# STATISTICAL ANALYSIS PLAN
# (SAP)

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|---|---|
| **Title:** | A Phase 1/2, Open-Label Safety and Dose-Finding Study of Adeno-Associated Virus (AAV) Serotype 8 (AAV8)-Mediated Gene Transfer of Glucose-6-Phosphatase (G6Pase) in Adults with Glycogen Storage Disease Type Ia (GSDIa) |
| **Protocol:** | 401GSDIA01 |
| **Investigational Product:** | DTX401 (Nonreplicating, recombinant AAV8 vector that contains a codon-optimized, human G6PC coding sequence) |
| **Phase:** | 1/2 |
| **Sponsor:** | Ultragenyx Pharmaceutical Inc.<br>60 Leveroni Court<br>Novato, CA, USA 94949 |
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| **Date:** | 12 July 2021 |
| **Date Amended:** | 04 March 2022 |
| **Version Number:** | Version 2.0 |

# CHANGE HISTORY

| Version | Changes and Rationale for Changes |
|---|---|
| **1.0** | Initial Version |
| **2.0** | Minor changes in the document include changes to match the language in the SAP with the corresponding language in the protocol, removing redundancy in analyses that were described multiple times in the document, and adding clarifications around endpoint or analysis.<br><br>Major changes in the document are summarized below.<br><br>**Section 3.7:**<br>• Added update on latest data monitoring committee (DMC) conducted for the study<br>• Removed text about the roles and responsibilities of the DMC because that is outside the scope of the SAP.<br><br>**Section 8.4.1:** Added derivation of actual dose administered to the subject<br><br>**Section 8.5.1:** Added summary of cornstarch used and amount of carbohydrates in the dinner prior to controlled fasting challenge (CFC) upon request from medical monitor to understand use of these quantities in CFC.<br><br>**Section 8.5.2**: Added analysis window for analysis of cornstarch data. Added plot for daytime, bedtime, and nighttime frequency of cornstarch doses.<br><br>**Section 8.5.3:**<br>• Added exploratory analyses of continuous glucose monitoring (CGM) data based on the request from medical monitor of the study to gain better understanding of this data.<br>• Added derivation for percentage of time spent in any glucose range in a week<br>• Removed text about the use of both Cenduit and Clarity data for analysis of CGM data because Clarity data will not be part of clinical dataset.<br><br>**Section 8.6.7:** Removed reference of few safety labs parameters from this section because analyses planned for these parameters are already described in other sections. Further, clarified that this section focuses on analyses for lab parameters collected at the central lab.<br><br>**Section 8.6.8:** Added detailed description of analyses planned for vector shedding and vector genome determination tables<br><br>**Section 8.7**: Added language about assessment of impact of COVID-19 on subjects' study participation |

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AAV8 | adeno-associated virus serotype 8 |
| AE | adverse event |
| ALT | alanine aminotransferase |
| BMI | body mass index |
| CRF | case report form |
| CRM | continual reassessment method |
| CGM | continuous glucose monitoring |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | dose-limiting toxicity |
| DMC | data monitoring committee |
| ECG | electrocardiogram, electrocardiographic |
| eCRF | electronic case report form |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| G6P | glucose-6-phosphate |
| G6Pase | glucose-6-phosphatase (protein) |
| G6PC | glucose-6-phosphatase (gene) |
| GC | genome copies |
| GSDIa | glycogen storage disease type Ia |
| IgG | immunoglobulin G |
| IV | intravenous |
| MedDRA | Medical Dictionary for Regulatory Activities |
| [redacted] | [redacted] |
| MTD | maximum tolerated dose |
| NCI | national cancer institute |
| OBD | optimal biological dose |
| PDFF | proton density fat fraction |
| PT | preferred term |

| Abbreviation | Definition |
|---|---|
| [redacted] | [redacted] |
| QTc | QT interval corrected for heart rate |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |

# 1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the 401GSDIA01 original Protocol dated 17 May 2017, Protocol Amendment 1 dated 13 December 2017, Amendment 2 dated 02 March 2018, Amendment 3 dated 18 February 2019, Amendment 4 dated 10 September 2019, Amendment 5 dated 28 October 2019, and Amendment 6 dated 16 February 2021.

# 2. STUDY OBJECTIVE(S)

## 2.1. Primary Objective

- To determine the safety of single intravenous (IV) doses of DTX401 in adults with GSDIa, including the incidence of dose-limiting toxicities (DLTs).

## 2.2. Secondary Objective

- To establish a dose of DTX401 that achieves symptom-free euglycemia (glucose ≥54 mg/dL [≥3.0 mmol/L])* in a setting of a controlled fasting challenge to allow further clinical development.

  * Following protocol amendment 6, the definition of euglycemia for the end of the controlled fasting challenge changed from ≥60 mg/dL (≥3.3 mmol/L) to ≥54 mg/dL (≥3.0 mmol/L)

## 2.3. Exploratory Objectives

# 3. STUDY DESIGN

## 3.1. Study Overview

401GSDIA01 is a Phase 1/2, open-label, single-arm, multicenter, safety and dose-finding study to determine the safety, tolerability, and efficacy of DTX401 in adults with GSDIa.

## 3.2. Dosage and Administration

DTX401 will be administered as a single peripheral IV infusion. The following doses will be evaluated using a continual reassessment method (CRM) to estimate the maximum tolerated dose (MTD):

- **Dose 1**: $2.0 \times 10^{12}$ genome copies (GC)/kg
- **Dose 2**: $6.0 \times 10^{12}$ GC/kg
- **Dose 3**: $1.0 \times 10^{13}$ GC/kg

Eligible subjects may be enrolled into 1 of the following cohorts of 3 subjects each and receive a single IV infusion of DTX401.

- **Cohort 1**: Dose 1 ($2.0 \times 10^{12}$ GC/kg) with a reactive steroid regimen (prednisone starting dose of 40 mg/day)
- **Cohort 2**: Dose 2 ($6.0 \times 10^{12}$ GC/kg) with a reactive steroid regimen (prednisone starting dose of 40 mg/day)
- **Cohort 3**: Dose 2 ($6.0 \times 10^{12}$ GC/kg) with an optimized reactive steroid regimen (prednisone starting dose of 60 mg/day)
- **Cohort 4**: Dose 2 ($6.0 \times 10^{12}$ GC/kg) with a prophylactic steroid regimen

A cohort may be expanded to include additional subjects to confirm the findings for the cohort.

Subjects in Cohorts 1 and 2 were dosed at a minimum of 2 weeks (14 days) apart. Subjects in subsequent cohorts will be dosed at a minimum of 1 week (7 days) apart.

After the third patient in a cohort reaches the 12-week time point, the CRM will propose a dose for the next cohort using the collected data from the previous cohort. The decision to proceed will be made after the data monitoring committee (DMC) has evaluated at least 12 weeks of safety data for all subjects in a dosing cohort.

Subjects will be followed for 52 weeks following DTX401 administration. After completion of the Week 52 visit or early withdrawal, subjects will be offered enrollment in a 4-year extension study to evaluate the long-term (a total of 5 years) safety and efficacy of DTX401.

## 3.3. Blinding and Randomization Methods

Not applicable.

## 3.4. Stratification Factors

Not applicable.

## 3.5. Sample Size Considerations

Simulations show that if all 3 doses are safe and no DLTs occur, the CRM will recommend dose escalation to $1 \times 10^{13}$ GC/kg (genome copies measured by [redacted] and the recruitment of 12 subjects. Based on safety and efficacy observations in Cohorts 1, 2, and 3 (3 subjects each) and a positive recommendation from the DMC, it was decided to enroll a fourth cohort of 3 subjects. The planned sample size of the study will therefore be 12 subjects including 4 cohorts.

## 3.6. Interim Analysis

No interim analyses were performed.

## 3.7. Data Monitoring Committee

An independent DMC will be responsible for monitoring safety data from the study. For Cohorts 1 and 2, the DMC met after all evaluable subjects in the dosing cohort completed Week 12 of the study to review the safety data and provided their recommendation for progressing to the next dosing cohort or enrollment of subjects into additional cohorts. So far, DMC has reviewed safety data up to Week 52 for Cohorts 1-3 and Week 24 for Cohort 4; there were no safety concerns from the DMC and the recommendation has been to continue the study. The DMC will meet at the end of the study and may, at any time, recommend modifying or pausing enrollment due to safety concerns based on their periodic data reviews.

Enrollment will be paused, and the DMC and regulators will be notified if, at any time during the study, any of the events listed below occur following administration of DTX401:

- Death of a subject
- An event with an intensity ≥Grade 3 (according to the National Cancer Institute Common Terminology Criteria for Adverse Events) develops
- Occurrence of a hepatic malignancy

If a stopping rule is met, enrollment will be paused, and the DMC will meet to review available data. If a decision is made to resume enrollment, this decision will be communicated to and, if required, approved by regulatory authorities according to country requirements.

# 4. STUDY ENDPOINTS AND COVARIATES

The full schedule of assessments is shown in Appendix 1.

## 4.1. Primary Endpoint(s)

The incidence of adverse events (AEs), including the incidence of DLTs at each dose level, treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) for each dosing cohort, assessed by severity and relationship to study product. Specifically,

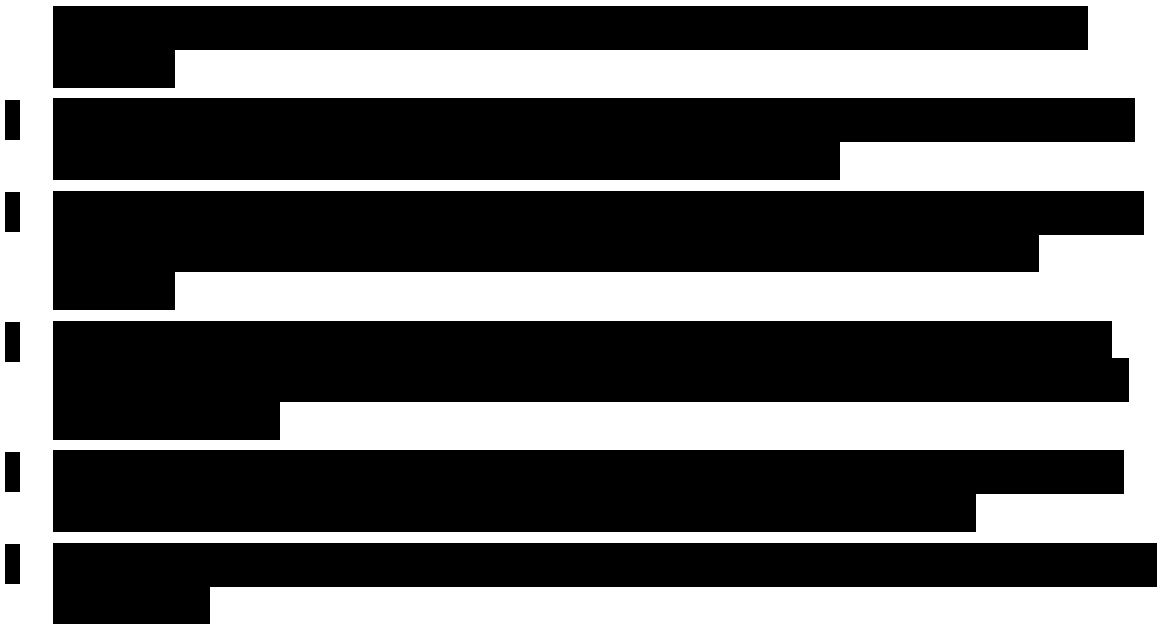
- TEAEs by SOC and PT
- DLTs by SOC and PT
- Related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- TEAEs by PT and greatest severity

## 4.2. Secondary Endpoint(s)

- The change from baseline in time (in minutes) to first hypoglycemic event (defined as glucose <54 mg/dL [<3.3 mmol/L])* during a controlled fasting challenge at 12, 24, and 52 weeks after IV administration of DTX401.

  * *Following protocol amendment 6, the definition of euglycemia for the end of the controlled fasting challenge changed from ≥60 mg/dL (≥3.3 mmol/L) to ≥54 mg/dL (≥3.0 mmol/L*

## 4.3. Exploratory Endpoints



# 5. DEFINITIONS

## 5.1. Baseline

Baseline is defined as the last non-missing assessment taken prior to the dose of DTX401, unless specified otherwise.

## 5.2. Study Day

If the visit date is on or after the date of the dose of DTX401:

Study day = (visit date – date of the dose of DTX401 + 1)

If the visit date is prior the date of the dose of DTX401:

Study day = visit date – date of the dose of DTX401.

## 5.3. Prior and Concomitant Medication

Prior medication is defined as any medication started before the DTX401 dose date (medication start date prior to the DTX401 dose date).

Concomitant medication is defined as any medication taken on or after the DTX401 dose date (medication end date on or after the DTX401 dose date, or ongoing).

## 5.4. Dose-Limiting Toxicity

A DLT is defined as any AE/SAE ≥Grade 3 that is considered by the Investigator and/or Sponsor to be related to DTX401, based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), the most recent version.

## 5.5. [redacted]

[redacted]

## 5.6. [redacted]

[redacted]

# 6. ANALYSIS POPULATIONS

## 6.1. Full Analysis Set

The full analysis set will consist of all enrolled subjects who received DTX401. The full analysis set will be used for all the analyses.

# 7. DATA SCREENING AND ACCEPTANCE

## 7.1. General Principles

Data will be reviewed periodically, and any questionable data will be reported to the data manager promptly for query and resolution.

## 7.2. Handling of Missing and Incomplete Data

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data quality review plan for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock or snapshot.

Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

### 7.2.1. Missing Medical History Related Dates

- If only day is missing, impute 1.
- If month is missing, impute January 1st.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is earlier than the birth date, then the birth date will be used.

### 7.2.2. Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date.

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the month and year of the DTX401 dose date, then impute the day of the DTX401 dose date.
  - Otherwise, assign the first day of the month.
- If the month is unknown, then:
  - If the year matches the year of the DTX401 dose date, then impute the month and day of the DTX401 dose date.
  - Otherwise, assign ‘January’
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

Missing Stop Dates and not ongoing

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing. If the AE has been recorded as resolved/recovered, all efforts should be made to obtain the date from the Investigator.
- If the resulting end date is after the date of study completion / discontinuation / data cutoff, set the imputed end date as close to the date of study completion / discontinuation / data cutoff as possible without overwriting existing information.
- If the year is missing for the start date and stop date (observed or imputed) is on or after the DTX401 dose or event is ongoing, the start date will be imputed as the DTX401 dose date.

### 7.2.3. Missing Causal Relationship to Investigational Product for Adverse Events

If the causal relationship to investigational product (DTX401) is missing for an AE that started on or after the date of the DTX401 dose, a causality of "related" will be assigned. The imputed values for causal relationship to DTX401 will be used for the incidence summary; the values will be shown as missing in the data listings.

## 7.3. Testing/Validation Plan

Data will be reviewed by a cross functional team periodically and issues will be addressed by data management.

## 7.4. Software

The CRM model will be used to evaluate each dose for dose escalation using software Fixed and Adaptive Clinical Trial Simulator (FACTS™; Berry Consultants, Austin, Texas, United States) Version 6.0 or later. SAS® software (SAS® Institute, Inc., Cary, North Carolina, United States) version 9.4 or higher will be used to perform statistical analyses unless otherwise specified.

# 8. STATISTICAL METHODS OF ANALYSES

## 8.1. General Principles

Continuous variables will be summarized by number of subjects and mean, standard deviation (SD), standard error (SE), median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. All summary tables will be presented by scheduled study visit and no analysis windows will be used, unless specified otherwise. All the summary tables will be presented by dosing cohort of DTX401 and overall, unless specified otherwise. The dosing cohorts are:

- Cohort 1: Dose 1 ($2.0 \times 10^{12}$ GC/kg) with a reactive steroid regimen (prednisone starting dose of 40 mg/day)
- Cohort 2: Dose 2 ($6.0 \times 10^{12}$ GC/kg) with a reactive steroid regimen (prednisone starting dose of 40 mg/day)
- Cohort 3: Dose 2 ($6.0 \times 10^{12}$ GC/kg) with an optimized reactive steroid regimen (prednisone starting dose of 60 mg/day)
- Cohort 4: Dose 2 ($6.0 \times 10^{12}$ GC/kg) with a prophylactic steroid regimen

### 8.1.1. The Continual Reassessment Method

Neuenschwander's CRM (or nCRM) (Neuenschwander et al., 2008) will be used to make recommendations for the dose to be administered in each cohort using all evaluable subjects (i.e., subjects who remain in the study for at least 12 weeks after dosing or for whom a DLT is observed within 12 weeks of dosing). The DLT assessment for each subject is based on the definition in Section 5.4. The DLT evaluation window for each subject starts on the date of administration of DTX401 and continues for up to 12 weeks (84 days) thereafter, or until all Week 12 safety assessments have been completed, whichever occurs later. Results of CRM model will be presented as part of DMC data review.

The target toxicity rate is 0.25. The cohort size is 3 subjects. The dose levels studied are specified in Section 3.2. The first cohort will be treated at $2 \times 10^{12}$ GC/kg. Subsequent cohorts will be treated at the lower of the current estimate of the MTD and the highest dose allowed by the escalation rule. The CRM model will evaluate subjects based on the dose administered regardless of the steroid approach used.

A logistic model will be used to model the dose-toxicity curve; further details are provided in Appendix 2.

The CRM model will recommend that the study is stopped once the MTD is determined the first time any of the following criteria are satisfied after a CRM model update:

- Six evaluable subjects have been treated at $1 \times 10^{13}$ GC/kg and the current estimate of the MTD is $>1 \times 10^{13}$ GC/kg
- Six evaluable subjects have been treated at the current estimate of the MTD
- The current estimate of the MTD is $<2 \times 10^{12}$ GC/kg (insufficient safety)

The study will stop when the maximum sample size of 12 subjects have been enrolled or at the Sponsor's discretion. If 12 subjects have been enrolled and the definition of having an MTD determined has not been reached, then the highest dose considered at or below the MTD will be considered the MTD.

Enrollment will be limited so that each dosing cohort includes no more than 3 subjects.
The optimal biological dose (OBD) will be based on the MTD and an assessment of clinical benefit.

## 8.2. Subject Accountability

The number and percentage of subjects in the full analysis set will be summarized. The number and percentage of subjects who complete the study and of subjects who prematurely discontinue will be summarized. The reasons for premature discontinuation from the study will be summarized as recorded in the electronic case report forms (eCRFs). The study duration will be summarized. A subject disposition listing, including study duration, will be provided for individual subjects.

The glucose-6-phosphatease (G6PC) genotyping results at screening will be listed. For subjects who fail to meet eligibility criteria, the inclusion/exclusion criteria the subjects fail will be listed.

## 8.3. Protocol Deviations

Major protocol deviations will be summarized for each type. Both major and minor protocol deviations will be listed.

## 8.4. Investigational Product Administration

### 8.4.1. Extent of Exposure

The actual dose and volume administered will be summarized and will also be listed. The actual dose will be calculated as dose level (GC/kg) multiplied by screening weight (kg) of the subject.

### 8.4.2. Demographic and Baseline Characteristics

Demographic parameters (age; race; ethnicity; sex; weight; height, body mass index [BMI]) will be summarized descriptively and will also be listed by subject.

### 8.4.3. Medical History and GSDIa Medical History

Medical history will be summarized by body system and will also be listed by subject. GSDIa medical history data will be summarized and will also be listed by subject.

### 8.4.4. Prior and Concomitant Medication

Both prior and concomitant medications will be coded by drug name and therapeutic class using WHO Drug dictionary. If a subject received a specific medication multiple times or received multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class. Prior and concomitant medications will be summarized in tables and will also be provided in listings.

### 8.4.5. GSDIa Diet

The prescribed and actual daily GSDIa diet parameters (including total calories, carbohydrates and non-utilizable sugars, protein, and fat) and change from baseline values will be summarized by study visit. Individual subject listing of GSDIa diet data will be provided.

## 8.5. Efficacy Analysis

### 8.5.1. Symptom-Free Euglycemia

The time (in minutes) to the first hypoglycemic event (defined as glucose <60 mg/dL [<3.3 mmol/L]) during a controlled fasting challenge at baseline (Day 0), Week 12, 24 and 52, and the change from baseline in time (in minutes) to first hypoglycemic event at Weeks 12, 24, and 52 will be summarized. If the controlled fasting challenge has to be stopped due to symptomatic hypoglycemic event, or the subject is administered intervention (e.g., cornstarch), the time to the first hypoglycemic event will be defined as the time to the controlled fasting challenge is terminated. If there is no hypoglycemic event during the fasting challenge, the time will be censored at the maximum evaluable time (15 hours).

A listing of the controlled fasting challenges and the glucose, lactate, and other local lab parameters (cortisol, free fatty acids, glucagon etc.), and capillary glucose levels (if available) collected during the controlled fasting challenges will be provided. Use of cornstarch and carbohydrates in the dinner prior to controlled fasting challenge and change from baseline will be summarized by visit.

In addition, plots for individual patient profile of controlled fasting challenge hours, plots for individual patient profile of glucose and lactate during controlled fasting challenges will be presented by study visits.

### 8.5.2. Use of Cornstarch (or Glycosade)

The prescribed and actual daily amount and frequency of cornstarch over time will be summarized by study visit in a table and provided in the listings. In addition, the percent change from baseline in daily cornstarch amount by study visit by subject by dosing cohort will be plotted. Daily frequency of cornstarch (total and by daytime, nighttime, and bedtime) by study visit will be plotted for each subject.

Data collected at a scheduled visit within an analysis window of +/- 14 days of the target day for a visit will be included in the analysis. If such a scheduled visit is not performed, data collected at the nearest unscheduled visit (if any) completed within that analysis window will be included.

### 8.5.3. Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) device data will be collected from cohort 3 and 4 subjects for this study. Glucose data will be summarized per subject per week and per subject per week per day (24 hours) Raw summary statistics will be provided. Study weeks are derived by (assessment dates – dosing date +1)/7.

Percentage of time spent in normal glucose ranges (between 60 mg/dL -120 mg/dL, between 70 mg/dL – 120 mg/dL), percentage of time spent in low and high glucose values (< 60 mg/dL, < 70 mg/dL, < 50mg/dL, > 120 mg/dL), number of low glycemic events (< 60 mg/dL,

<70 mg/dL, <50 mg/dL), time spent in minutes under glucose values (< 60 mg/dL , < 70 mg/dL, < 50 mg/dL), time spent in minutes for glucose ranging in (60 -120, 70 – 120 and >120 mg/dL) will be summarized by subject by week and by subject by week by day ( 24 hours).

Percentage of time spent in any glucose range in a week is calculated as time duration (minutes) of glucose values spent in that range in a week, divided by total time duration (minutes) in a week and multiplied by 100 where

- Time duration (in minutes) of glucose values spent in that range in a week= sum of all the time intervals where glucose value is in the range where time interval for any glucose value is calculated as the difference between collection time of that glucose value and the next collection time. If the glucose value is missing at any collection time between first glucose value and last glucose value collected in that week, the last available glucose value prior to the collection time will be carried over.
- Total time duration (in minutes) in a week= (Last time/date of non-missing glucose value of the week – first time/date of non-missing glucose value) + 5 minutes
- Only glucose value between 40 and 400 mg/dL collected by CGM device will be considered as non-missing value.

The percentage of time spent in a glucose range in an hour will be calculated in similar fashion where only recordings in that hour will be considered. Percentage time spent in a glucose range in a month (4-weeks) will be calculated by calculating the percentage time spent in each week and taking average of these weekly values.

The percentage of subjects with >=85% of weekly glucose values in the range 60-120 mg/dL and >=90% of glucose values in the range 60-120 mg/dL will be summarized by week for each cohort. Summary of total time spent, percent of time spent, and average time of episodes in glucose ranges (<60, <70, 60-120, 70-120, > 120 mg/dL) will be provided by week and by day (24 hours) for all subjects combined.

In addition, individual glucose profile over 24 hours together with cornstarch prescription will be plotted weekly (up to 7 days) by subject. Summary of glucose values (mean, median, min, max, etc.) will be plotted by study days for each subject. Summary of glucose values (mean, min, max) will be plotted by day (24 hours) and week for each subject. Variability (SD) of glucose values in a week will be plotted by week for each subject.

Number of low glycemic events and their duration will be summarized by week for each subject. Number of low glycemic events will be plotted by study days and by week for each subject. A low glycemic (hypoglycemic) event is defined as a series of at least two sensor glucose values less than 60 mg/dL, lasting at least 15 min, with no intervening values of 60 mg/dL or more. The end of a hypoglycemic event is defined as a minimum of 15 consecutive minutes with at least two sensor glucose values of at least 60 mg/dL and at least 10 mg/dL above the nadir of the event or at the end of a week. Further, daily, and weekly number of low glycemic events together with cornstarch use will be plotted for each subject. For cornstarch use, data collected at all visits (scheduled and unscheduled) will be included in the analysis.

Percentage of time of glucose values under 60 mg/dL, percentage of time spent in normal glucose ranges (between 60mg – 120 mg/dL), total time (minutes) of glucose values under 60 mg/dL will be plotted by subject by week.

Percentage of time spent in normal glucose ranges (60–120 mg/dL) together with cornstarch intake will be plotted by week for each subject, by week for each cohort, and by month (4-weeks) for each cohort. Percentage of time spent in different glucose ranges (<60, 60 – 120, >120 mg/dL) together with cornstarch intake (in grams) will be plotted by month (4-weeks) for each cohort. Total time (minutes) of glucose values under 60 mg/dL together with cornstarch intake will be plotted by week for each subject.

Additional cutoffs and glucose variability may be analyzed as appropriate. Additional summary may be performed by dosing cohort by week.

### 8.5.4. Morning Glucose Levels

Morning glucose levels will be summarized in a table and provided in the listings. Plots for individual patient profile of morning glucose level and overnight cornstarch dose will be presented by study day. Plots for individual patient profile of weekly mean morning glucose level and overnight cornstarch dose will also be presented.

### 8.5.5. [redacted]

[redacted]

### 8.5.6. [redacted]

[redacted]

## 8.6. Safety Analysis

The safety parameters will include AEs, SAEs, vital sign measurements, complete and targeted physical examination findings, electrocardiogram (ECG) results, documented symptomatic hypoglycemic events, clinical laboratory assessments (clinical chemistry [including liver function tests], hematology, coagulation panel, and urinalysis), vector shedding, vector genome determination, measurement of neutralizing antibody titer to AAV8, measurement of AAV8 binding antibody immunoglobulin G (IgG), assessment of any cell-mediated immune responses to AAV8 and G6Pase, and measurement of anti-G6Pase antibodies.

Except for the CRM modelling described above, all statistical analyses of safety outcomes will be descriptive.

### 8.6.1. Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the current version of Medical Dictionary for Regulatory Activities.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurs on or after the DTX401 dose and is not present prior to the DTX401 dose, or it is present at the DTX401 dose but increases in intensity, severity, or frequency during the study.

Subject incidence of AEs will be tabulated as the following:

- Summary of AEs
- TEAEs by SOC and PT
- DLTs by SOC and PT
- Related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- Grade 3 or 4 TEAEs by SOC and PT
- Fatal TEAEs by SOC and PT
- TEAEs leading to discontinuation of study by SOC and PT
- TEAEs by PT
- TEAEs by PT and greatest severity

Summary tables by SOC and PT will include number of subjects as well as number of events. Detailed listings for all AEs, DLT, TEAEs leading to the discontinuation of study, and death will also be generated.

The severity will be based on the most current version of CTCAE. If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = death.

### 8.6.2. Physical Examination

Physical examination date will be listed by study visit. Physical examination findings that are clinically significant per study investigator are documented and summarized as AEs.

### 8.6.3. Vital Signs

Vital sign measurements (heart rate, blood pressure [systolic and diastolic], and respiratory rate) and changes from baseline values will be summarized by study visit. Height, weight, and BMI will be summarized. Individual profile of weight and BMI over time will be plotted. Individual subject listing of vital signs will be provided.

### 8.6.4. Electrocardiogram

Each ECG will be interpreted as “normal”, “abnormal not clinically significant”, or “abnormal clinically significant” by the study investigator and captured on eCRF. Shift from baseline in ECG interpretation will be summarized at Week 52/EOS. The interpretation of the ECG data will be listed by study visit.

A listing of ECG results will be provided.

### 8.6.5. Liver Ultrasound

An ultrasound of the liver will be conducted during the screening period. Ultrasound results will be provided in a listing.

### 8.6.6. Symptomatic Hypoglycemic Events

The number of subjects who reported symptomatic hypoglycemic events will be summarized by study visit. Symptomatic hypoglycemic events resulting in a visit to the emergency room or hospitalization are also reported as AEs on AE eCRF.

Details of the symptomatic hypoglycemic events will be provided in a listing.

### 8.6.7. Clinical Laboratory Assessments

Clinical laboratory assessments are mainly collected at central laboratory (Table 2), except for data collected during CFC which is collected at local laboratory and analyzed as described in Section 8.5.1. For all central clinical laboratory parameters (Table 2) with continuous results, absolute values and changes from baseline will be summarized by study visit. For central laboratory parameters with categorical results, results will be included in a listing because these parameters are either non-critical for analysis (e.g., Urinalysis blood (by dipstick), or microscopic examination parameters, etc.) or they are collected only at screening visit (e.g., HBV surface antigen).

Listings of laboratory parameters will be provided. Individual patient profile of triglyceride with daily cornstarch intake over time will be plotted.

**Table 2: Central Clinical Laboratory Parameters**

| | |
|---|---|
| **Clinical chemistry:** | Lipid panel, uric acid, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, albumin, total protein, creatine kinase, bilirubin (total, direct, and indirect), ALT, AST, ALP, gamma-glutamyl transferase, and lactate dehydrogenase |
| **Hematology:** | Complete blood count with differential |
| **Urinalysis:** | Specific gravity, pH, glucose, protein, blood (by dipstick), ketones (by dipstick), and microscopic examination (if blood or protein is found) |
| **Other:**<br>**(collected only at Screening)** | HBV surface antigen, HCV RNA, HIV, |
| **Coagulation panel:** | PT/INR, aPTT |
| **24-Hour urine:** | Total protein, microalbumin, and creatinine |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PT/INR = prothrombin time/international normalized ratio.

#### 8.6.7.1. Liver Function Tests and Treatment

Liver function tests will be assessed as part of clinical chemistry. When a subject's ALT level is greater than the upper limit of normal (ULN) and is considered by the investigator to be related to treatment with DTX401, prednisone (or prednisolone) treatment, per protocol, for possible vector-induced hepatitis will be started. Individual patient profile of ALT and prednisone/prednisolone dose over time will be plotted.

### 8.6.8. Other Safety Parameters

Neutralizing antibodies to AAV8, cell-mediated immune response to AAV8 and G6Pase, AAV8 binding antibody IgG assay, anti-G6Pase antibody assay, vector shedding, and vector genome determination will be summarized by study visit. Listings for these safety parameters will be provided. Associations between these parameters and dose may be explored using these listings.

In addition, vector shedding and vector genome determination below limit of detection will be summarized by study visits. Summary table for individual subject will be provided depicting the peak value of GC, time for peak, and timepoint when GC reaches below level of detection which is the 3rd consecutive post-baseline timepoint with negative result. Individual patient profile of vector shedding over time will be plotted and median vector shedding over time will be plotted for each cohort.

For female subjects of childbearing potential, serum pregnancy test results at screening and urine pregnancy test results at scheduled visits will be listed.

## 8.7. Impact of COVID-19 on Study Participation

The study has been ongoing during the COVID-19 pandemic. To capture the impact of COVID-19 on subjects' study participation, the study eCRFs and eCRF completion guidelines were modified during the study as per the regulatory guidance to capture COVID-19 related AEs and reasons for study discontinuation, missed/delayed visits, and missed assessments due to COVID-19 as "COVID-19 related reason". Study data listings will include this information e.g., listing of AEs will include any AEs related to COVID-19 and listing of protocol deviations will include deviations related to missed visits and missed assessments due to COVID-19. These listings will be used to assess any potential impact of COVID-19 on subjects' study participation.

# 9. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None

# 10. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

List of planned tables, figures, and listings will be included in the shell document which will be maintained separately.

# 11. REFERENCES

Broderick JE, DeWitt EM, Rothrock N, et al. (2013) Advances in Patient-Reported Outcomes: The NIH PROMIS Measures. *EGEMS (Wash DC)* 1: 1015.

Neuenschwander B, Branson M and Gsponer T. (2008) Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med* 27: 2420-2439.

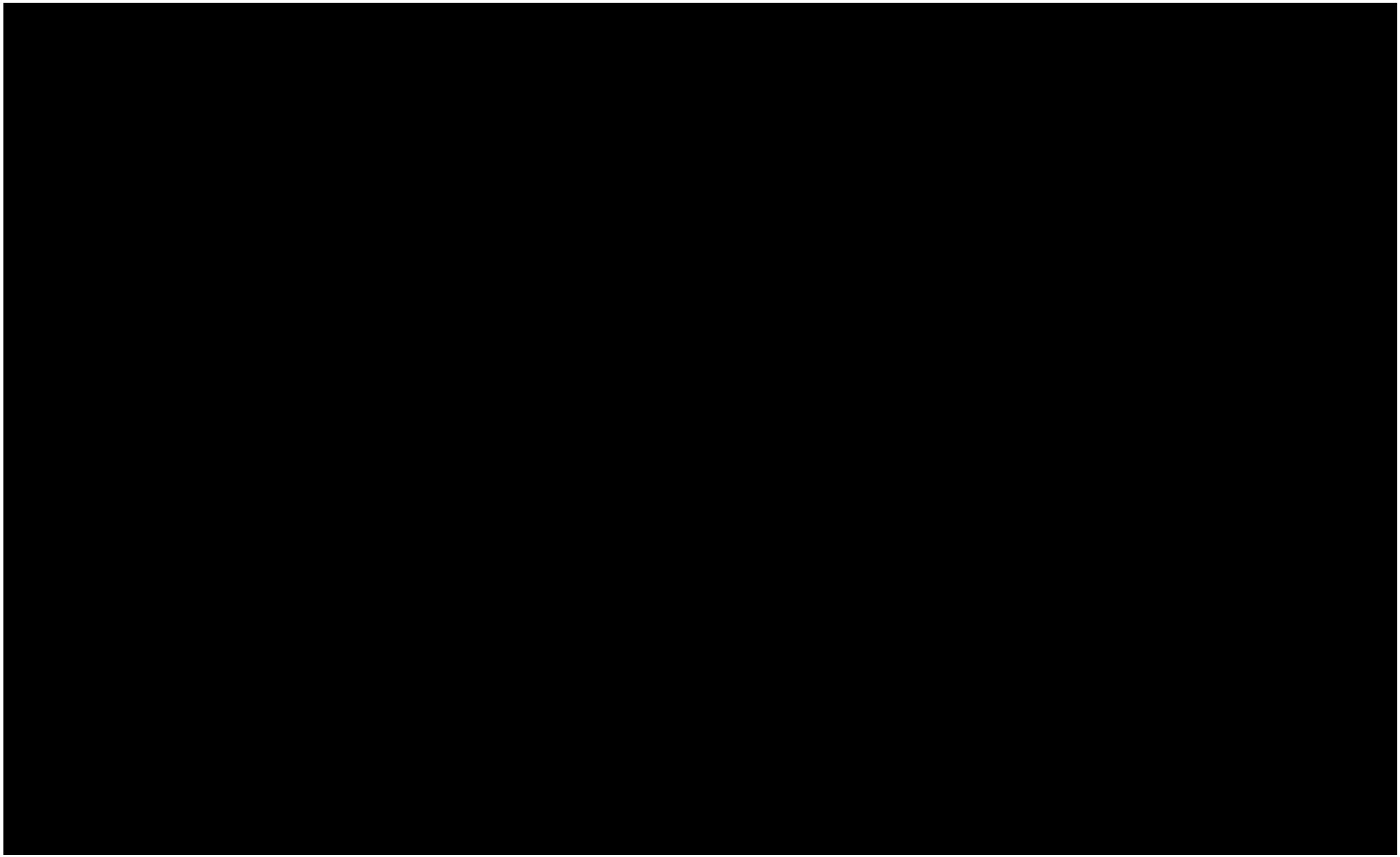
NIH. (2015) *PROMIS*. Available at: http://www.nihpromis.org/default.aspx#6.

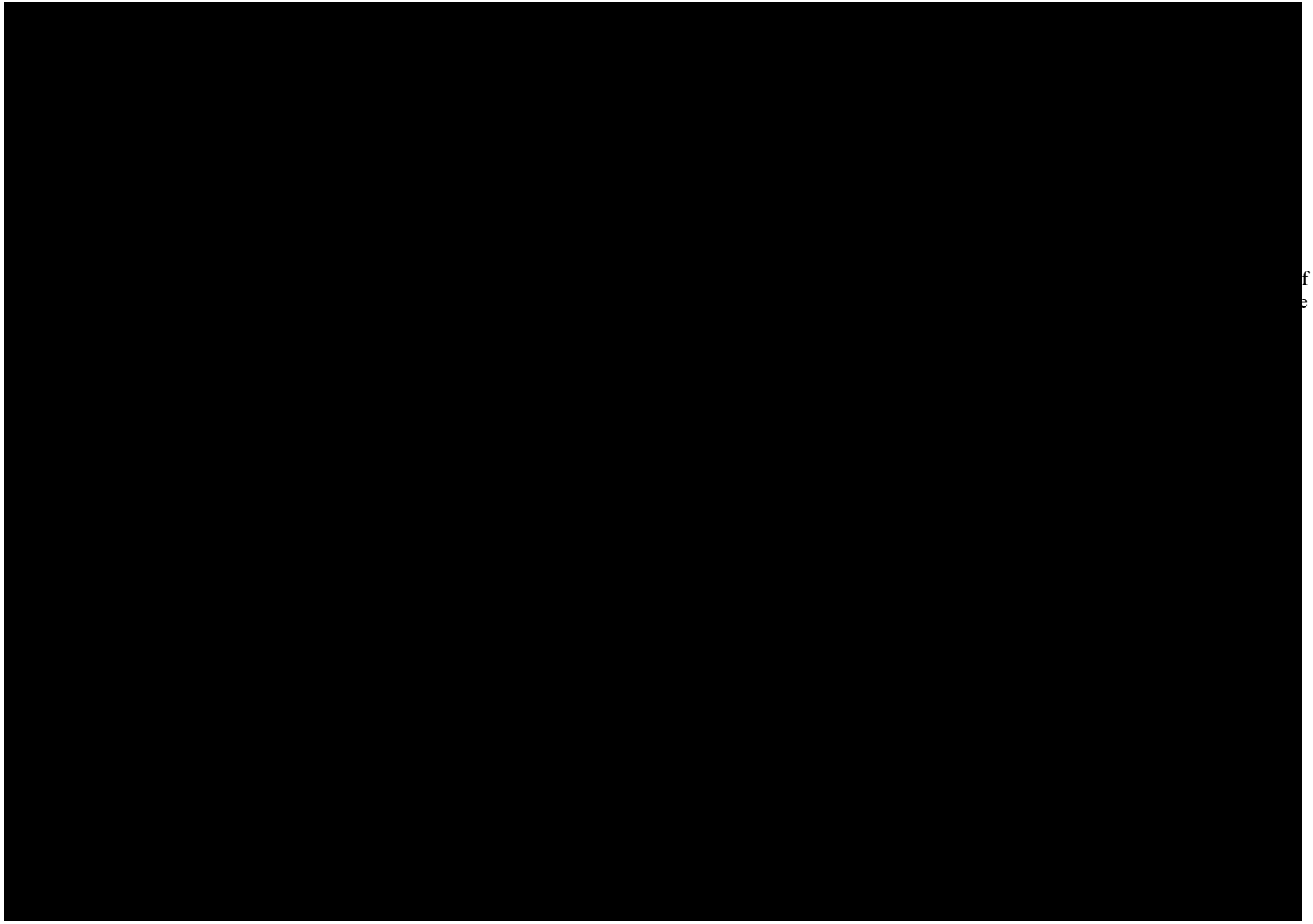
# 12. APPENDICES

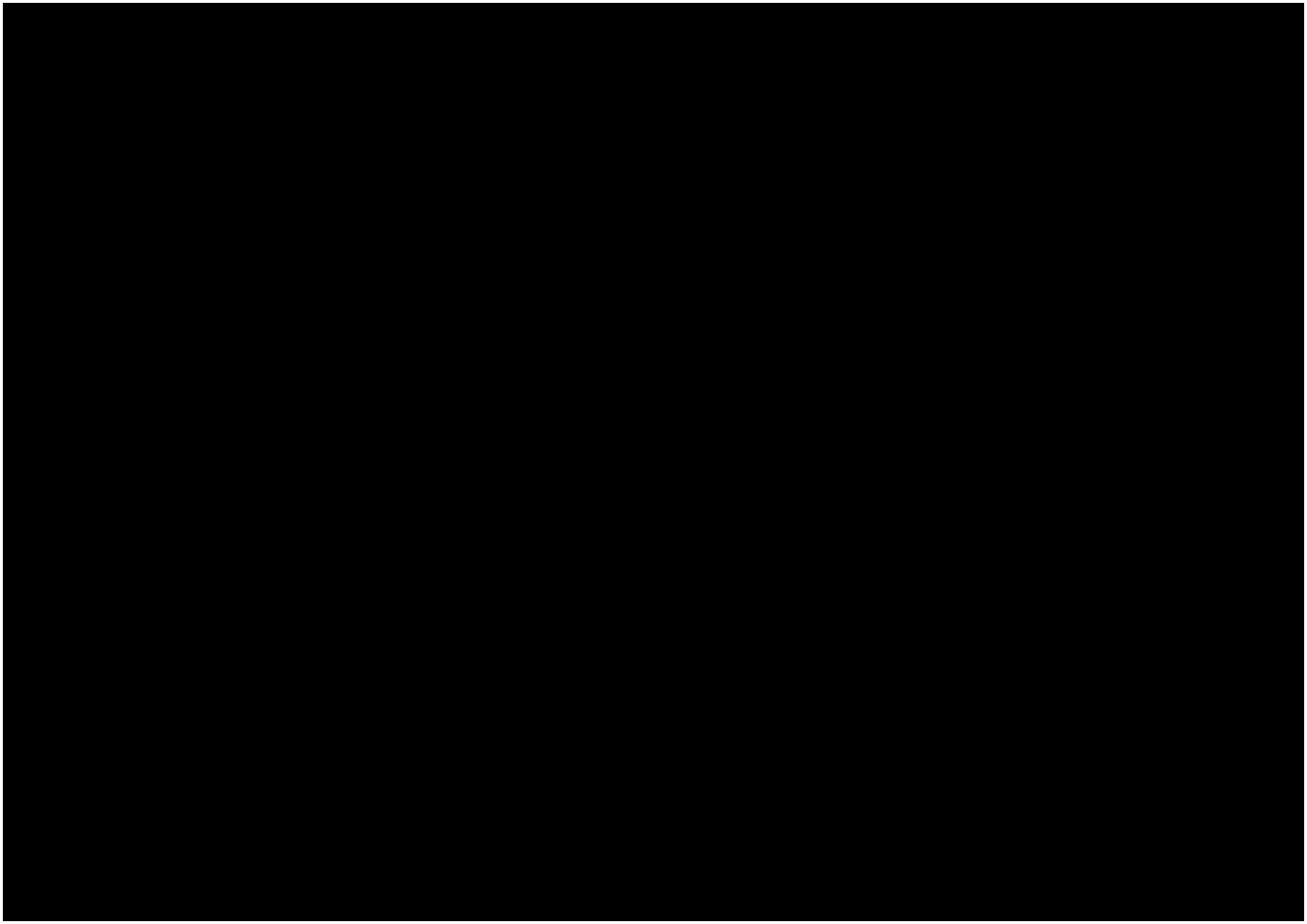
## APPENDIX 1. SCHEDULE OF EVENTS

[redacted]

[redacted]







# APPENDIX 2. CONTINUAL REASSESSMENT METHOD DETAILS

The nominal doses used in the continual reassessment method, the x-hats, will be derived as:

$$\hat{x}_i = \log\left(\frac{d_i}{d_{ref}}\right)$$

Where $d_1 = 2$, $d_2 = 6$, $d_3 = 10$ and $d_{ref} = 6$. The $d_i$ correspond to the amount of DTX401 administered at each dose level, in units of $10^{12}$ genome copies/kg.

A logistic model will be used to model the dose-toxicity curve. Let

$$Y_i = \begin{cases} 0 \; if \; the \; ith \; subject \; does \; not \; experience \; a \; DLT \\ 1 \; otherwise \end{cases}$$

Then

$$p(Y = 1|\hat{x}_i, \alpha, \beta) = \frac{e^{\alpha+\beta\hat{x}_i}}{1 + e^{\alpha+\beta\hat{x}_i}}$$

The joint distribution of α and β is given by

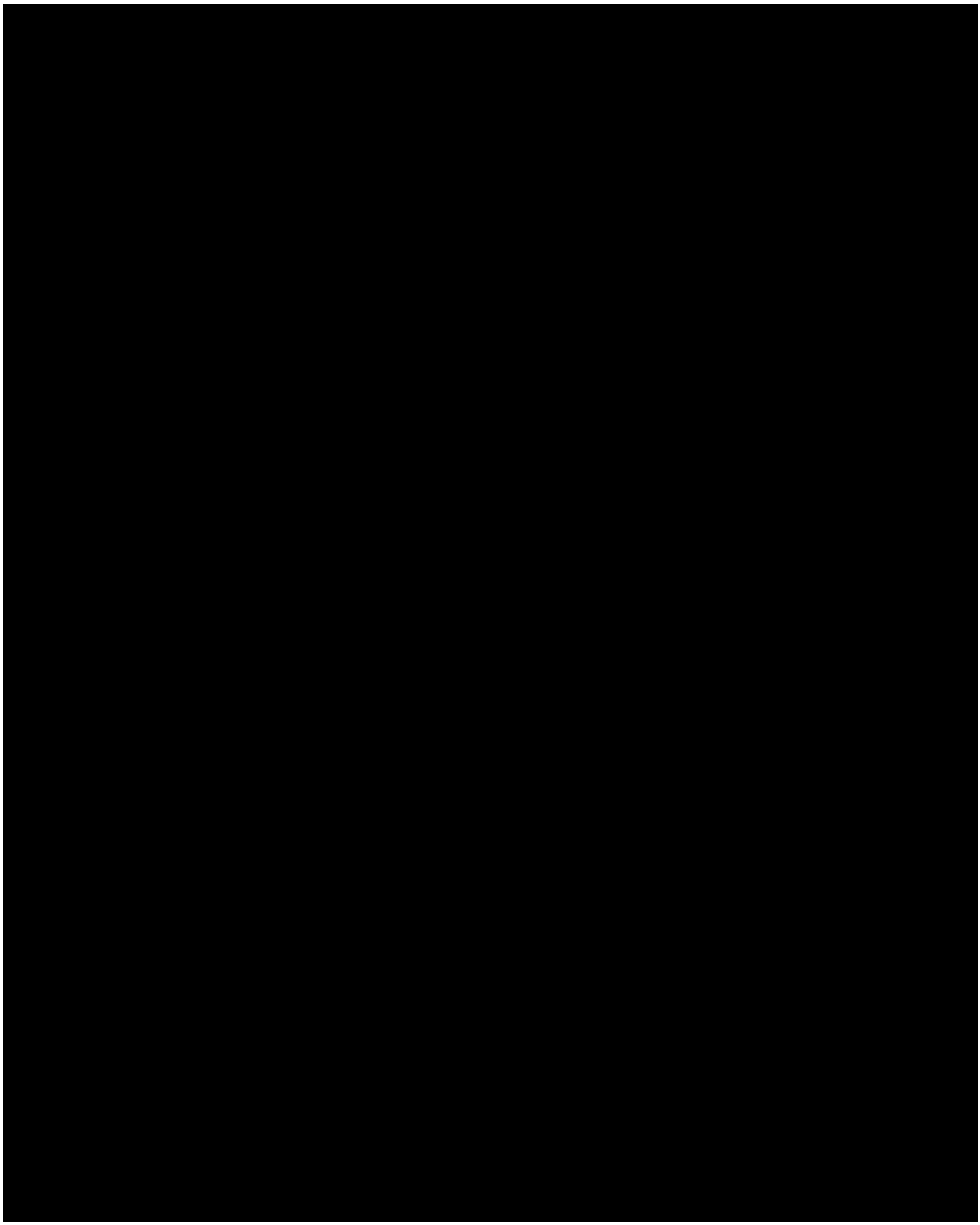
$$\begin{pmatrix} \alpha \\ \log\beta \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_\alpha \\ \mu_\beta \end{pmatrix}, \begin{pmatrix} \sigma_\alpha \times \sigma_\alpha & \sigma_\alpha \times \sigma_\beta \times \rho \\ \sigma_\alpha \times \sigma_\beta \times \rho & \sigma_\beta \times \sigma_\beta \end{pmatrix}\right)$$

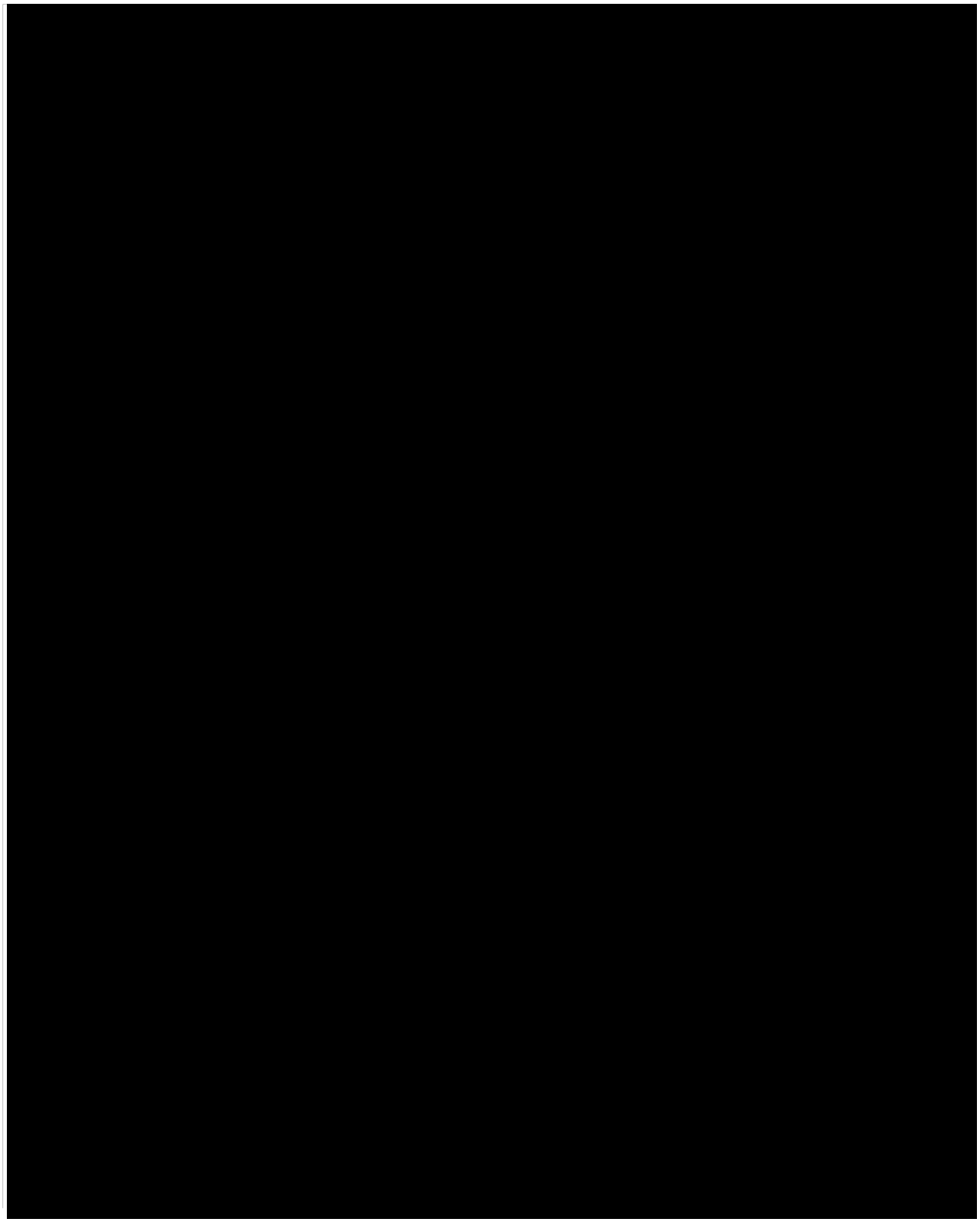
Initial (prior) values $\mu_\alpha$= -2.3097, $\log\mu_\beta$ = -0.4323, $\sigma_\alpha$ = 1.6604, $\log\sigma_\beta$ = 0.0044 and $\rho$ = -0.2405 are used based on simulations.

The estimate of the maximum tolerated dose will be the highest dose for which the full Bayes posterior estimate of $p(DLT|d_i)$ is strictly less than or equal to the target toxicity rate.

A dose is cleared if it is either $2 \times 10^{12}$ genome copies/kg or if it is no more than 1 dose level higher than the highest dose at which at least 3 subjects have been treated.

[redacted]





# APPENDIX 4. [redacted]

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# APPENDIX 5. [redacted]

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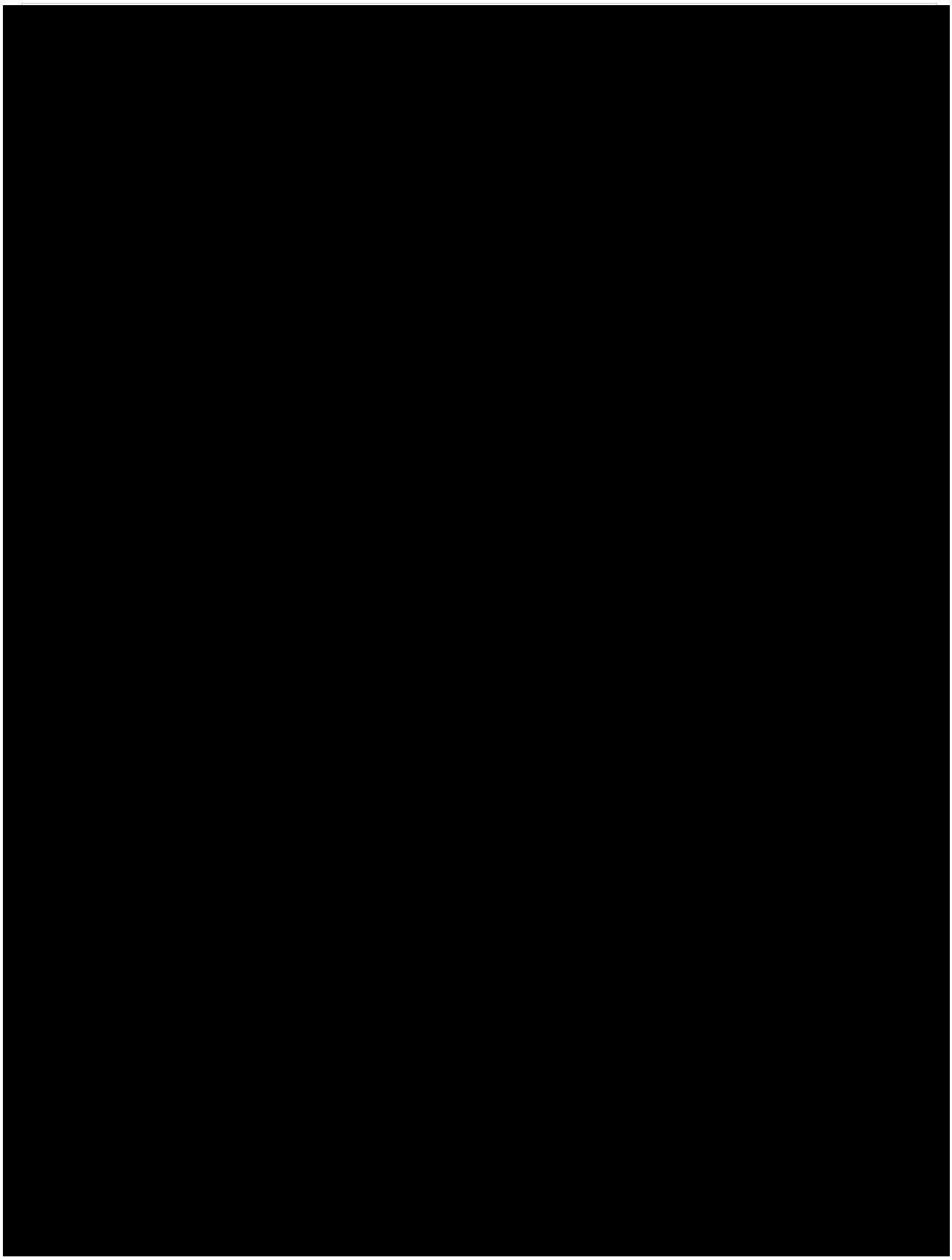
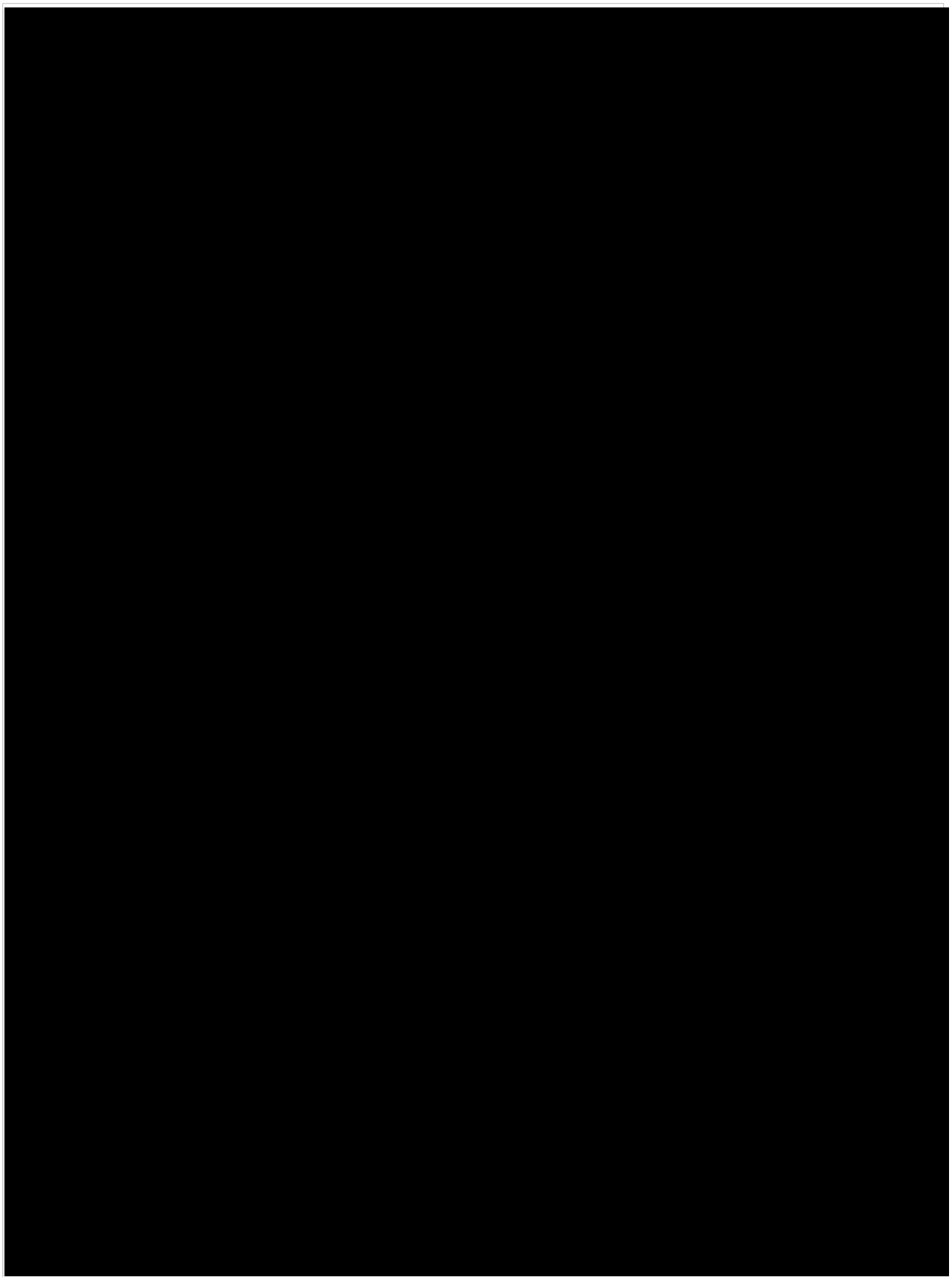
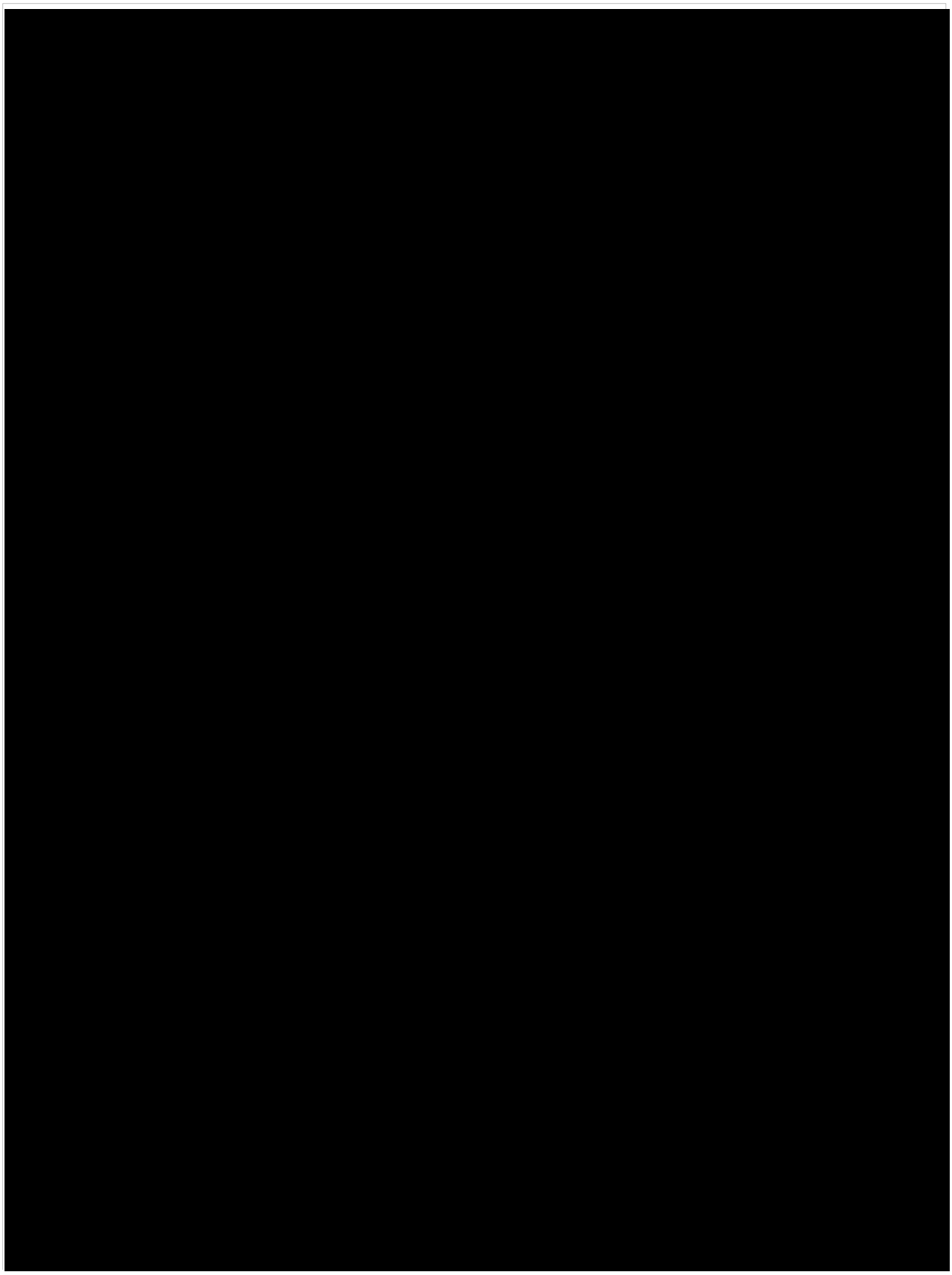
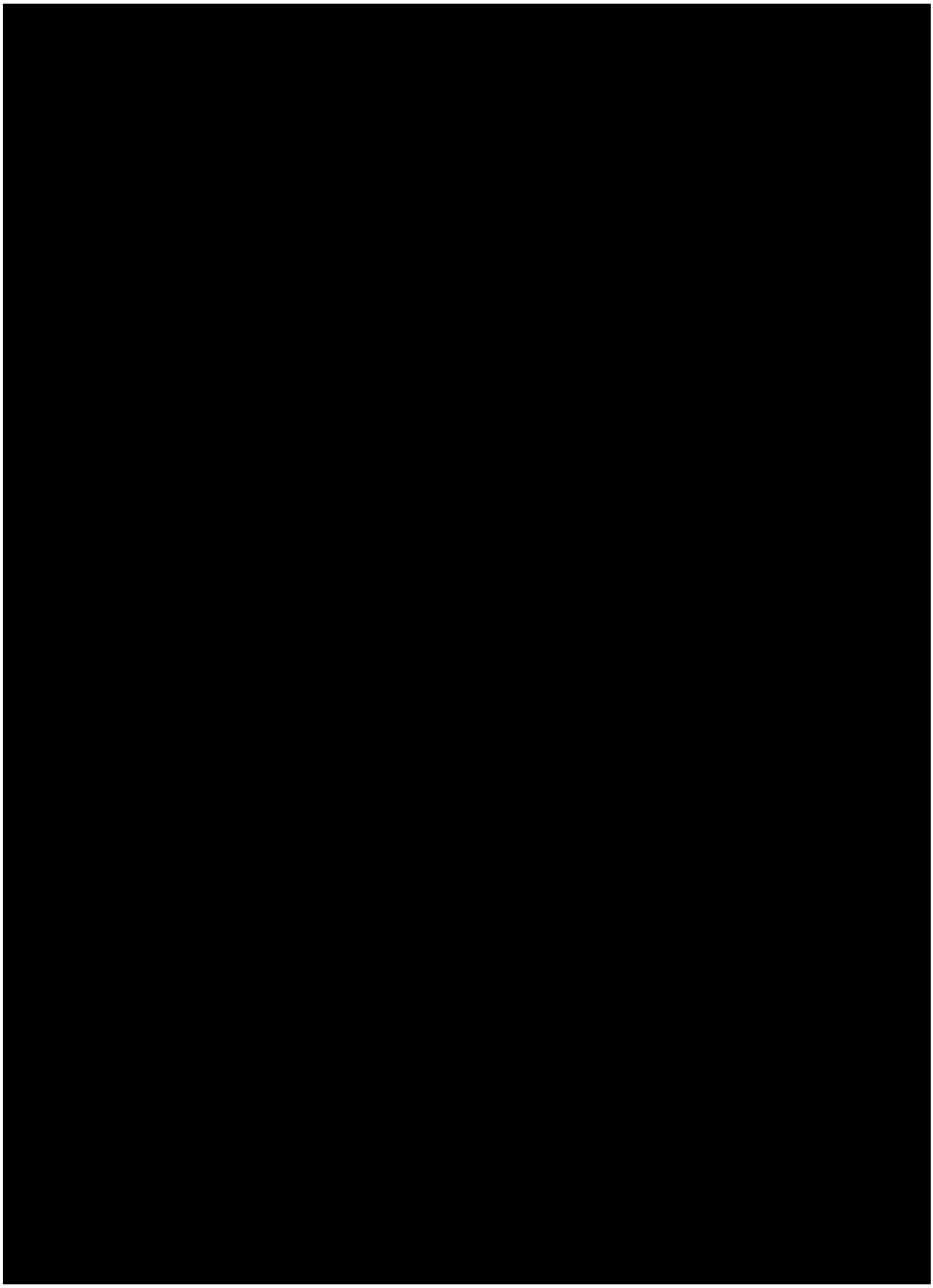
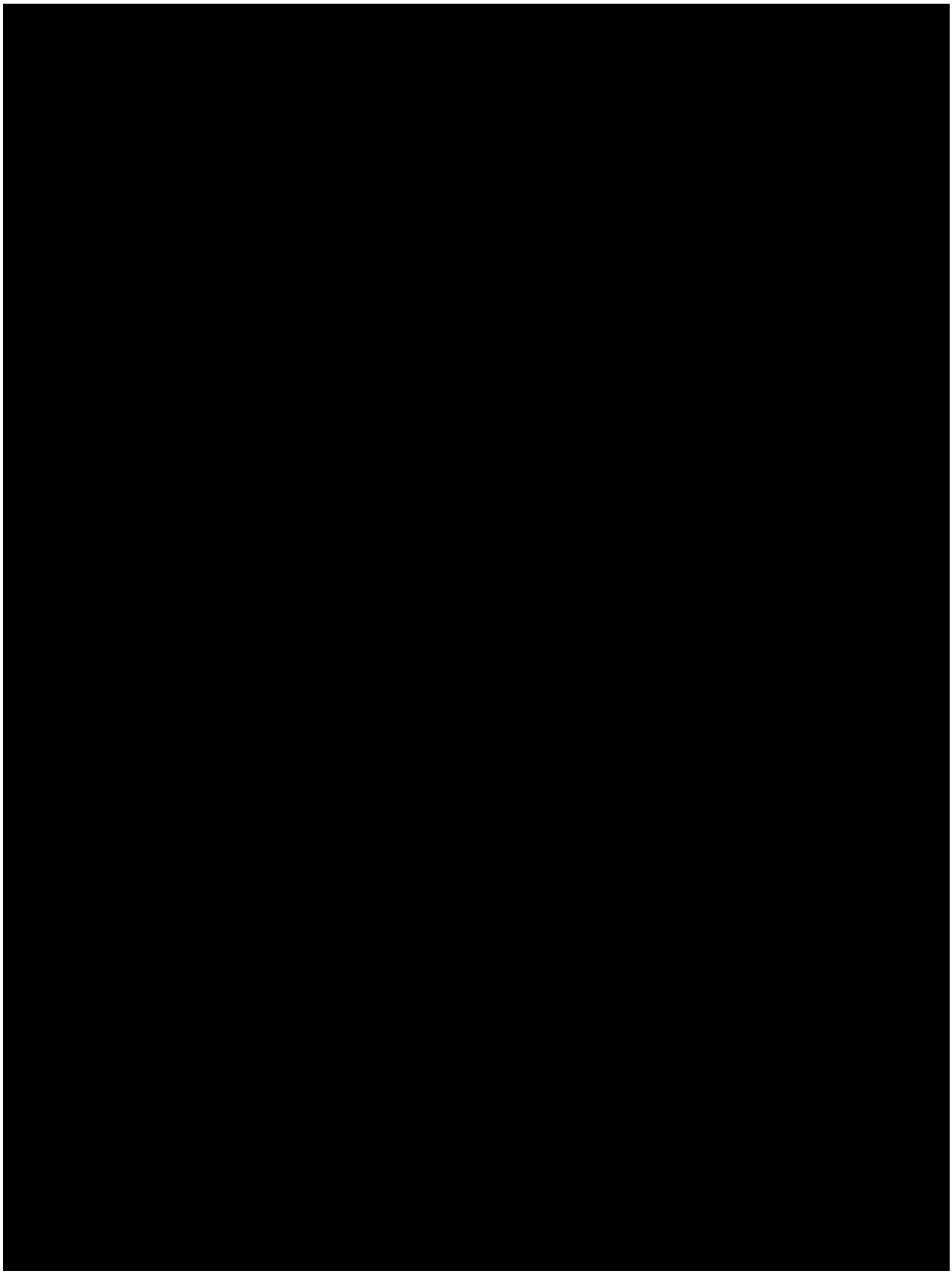




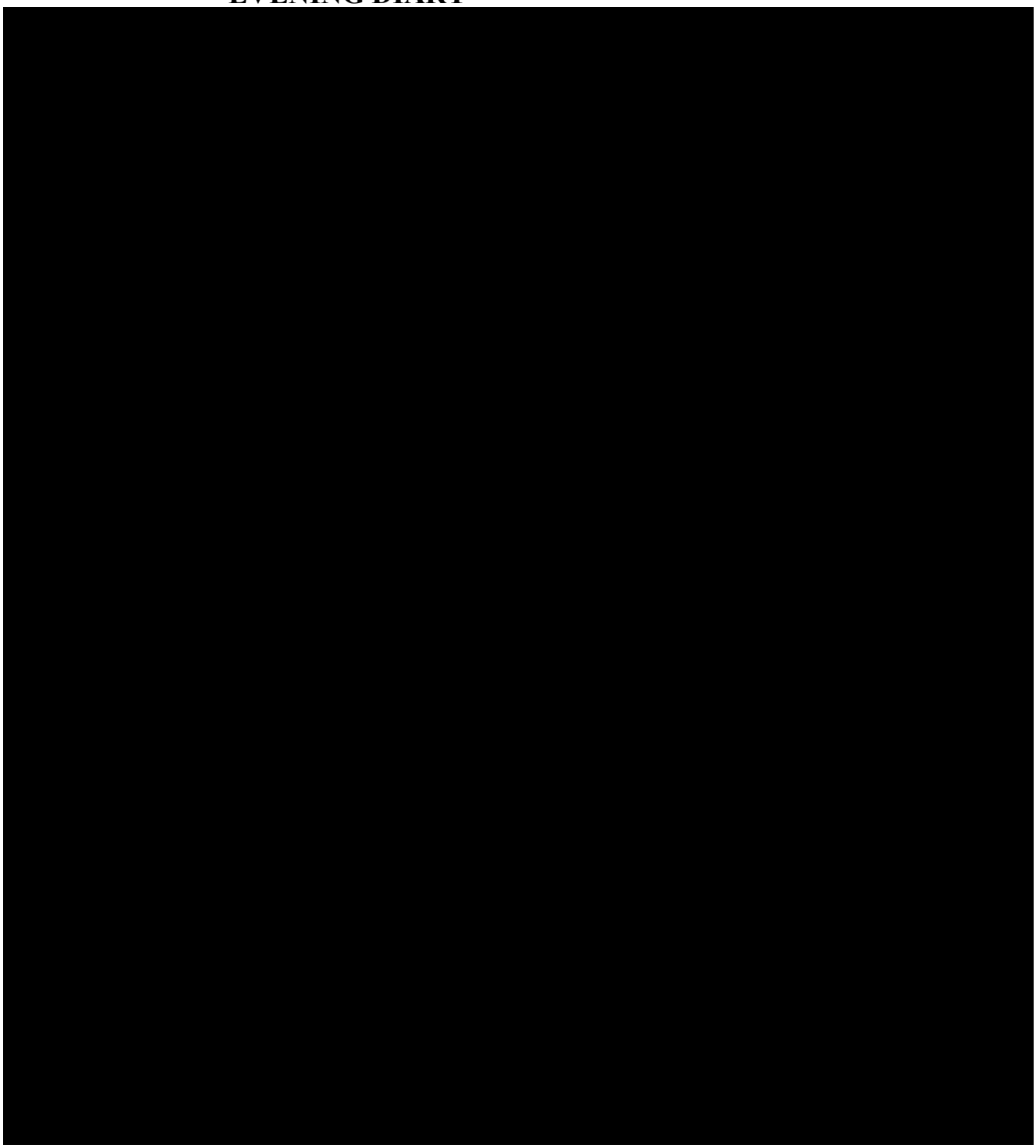


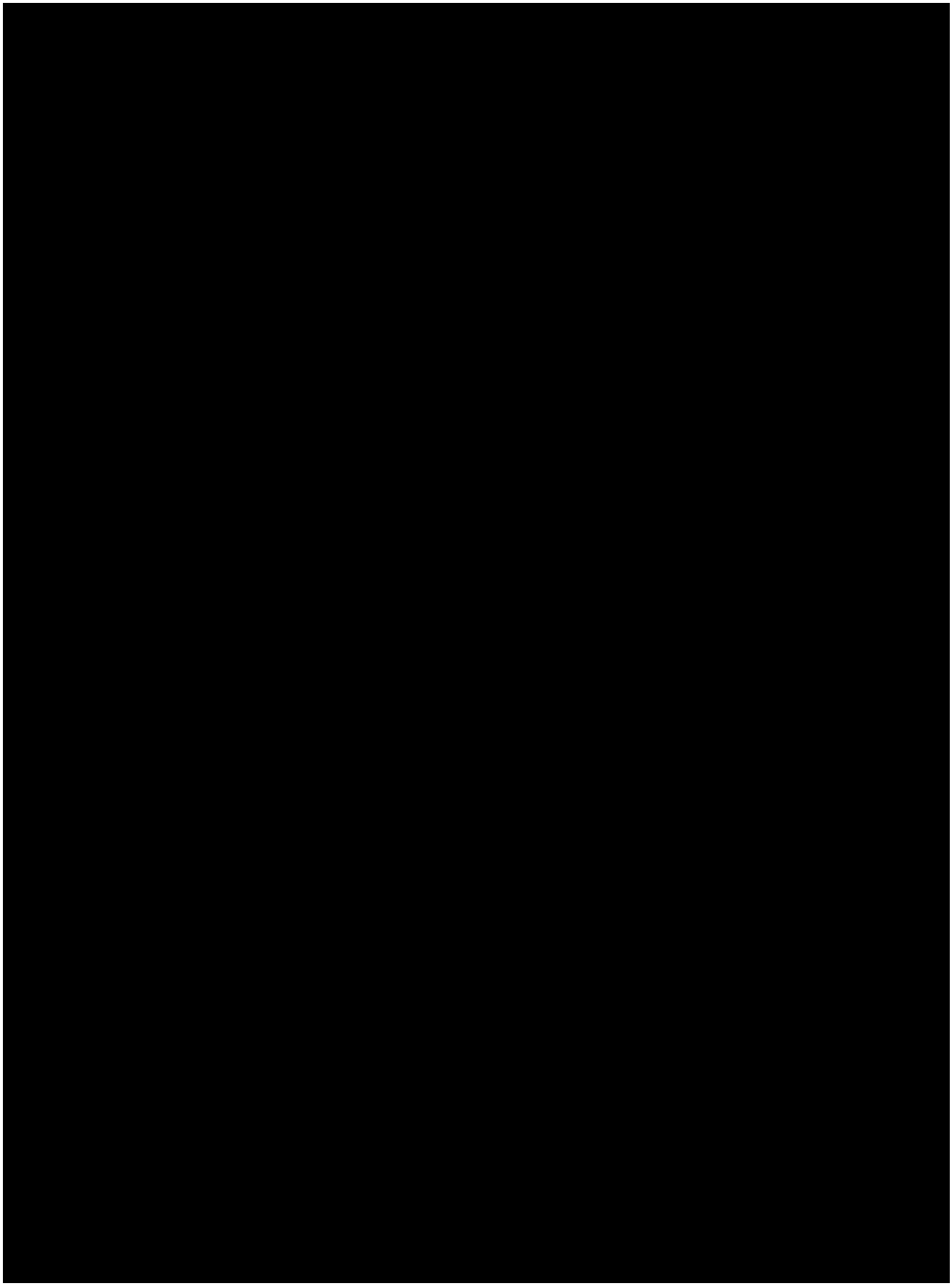


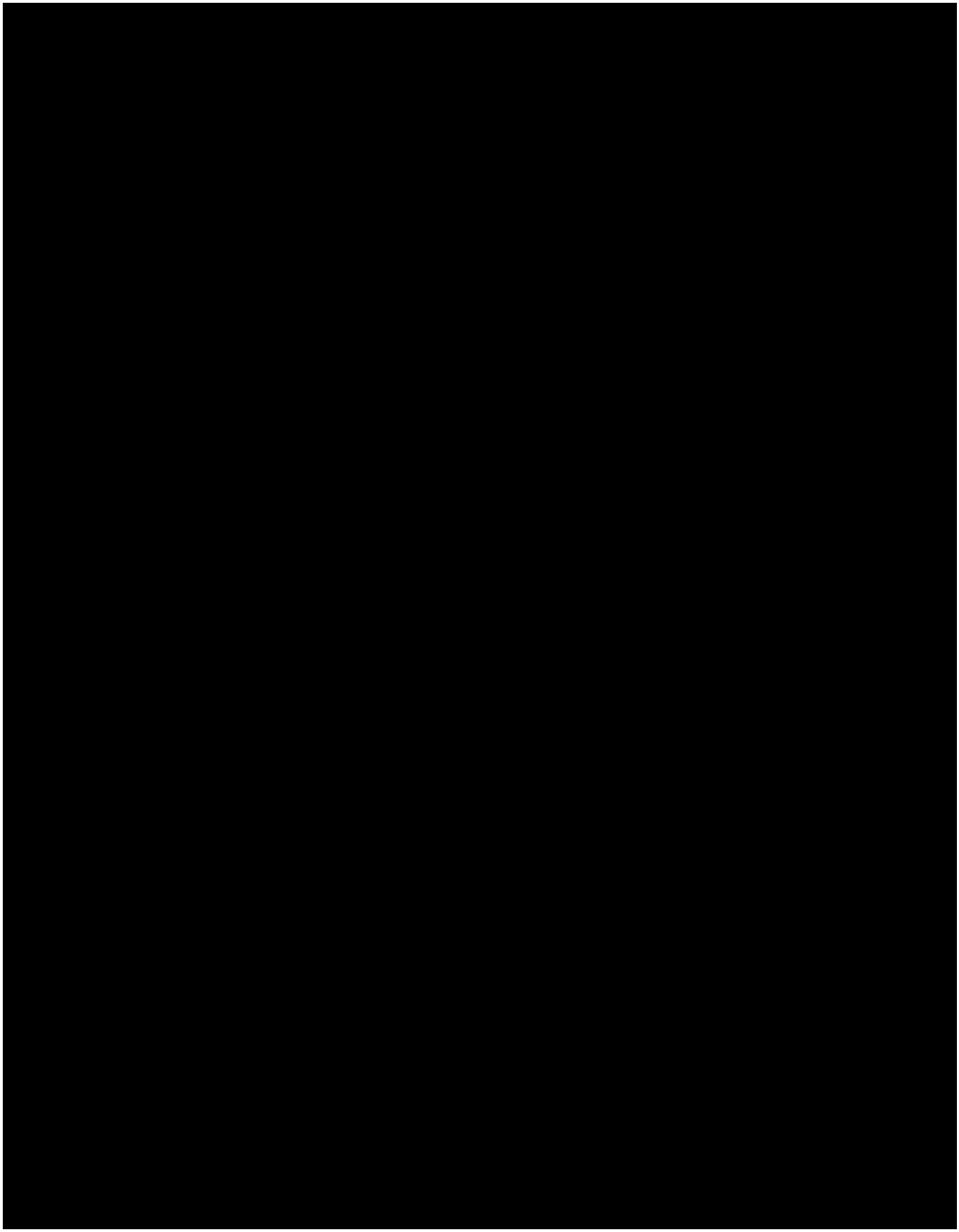


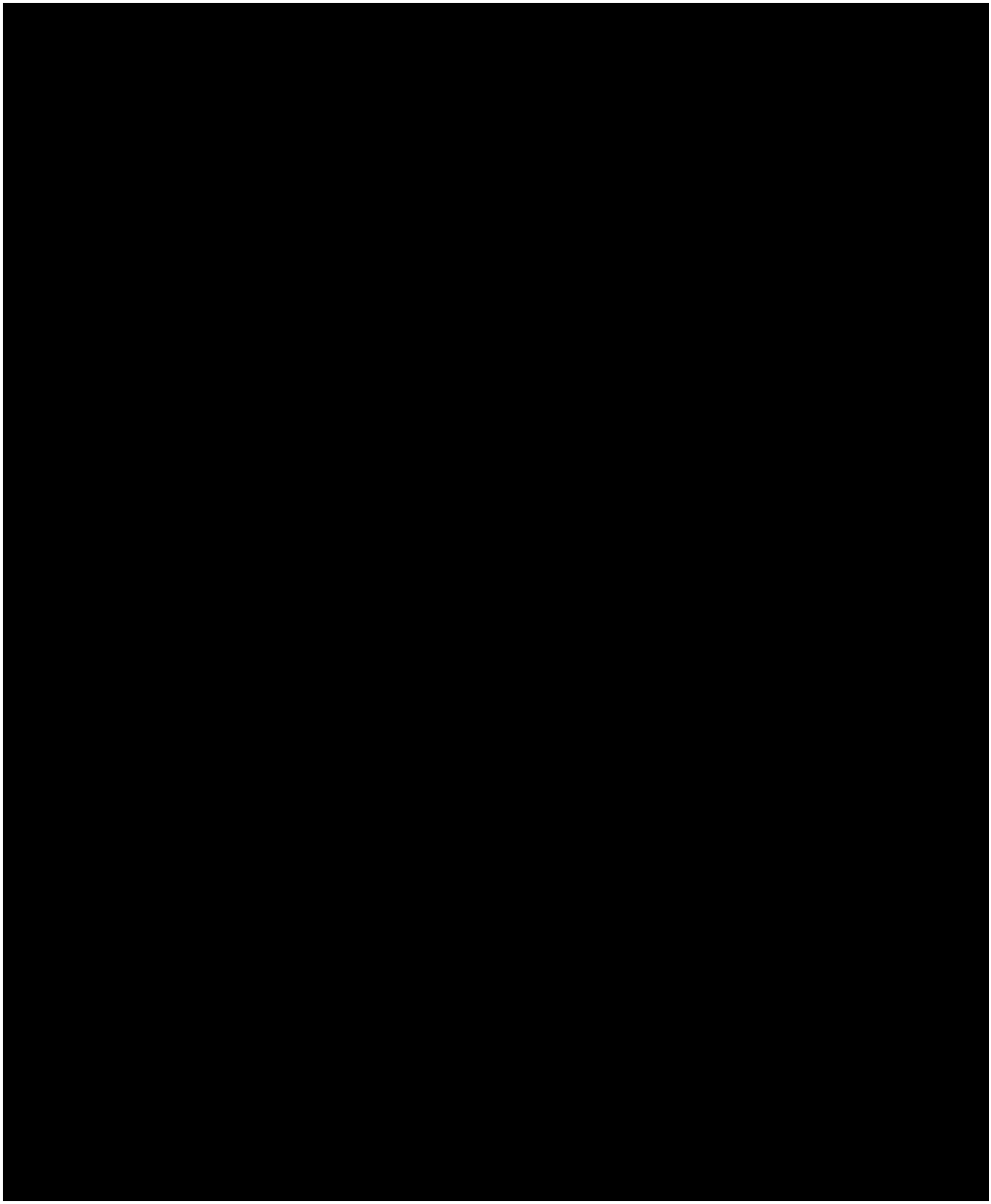
# APPENDIX 6. GLYCOGEN STORAGE DISEASE TYPE IA (GSDIA) MORNING DIARY

# APPENDIX 7. GLYCOGEN STORAGE DISEASE TYPE IA (GSDIA) EVENING DIARY









# APPENDIX 8. [redacted]

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# APPENDIX 9. [redacted]

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