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Statistical Analysis Plan: DIAZ.001.08

Document Title: DIAZ.001.08 Statistical Analysis Plan

Study Title: An Open-Label, Single-Dose, Pharmacokinetics Study of VALTOCO® with Open-Label Safety Period in Pediatric Subjects with Epilepsy

Study Number: DIAZ.001.08

Study Phase Phase 1/2a (Pharmacokinetics in Pediatric Subjects with Epilepsy)

Product Name: VALTOCO®

Sponsor: [REDACTED]
[REDACTED]
[REDACTED]

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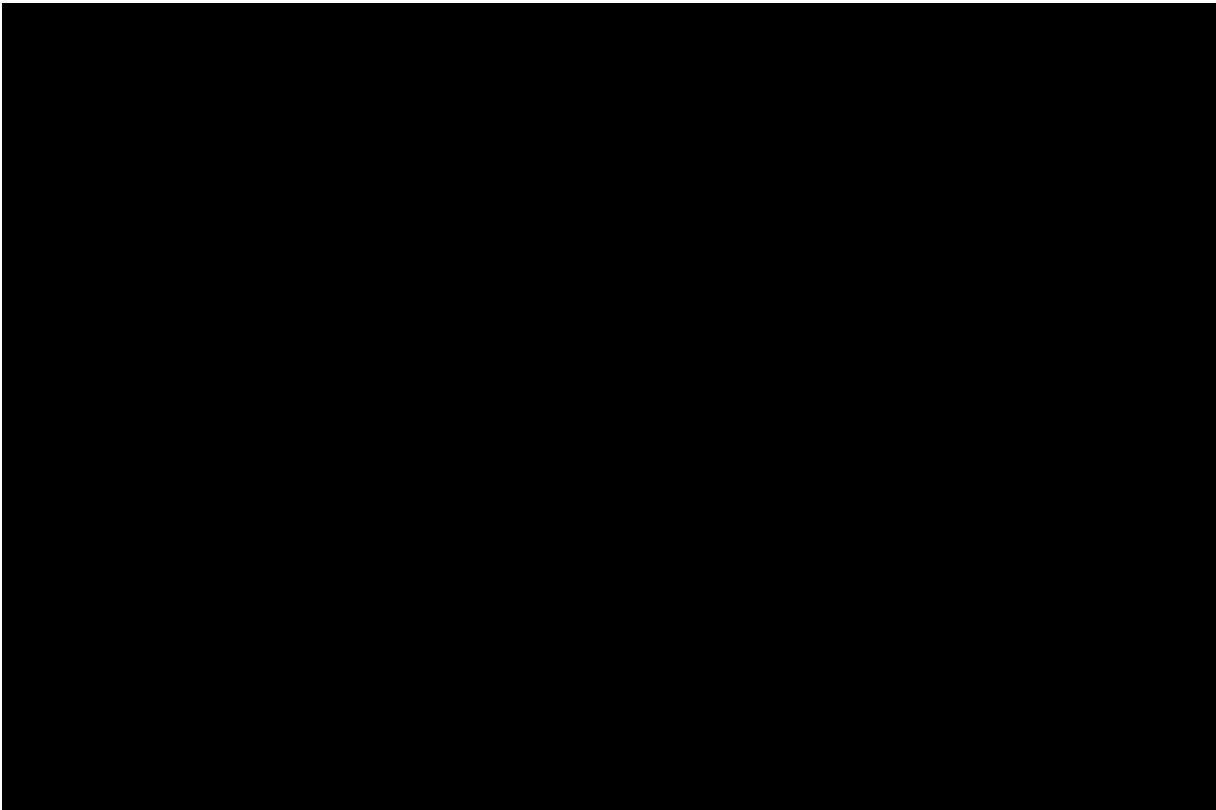
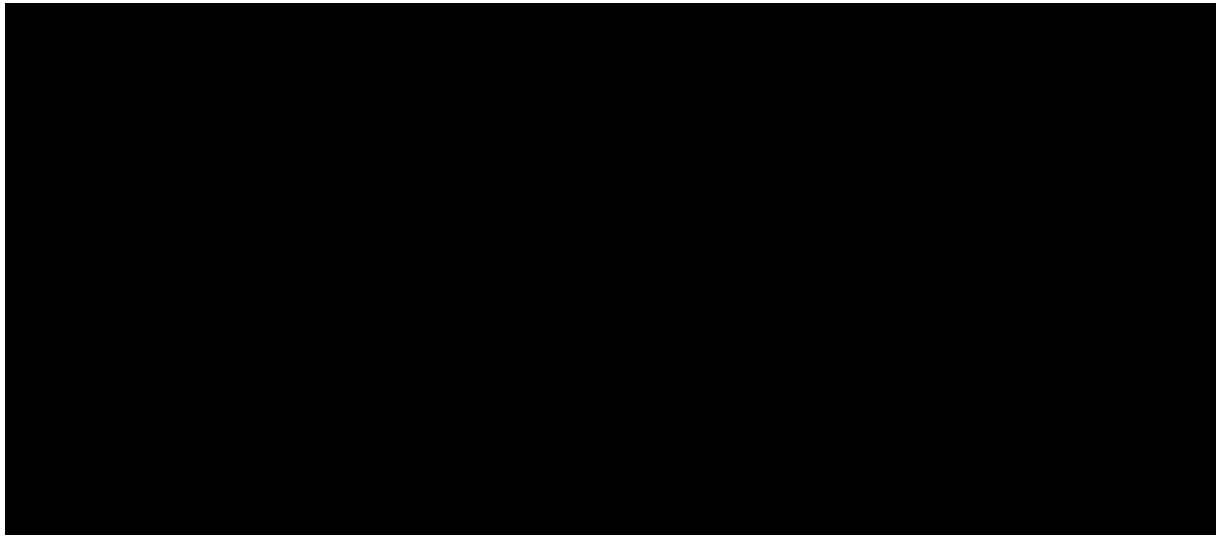


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LIST OF ABBREVIATIONS

AE	Adverse Event
ARS	Acute repetitive seizures
ATC	Anatomical Therapeutic-Chemical classifications
AUC	Area under curve
AUC ₍₀₋₆₎	Area under the plasma concentration time-curve to 6 hours post dose
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAEs	Treatment-Emergent Adverse Events
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) for study DIAZ.001.08 describes the detailed procedures for executing the planned statistical analyses for this study.

This version of SAP has been written to be in accordance with Protocol version 5 dated May 31, 2023 and the Case Report Form (CRF) dated March 2024. Any further changes to the protocol or CRF may necessitate updates to the SAP. This SAP was written as a separate document, completed after finalizing the protocol, and prior to locking the clinical datasets. This SAP includes a more technical and detailed elaboration of the statistical analyses stated in the protocol.

The statistical analyses will be conducted by Neurelis Inc. or a designated contract research organization (CRO) using the SAS® software version 9.4 or later.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the PK of diazepam after a single intranasal dose of VALTOCO administered to subjects with epilepsy 2 to 5 years of age. The primary PK variables to determine bioavailability will be $C_{\max}$ and the area under the curve through 6 hours ($AUC_{(0-6)}$).

2.2 Secondary Objectives

The secondary objectives of this study include:

- To assess the safety and tolerability of diazepam after intranasal administration of VALTOCO in the subject population.
- To assess the long-term safety and tolerability of diazepam after repeated exposure to intranasal administration of VALTOCO in the subject population.

3 STUDY DESIGN

This is a Phase 1/2a, open-label, single-dose, PK study of VALTOCO with open-label safety period in pediatric subjects with epilepsy age 2 to 5 years. A single 5 mg, 10 mg or 15 mg

dose of intranasal VALTOCO will be administered based on the subject's body weight in a clinical setting followed by PK sampling. All doses for the single-dose PK visit will be administered by a trained medical professional as per the Instructions for Use for VALTOCO. Appropriate entertainment is allowed to help the subject remain relaxed and distracted during study procedures. The study consists of a screening period, a baseline period, a single-dose period, an open-label safety period, and a follow-up phone call and an optional extension period.

In the single-dose period, VALTOCO will be administered during an interictal period to pediatric subjects with epilepsy 2 to 5 years of age. The pre-dose PK blood samples will be collected at baseline after all pre-dose safety assessments are completed. Once the pre-dose PK sample has been collected, a single dose of VALTOCO will be administered and the PK collection will continue for up to 6 hours after dosing to determine the diazepam plasma concentration versus time profile.

At the screening and after signing informed consent, each subject will be assigned a screening number at the time of enrollment in the format xx-yyy, where xx represents the site number (e.g., 01 for site #1), and yyy represents the subject screening number, which will increase sequentially at each site (e.g., 001, 002). At the baseline visit and after all pre-dose assessments are completed, the system will automatically assign to each qualified subject a 'subject ID' in the format xx-yyy-z, where xx is the site number, yyy (e.g., 001, 002) represents the subject number and z=1, 2 or 3 represents the blood sampling sequence as listed below. The system will automatically rotate the sequence numbers as subjects are sequentially enrolled across all sites. The process will continue until at least 30 PK subjects have completed the single-dose period with at least one post-dose PK sample collected. The sponsor has the option to enroll additional subjects if any do not complete the full 360 minutes of PK sampling.

A total of six (6) blood samples for PK evaluation will be collected from each subject at specific times depending on sequence:

- [REDACTED]
- [REDACTED]

- [REDACTED]

[REDACTED] 60 minutes and ± 10 minutes for time points from 75 to 360 minutes. For all blood samples the actual time of collection will be recorded and entered into the electronic case report form (e-CRF).

Subjects who discontinue for any reason prior to dosing and/or obtaining at least 120 minutes of blood samples for PK assessment may be replaced at the discretion of the Sponsor. If a subject discontinues after dosing but prior to completing the PK assessment, they may continue into the open-label safety portion of the study.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Subjects may be discharged after the 6-hour post-dose assessments are complete provided there are no clinically meaningful signs of sedation. For the open-label safety portion of this study, subjects will be supplied with VALTOCO to use as rescue medication as needed for frequent breakthrough seizures or ARS (as per the VALTOCO prescribing information). Subjects and caregivers will be provided an electronic diary on their own device to record any seizures and usage of VALTOCO for seizures including the type of seizure, date of use, time of seizure onset, time of dosing, and time of seizure resolution.

Subjects will return to the site on Day 30 (± 4 days) and Day 90 (± 4 days) for safety evaluations and to be provided with additional supply of study medication, and on Day 180 (± 4 days) for safety evaluations. A phone call will be conducted on Day 60, Day 120, and Day 150 (± 4 days) to determine if any AEs have occurred and to follow-up on any ongoing AEs. In addition, any concomitant medications taken during this time will be collected.

Seven days (± 4 days) after the last study visit, a follow-up phone call will be conducted to determine if any AEs have occurred and to follow-up on any AEs ongoing since last communication with the subject. In addition, any ongoing or new concomitant medications taken during this time will be collected.

Safety assessments include AEs, physical examination, vital signs, laboratory evaluations and nasal irritation assessments. Site personnel will be trained on the conduct of nasal irritation assessments based on a standardized scale. Additional assessments including the seizure severity questionnaire and caregiver assessment will also be conducted at clinic visits by trained study personnel. All study drugs received, dispensed, and returned must be accounted for in the study Drug Accountability Log.

4 STUDY POPULATIONS

4.1 Enrolled Population

The Enrolled Population will consist of all subjects who passed screening criteria and completed baseline visit assessments.

4.2 Safety Population

The Safety Population will include all subjects who receive at least one dose of study drug. Analysis of safety data will use the Safety Population.

4.3 Pharmacokinetic (PK) Population

Please see definition on PK population in a separate Pharmacokinetic Analysis Plan.

5 STUDY ENDPOINTS

5.1 Primary Endpoints

The primary endpoint of this study is to characterize the PK of diazepam after a single intranasal dose of VALTOCO administered to subjects with epilepsy 2 to 5 years of age.

5.2 Secondary Endpoints

The secondary endpoints in this study include:

- Assessment of the safety and tolerability of diazepam after a single intranasal administration of VALTOCO in the subject population.
- Assessment of the long-term safety and tolerability of diazepam after repeated exposure to intranasal administration of VALTOCO in the subject population.

6 STATISTICAL CONSIDERATIONS

6.1 Sample Size

Approximately 30 male or female subjects aged 2 to 5 years with a clinical diagnosis of epilepsy who, in the opinion of the Investigator, may need a benzodiazepine intervention for seizure control and have used or will use rescue medication at least once in the last three months will be enrolled.

6.2 General Considerations

Summary statistics for continuous variables will include mean, standard deviation, median and range (minimum and maximum). Categorical variables will be presented as frequency counts and percentages. Data listings will be created to support tables and present data.

All statistical analyses will be conducted using SAS® Version 9.4 or above (SAS Institute, Cary, NC). For presentation of untransformed data, the mean and median will be presented to one decimal place greater than the original data, standard deviation will be to two decimal

places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

Unless otherwise specified, data summarized in tables will be presented by subjects' dose strength (5 mg, 10 mg, 15 mg) in the single dose period. It is possible that a subject's dose strength would change per the subject's changing weight or for efficacy or safety reasons during the open-label safety period or/and the optional extension period. Subjects' weight and corresponding dose strength will be listed in a listing by visit and change of dose strength from the previous visit will be flagged.

6.3 Analysis Definitions

6.3.1 Naming Conventions for Study Day

For the purpose of statistical computation, the study day of all assessments that are performed on or after treatment start date (i.e., the single dose date in the single dose period) will be calculated as:

$$\text{Study Day} = \text{date of the assessment} - \text{treatment start date} + 1.$$

For assessment performed before the treatment start date, the study day calculation is similar except without adding 1:

$$\text{Study Day} = \text{date of assessment} - \text{treatment start date}.$$

6.3.2 Baseline Values and Change from Baseline

The baseline values are defined as the last non-missing data prior to the treatment start date and time.

Change from baseline is defined as post-baseline value – baseline value.

7 DATA ANALYSIS

7.1 Subject Disposition

Subject disposition data will be summarized for all screened subjects. The number of subjects who were screened will be presented; number of subjects who failed the first time screening,

number of subjects who were rescreened and subsequently enrolled, and number of subjects who failed the second time screening will also be presented, along with the percentages based on number of screened subjects.

The following subject disposition data will be summarized with percentages based on the number of subjects treated, by dose strength (5mg, 10mg and 15mg) in the single dose period:

- The number and percentage of subjects who completed the study.
- The number and percentage of subjects who prematurely discontinued from the study, along with the reason for premature discontinuation.

Subjects' informed consent date, single dose date, completion date or premature disposition date, premature disposition day relative to the single dose date and premature disposition reason if applicable, will be listed in a listing.

7.2 Demographic and Baseline Characteristics

Statistical summaries and analysis of the demographic and baseline data will be based on the Safety and PK Populations. Tables will be presented by dose strength in the single dose period. These variables may include the following:

- Gender
- Race
- Ethnicity
- Age (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m²)

For continuous variables (e.g., age, weight, etc.), descriptive summary statistics will include the number, mean, standard deviation, median, minimum and maximum values. For categorical variables (e.g., sex, race, etc.), descriptive summary statistics will include the frequency distribution (i.e., number and percentage) among the categories.

Medical history data will be summarized by dose strength in the single dose period. Medical History verbatim terms will be coded by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

Seizure history data including age the child's seizures started, monthly average number of seizures and seizure clusters experienced, medications ever used to treat the seizures etc. will also be summarized by dose strength in the single dose period and listed in a listing.

Prior and concomitant Medications verbatim terms will be encoded using WHO Drug Dictionary (WHODD) codes and presented by preferred term by dose strength in the single dose period. Prior medications are defined as medications that were taken within 30 days prior to initial dosing with study drug. Concomitant medications are defined as medications taken any time after the start of dosing. For partial medication start dates, if the day portion (and only the day portion) is missing, the medication start date will be assumed to be the first day of the month. If both day and month portion are missing, impute it to the first day of January.

7.3 Treatment Exposure

Treatment exposure data including total number of doses, number of doses per month in subject level and population level, doses per month in subject level and population level, and number of second doses within 24 hours will be summarized by dose strength in the single dose period. Number of subjects with single dose, and number of subjects with multiples doses, along with their percentages will be presented. The detailed dosing date, dose amount, number of devices used (if 15mg was administered) will be listed in a listing.

[REDACTED]

Regarding the calculation of median of number of doses per month, the algorithm is shown below:

(1). In the subject level

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(2). [REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

1. 2022-01-03T03:50

2. 2022-01-04T02:08

3. 2022-01-04T03:40

4. 2022-01-04T05:18

This subject has one second dose (record 2), because record 2 occurs within 24 hours of record 1; record 3 is the third dose within 24 hours of record 1; record 4 is an initial dose of a new 24-hour period.

7.4 Safety Evaluation

Safety evaluations will be conducted on Safety Population.

7.4.1 Adverse Events

Adverse events (AEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Severity of the adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Causality (relationship to study drug, i.e., unlikely, possible, or probable) will be classified. If more than one adverse event is recorded for a subject within any SOC or PT term, the subject will only be counted once on the most severe grade and the closest relationship to treatment in summary tables.

Treatment-emergent adverse events (TEAEs) will be defined as the adverse events that started on or after the initial dosing date.

Immediate AEs are defined as adverse events with dose administered on the same day; delayed AEs are those adverse events without dose administration on the same day. The day relative to the prior adjacent dosing date will be listed in listing, calculated as:

Day relative to the prior adjacent dosing date = date of AE – prior adjacent dosing date + 1.

Therefore for immediate AEs, the day relative to the prior adjacent dosing date will be 1.

The following AE summaries will be presented in tables:

- An overall summary of the AEs, including the number of AEs reported, number and percentage of subjects reporting AEs, the number and percentage of subjects with AEs possibly related or probably related to study treatment, number and percentage of subjects with TEAEs, the number and percentage of subjects with TEAEs possibly related or probably related to study treatment, number and percentage of subjects reporting serious AEs, the number and percentage of subjects with serious AEs possibly related or probably related to study treatment, the number and percentage of subjects with AEs leading to treatment discontinuation, the number and percentage of subjects' death due to AE, presented by dose strength in the single dose period.
- A breakdown of the number and percentage of subjects reporting TEAEs, categorized by SOC and PT, presented by dose strength in the single dose period.

- A breakdown of the number and percentage of subjects reporting TEAEs, categorized by SOC and PT, presented by dose strength in the single dose period and severity.
- Subjects with TEAEs probably related or possibly related to study treatment, categorized by SOC and PT, presented by dose strength in the single dose period.
- Number and percentage of subjects reporting Serious AEs (SAEs), categorized by SOC and PT, presented by dose strength in the single dose period.

Following category AEs will be listed in separate listings: all AEs, serious AEs (SAE), AEs leading to treatment discontinuation.

Immediate TEAEs will be summarized in table reported by PT; delayed TEAEs will be summarized in a separate table reported by PT. The immediate TEAEs that occur on the single dose date in the single dose period will be listed in a listing.

7.4.2 Laboratory Data

Laboratory data will be presented in following ways:

- Descriptive statistics will be tabulated for serum chemistry, hematology and continuous urinalysis parameters by dose strength in the single dose period and visit. Descriptive statistics of change from baseline will also be summarized in the table. Number and percentages will be tabulated for qualitative urinalysis parameters. Laboratory parameters will be grouped by panel (serum chemistry, hematology and urinalysis) and sorted alphabetically.
- All laboratory test results will be listed for each subject.
- Abnormal clinically significant lab values will be listed separately for each subject.
- HIV antibody and hepatitis screening results will be listed.

7.4.3 Physical Examination

The results of the physical examinations included at each visit are recorded as “Normal”, “Abnormal, not clinically significant” or “Abnormal, clinically significant”. Number and percentage of subjects in each category will be summarized. A shift table will be presented

to show baseline and post-baseline physical examination results. Abnormal results will be listed in a listing.

7.4.4 ECG

Subjects with abnormal ECG results will be included in a listing.

7.4.5 Vital Signs

Descriptive statistics of subjects' vital signs by dose strength in the single dose period and scheduled study visit will be summarized including number of subjects, mean, standard deviation, median and range. Descriptive statistics on change from baseline will also be summarized.

7.4.6 Nasal Irritation Assessments

For each nasal irritation evaluation parameter, number and percentage of subjects with each score will be summarized in table by dose strength in the single dose period and scheduled study visit. A shift table will be presented to show baseline and post-baseline nasal irritation grades.

7.5 [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Record Date/time of seizure record

1. 2019-07-08T13:00

2. 2019-07-09T14:00

3. 2019-07-10T01:00

4. 2019-07-10T02:00

5. 2019-07-19T05:00

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.6 Efficacy Evaluation

No efficacy evaluation is planned during this study.

For Seizure Severity Questionnaire, for each question, number and percentage of subjects with each score/answer will be summarized in table by dose strength in the single dose period and scheduled study visit.

For Caregiver Assessment, for each question, number and percentage of subjects with each answer will be summarized in table by dose strength in the single dose period and scheduled study visit.

Seizure Severity Questionnaire and Caregiver Assessment will also be listed in listings.

7.7 PK Analysis

Detailed pharmacokinetic analysis will be described in a separate Pharmacokinetic Analysis Plan.

7.8 Protocol Deviations

Protocol deviations will be reviewed to determine if it is a minor or major deviation. The number and percentage of subjects in each dose group in the single dose period with protocol deviations will be presented. Individual minor and major protocol deviations will be listed with detailed deviation term.

7.9

[REDACTED]	
[REDACTED]	
[REDACTED]	
I	[REDACTED]
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I	[REDACTED]
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	[REDACTED]
I	[REDACTED]
	[REDACTED]

8 INTERIM ANALYSIS

An interim analysis is considered to re-assess and possibly adjust the sample size; and to provide safety reviews of diazepam after intranasal administration of VALTOCO to pediatric subjects. Detailed pharmacokinetic analysis for interim analysis will be described in a separate Pharmacokinetic Analysis Plan.

Following analysis are planned for interim analysis: subject disposition, demographic characteristics, treatment exposure, adverse events, nasal irritations, and e-Diary data.

9 PLANNED SUMMARY TABLES AND LISTINGS

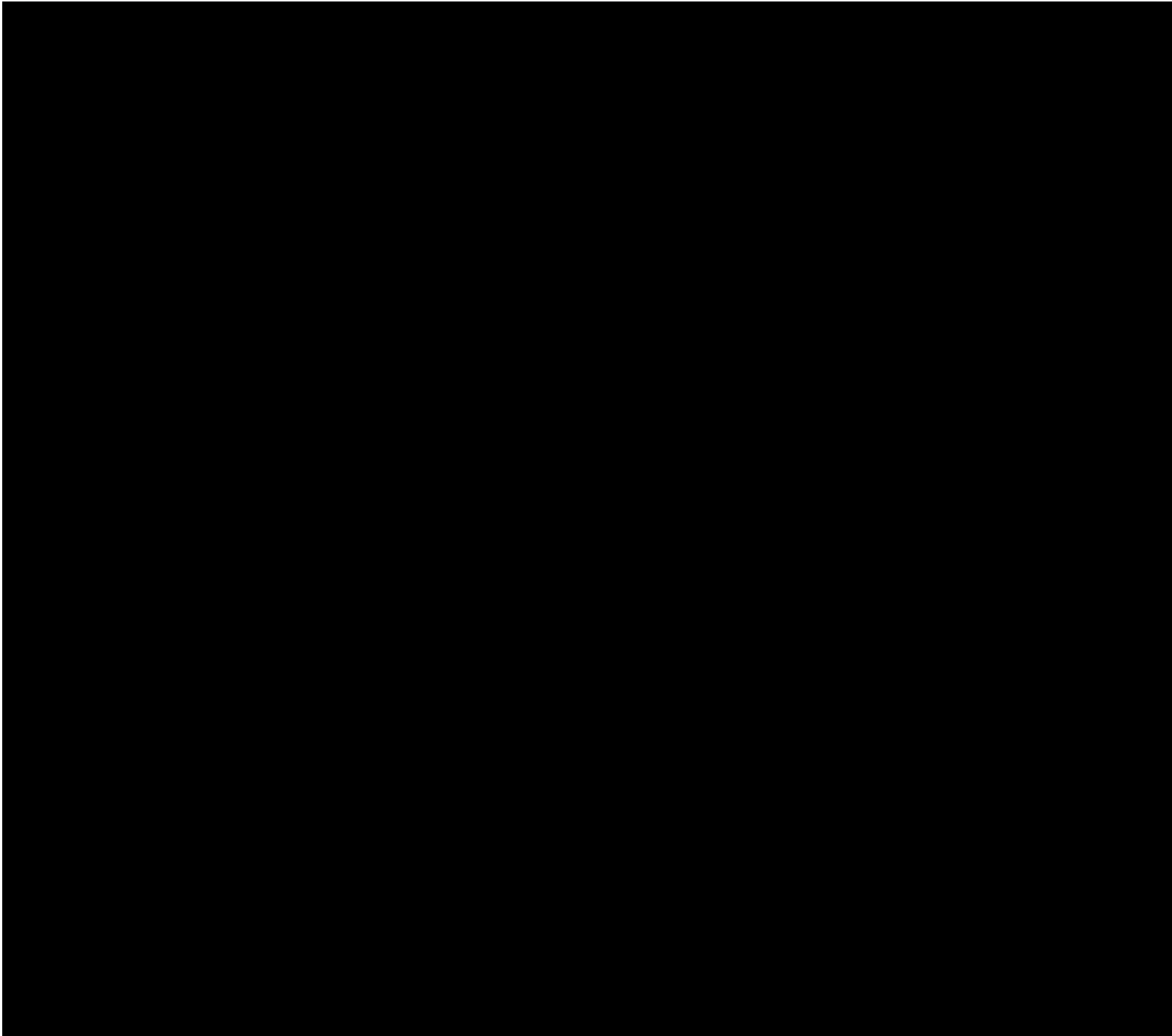
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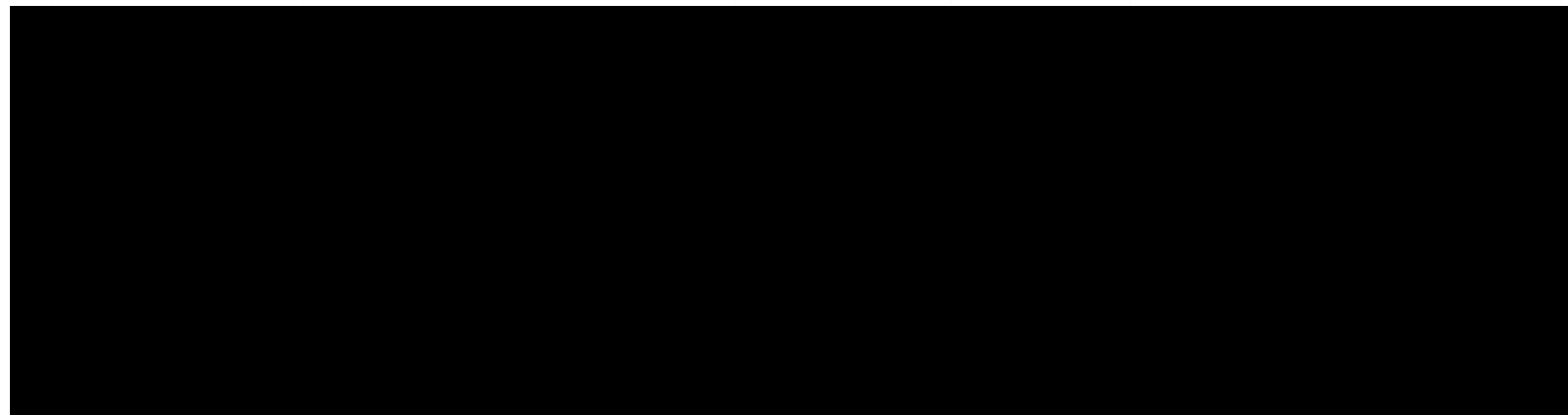
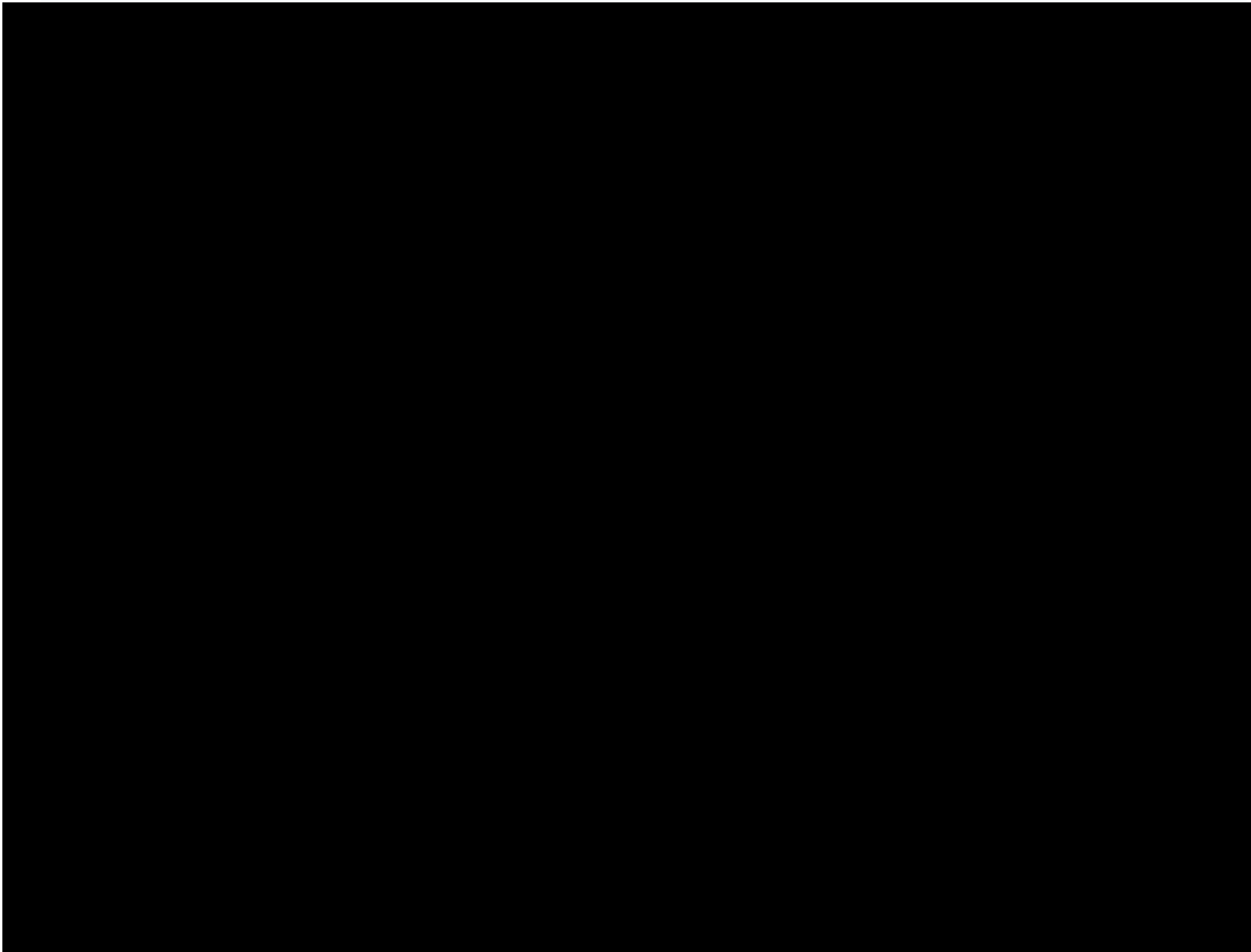
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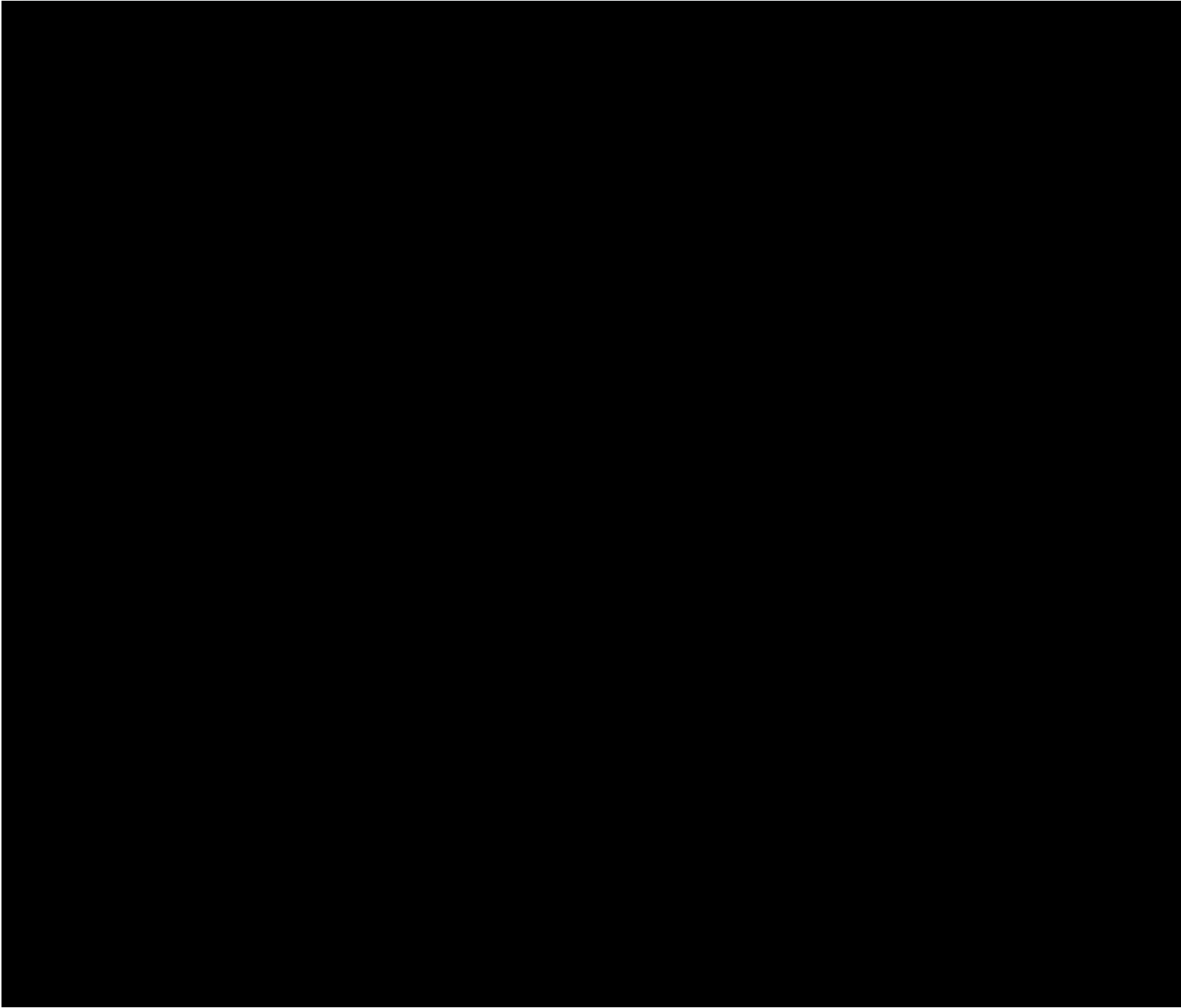


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