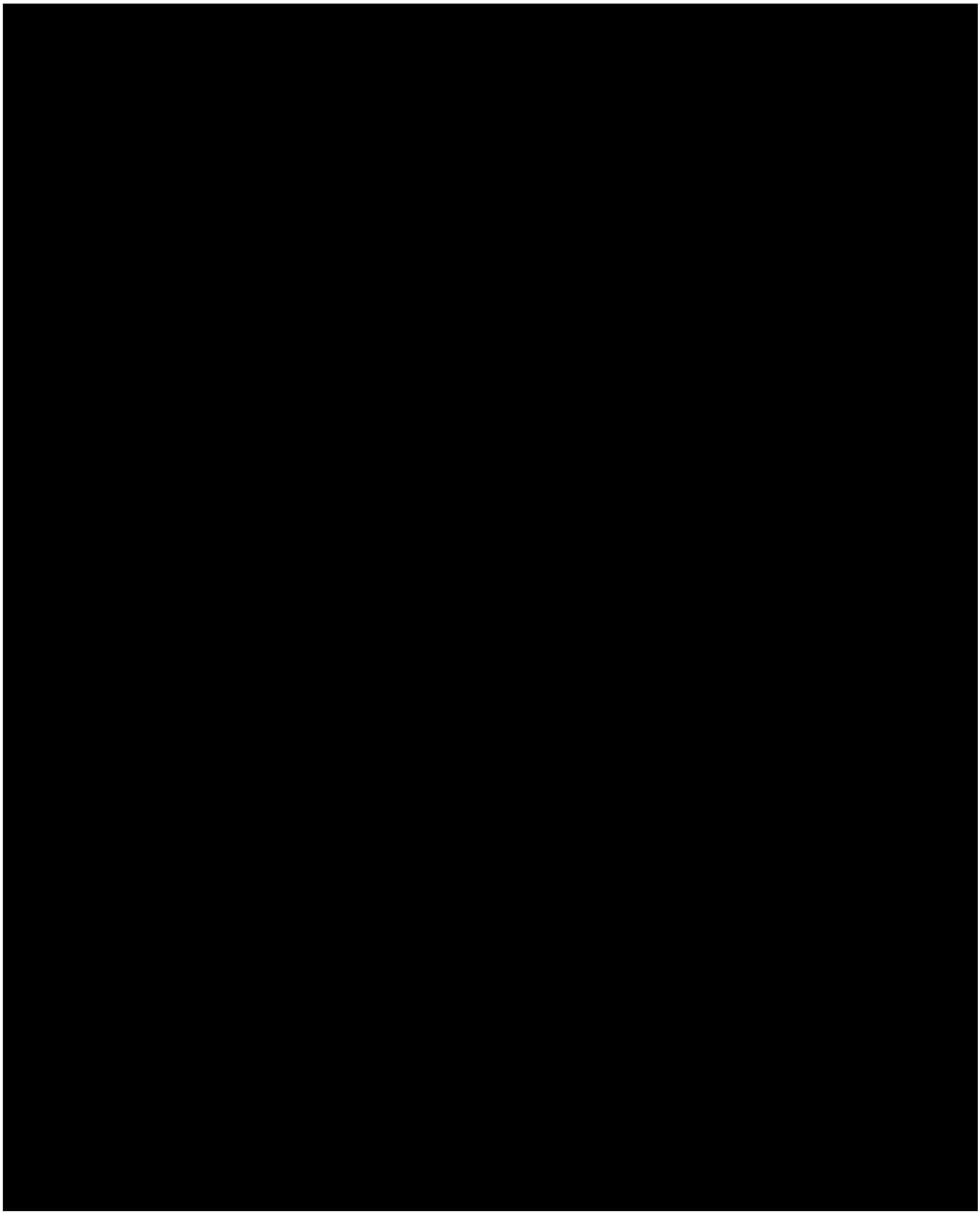
Medicinal Product Class	**Drugs that are Allowed but Must be Taken with Precaution During Intake of Study Drug *(Mechanism)***
Acid-reducing agents (H_2 receptor antagonists, antacids, proton-pump inhibitors [PPIs])	Acid-reducing agents should be administered at least 2 hours after the CVC dose to ensure that adequate CVC concentrations are maintained. When possible, use of an H_2 receptor antagonist (except cimetidine) or antacids is preferred over a proton pump inhibitor (PPI). It is recommended to start with the lowest dose of these agents and titrate according to clinical response. H_2 receptor antagonists (eg, famotidine or ranitidine) should preferably be given from 2 to 12 hours after administration of study drug at a dose that does not exceed doses comparable to famotidine 40 mg daily. Antacids (eg, aluminum hydroxide, calcium carbonate, magnesium carbonate, magnesium hydroxide, or bismuth subsalicylate) should preferably be given at least 4 hours after administration of study drug due to their immediate effect in increasing gastric pH. PPIs (eg, omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, or dexlansoprazole) should preferably be given approximately 3 hours after administration of study drug at a dose that does not exceed doses comparable to omeprazole 20 mg daily. Due to the prolonged acid-reducing effect of PPIs (~16 – 24 hours), it is advised to follow these dosing recommendations to reduce their potential impact on CVC absorption at subsequent dosing
Lipid-lowering agents	atorvastatin, simvastatin, lovastatin, *(CYP3A4 substrates);* pravastatin *(CYP3A4 substrate, weak CYP2C8 inhibitor)*; rosuvastatin *(BCRP substrate)* The maximum recommended daily doses are as follows: atorvastatin 40 mg, simvastatin 20 mg, lovastatin 40 mg, pravastatin 40 mg, and rosuvastatin 20 mg; pitavastatin use is allowed without dose restriction The medical monitor must be consulted prior to use of higher doses of statins than those recommended above.
PDE5 enzyme inhibitors	sildenafil, tadalafil, vardenafil *(CYP3A4 substrates)* The recommended starting doses for these medications are as follows: sildenafil 25 mg, tadalafil 2.5 mg, vardenafil 2.5 mg

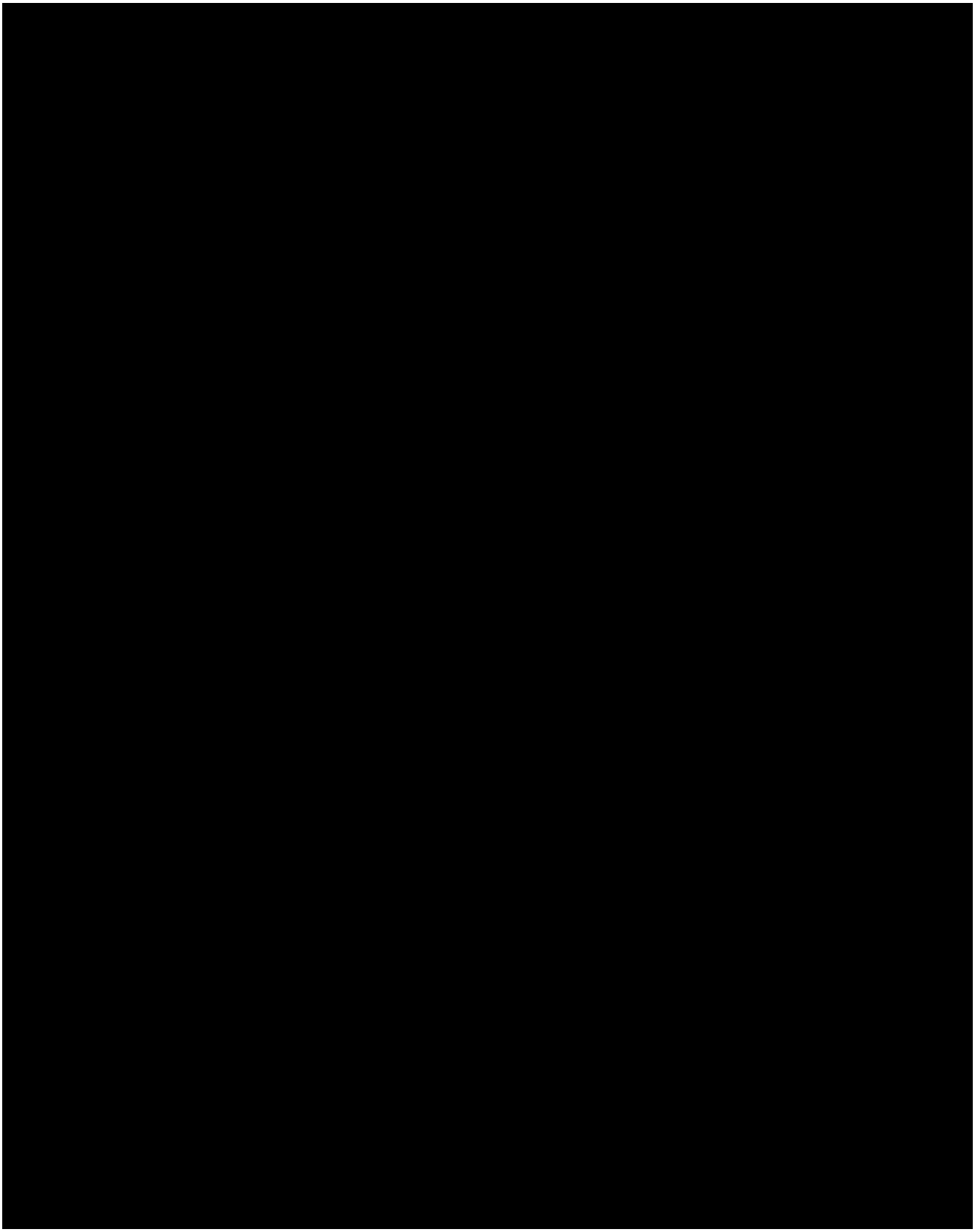
Source:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

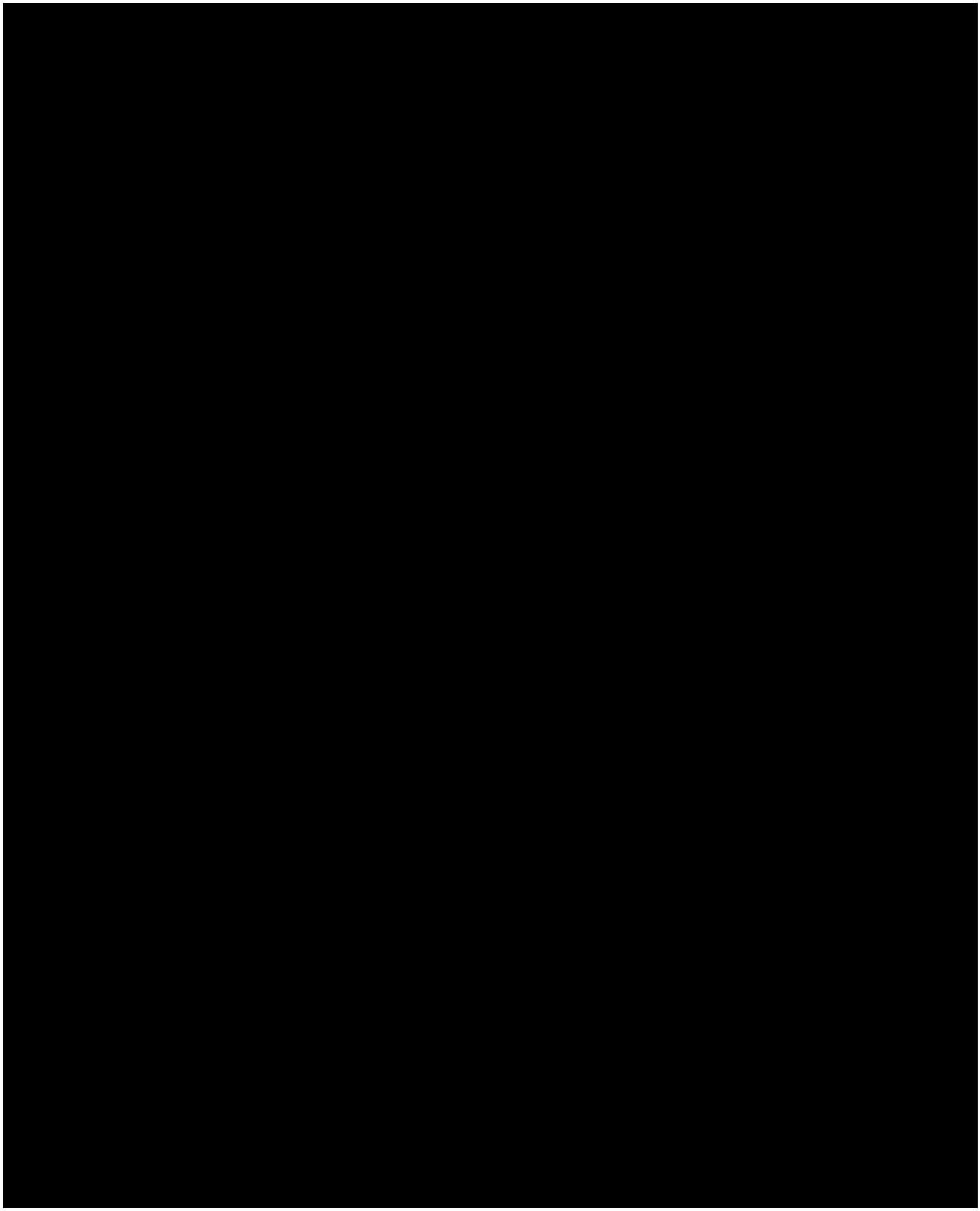
20.5. Clinical Laboratory Tests

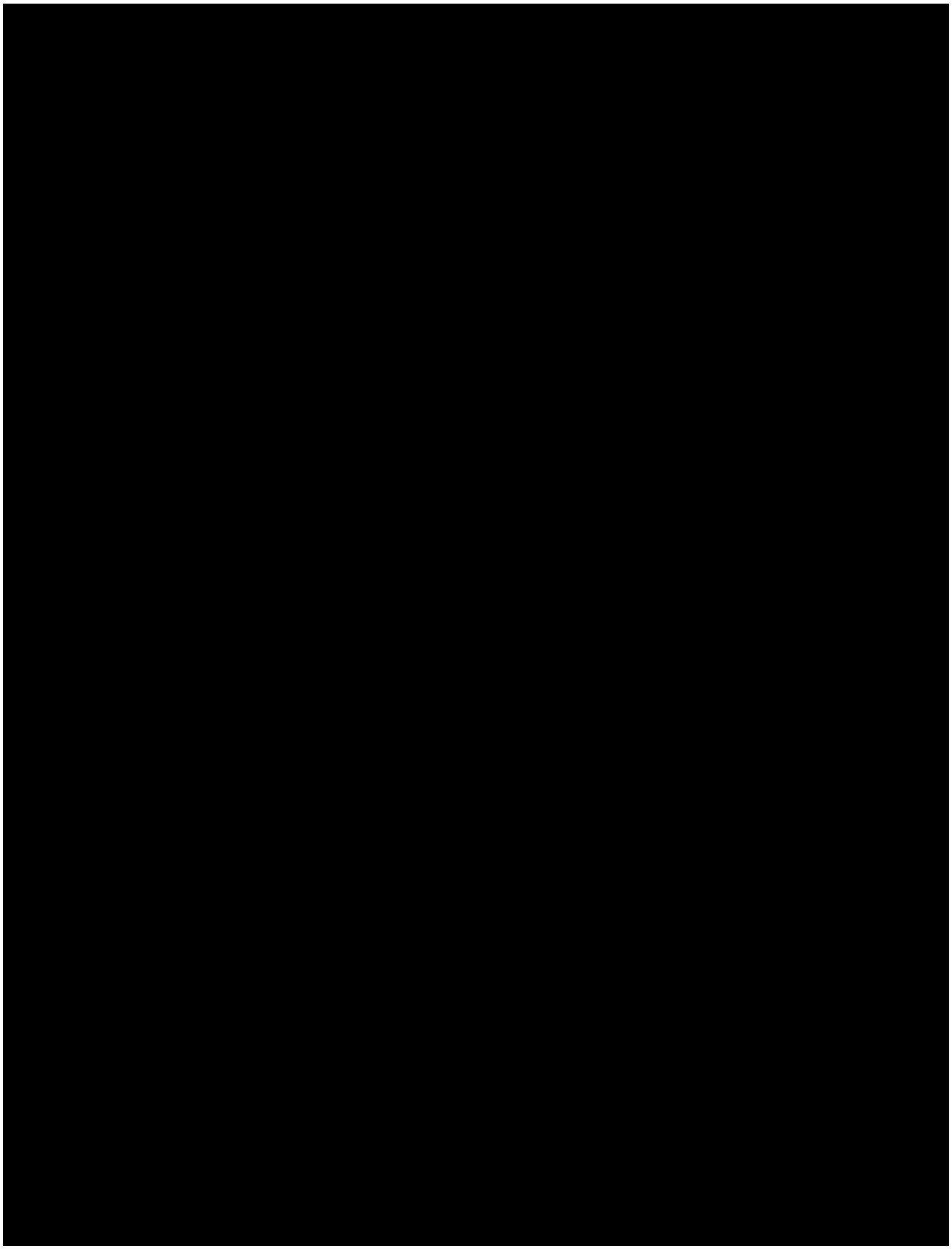


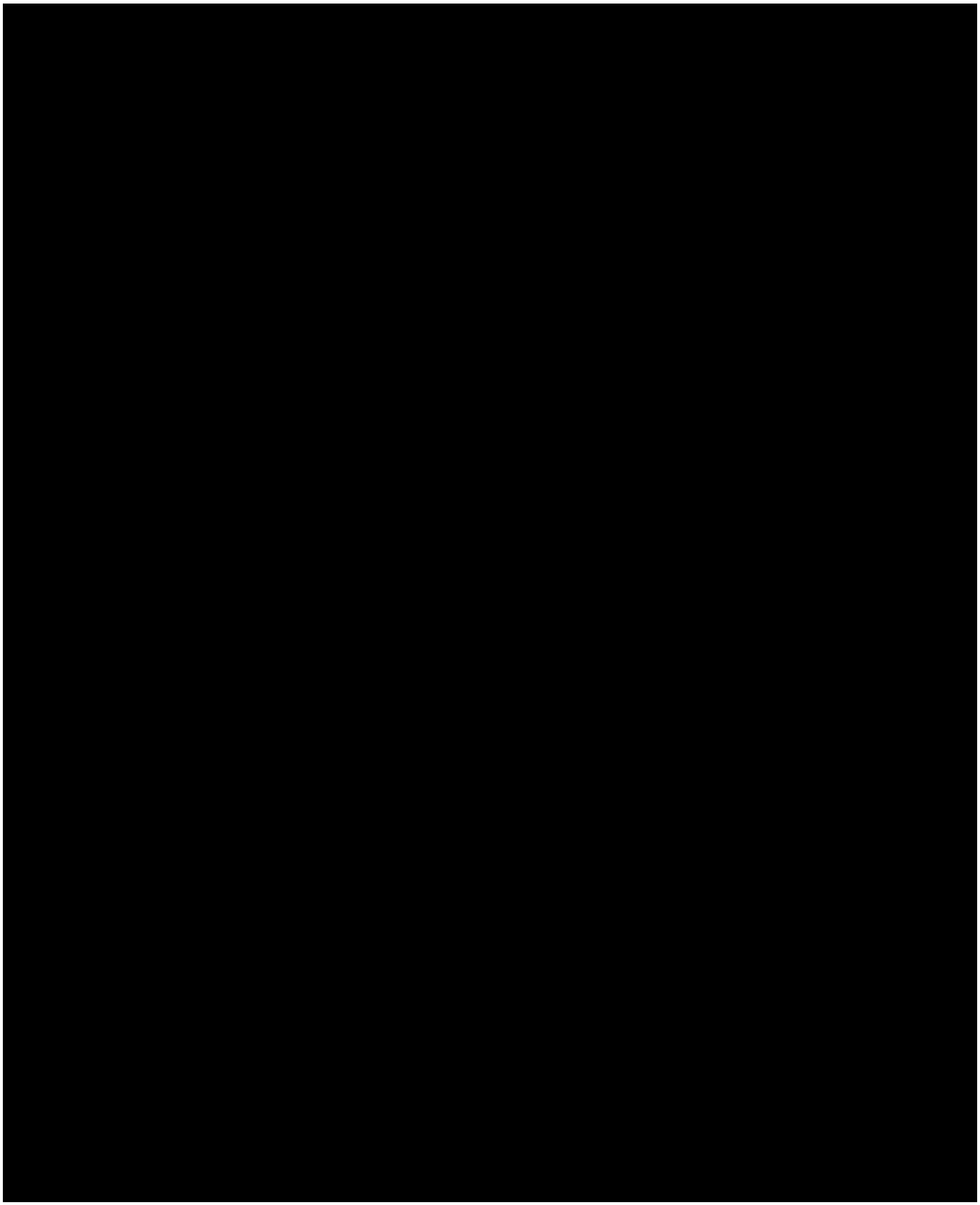












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