

PAREXEL International
Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

1024.9

Bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl compared to two film coated fixed dose combination tablets RhinAdvil® (200 mg Ibuprofen and 30 mg Pseudoephedrine- HCl) administered in at least 48 healthy male and female subjects (Open-label, randomised, laboratory blind, single dose, two-way crossover, Phase I trial).

Version: Final 4.0

Date: 09/Mar/2017

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REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
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Draft 2.0	20/Feb/2017	██████████	Comments from sponsor from 10 Feb. 2017 processed
Draft 3.0	03/Mar/2017	██████████	Added rounding for percentages in safety tables. All percentages now at 2 decimal places. Added abbreviations. Cleaned up text. Added codes to protocol deviation categories. Added flag for topline results. Corrected title listing 16.2.6.5. Removed change from baseline from safety laboratory.
Draft 4.0	09/Mar/2017	██████████	Comments sponsor received 8 March processed

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Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

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Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

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ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ANOVA	Analysis of Variance
AUC	Area under the concentration-time curve
AUC _{0-∞}	AUC of the analyte in plasma from 0 hours extrapolated to infinity
AUC _{0-tz}	AUC of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence interval
C _{last}	Last quantifiable concentration at t _{last}
CL/F	Apparent clearance following oral administration
CSP	Clinical Study Protocol
C _{max}	Maximum observed concentration
CS	Clinically significant
CV%	Coefficient of variation
DRM	Data Review Meeting
ECG	Electrocardiogram
gCV%	Geometric CV%
gMean	Geometric mean
ICF	Informed Consent Form
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
NK	Not known
NR	Not Reportable
NS	No Sample

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Abbreviation / Acronym	Definition / Expansion
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis population
PR	Pulse Rate
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation or single dose
SOC	System Organ Class

TEAE	Treatment-emergent adverse event
TLFs	Tables, Listings and Figures
t_{\max}	Time corresponding to occurrence of C_{\max}

WHO-DD	World Health Organisation - Drug Dictionary
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1. STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final CSP Version 2.0, dated, 30/Jan/2017. The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum.

2. STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate the bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl vs. RhinAdvil® (2 tablets containing 200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) as a fixed dose combination tablet with respect to the analytes ibuprofen and pseudoephedrine.

2.2 Secondary Objective

To assess the bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl vs. RhinAdvil® (2 tablets containing 200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) as a fixed dose combination tablet with respect to R- and S-ibuprofen (enantiomers of ibuprofen).

3. ENDPOINTS

3.1 Primary Endpoints

The following primary endpoints will be determined for the analytes ibuprofen and pseudoephedrine:

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- AUC_{0-tz} (area under the concentration-time curve of the analytes in plasma over the time interval from 0 to the time of last quantifiable time point)
- C_{max} (maximum measured concentration of the analytes in plasma)

3.2 Secondary Endpoints

The following secondary endpoint will be determined for the analytes ibuprofen and pseudoephedrine-HCl:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analytes in plasma over the time interval from 0 extrapolated to infinity)

The following secondary endpoints will be determined for the analytes R-ibuprofen and S-ibuprofen:

- AUC_{0-tz} (area under the concentration-time curve of the analytes in plasma over the time interval from 0 to the time of last quantifiable time point)
- C_{max} (maximum measured concentration of the analytes in plasma)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analytes in plasma over the time interval from 0 extrapolated to infinity)
- S/R-ibuprofen ratio for AUC_{0-tz} (i.e., AUC_{0-tz} S-ibuprofen / AUC_{0-tz} R-ibuprofen)

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3.3 Assessment of safety

Safety and tolerability of the investigational drug(s) will be assessed based on:

- Vital signs (BP, PR)
- 12-lead ECG (electrocardiogram)
- Clinical laboratory tests (haematology, clinical chemistry and urinalysis)
- Adverse events (including clinically relevant findings from the physical examination)
- Assessment of tolerability by the investigator

4. STUDY DESIGN

The study will be performed as an open-label, single dose, randomised, laboratory blind, two-way crossover trial. The following treatments will be administered in the fasting state:

Test (T): Film coated fixed dose combination tablet containing Ibuprofen 400 mg and Pseudoephedrine 60 mg

Reference (R): **RhinAdvil®** two fixed dose combination tablets containing Ibuprofen 200 mg and Pseudoephedrine 30 mg

The two treatment sequences T-R and R-T will be randomly allocated to the subjects.

The schedule of assessments is given in the flow chart in section 13.

5. STUDY POPULATION

The study population will consist of 56 adult healthy subjects.

Detailed lists of inclusion and exclusion criteria are shown in Sections 3.3.2 and 3.3.3 of the CSP.

6. STATISTICAL BASIS FOR SAMPLE SIZE

For details on sample size are shown in section 7.7 of the CSP.

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The sample size for this trial was determined based on the C_{\max} , accounting for multiple testing of the two analytes (ibuprofen and pseudoephedrine), i.e. the overall power of the study is the product of the power of the test of each analyte, as their endpoints are assumed to be uncorrelated.

A sample size of 48 will have a more than 90% power to conclude bioequivalence if the T/R ratio is not lower than 91%, the lowest ratio in study 1014.7 (C_{\max} of ibuprofen). Accounting for up to 8 dropouts, a total of $N = 48 + 8 = 56$ subjects will be entered into the study

7. RANDOMIZATION

Subjects will be randomized to one of the two treatment sequences (T-R, R-T) in a 1:1 ratio.

8. STATISTICAL ANALYSIS CONVENTIONS

8.1 Analysis Variables

8.1.1 Demographic and Background Variables

The following demographic and anthropometric information will be recorded:

- Date of informed consent
- Medical history (including previous and current medical conditions and medications)
- Drug, alcohol and smoking history
- Age calculated as (date of informed consent – date of birth)/365.25
- Gender
- Ethnic origin
- Race
- Height, without shoes (cm)
- Body weight (kg)
- Body mass index (BMI) calculated as [weight/height²] (kg/m²)

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All medical history will be coded using Version 19.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

8.1.2 Safety Variables

8.1.2.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a 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, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AE intensity should be judged based on the following:

- Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or to perform usual activities.

All AEs will be coded using version 19.1 of the MedDRA.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

- All AEs with start date/time prior to dosing in period 1 are pre-treatment AEs and will be assigned to screening.
- All AEs with start date/time after the date/time of dosing in period 1, but before dosing in period 2, will be assigned to the treatment received in period 1.
- AEs with start date/time after the date/time of dosing in period 2 will be assigned to the treatment received in period 2.

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK:NK in the listings (where NK =

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Not Known). If the date is a treatment date, then the AE will be assigned to the treatment of that date.

- Adverse events with completely unknown start dates will be considered as treatment-emergent using the period 1 treatment for the tabulations and will be shown as NK in the listings.

8.1.2.2 Clinical Laboratory Tests

The safety laboratory tests (haematology, clinical chemistry and urinalysis) specified in section 5.3.3 of the CSP will be measured according to the schedule displayed in section 13.

8.1.2.3 Vital Signs

The following vital signs measurements will be obtained according to the schedule of assessments in section 13:

- Blood pressure (BP), systolic and diastolic (mmHg)
- Pulse rate (PR)
- Body temperature [°C]

8.1.2.4 Electrocardiograms

12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded according to the schedule in section 13. ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, Not Clinically Significant (NCS)' or 'Abnormal, Clinically Significant (CS)'.

8.1.2.5 Physical Examination

Physical examination will be performed at screening and follow up.

8.1.2.6 Concomitant Medication

Concomitant medication will be coded using the World Health Organisation-Drug Dictionary (WHO-DD) (Version **SEP 2016**).

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8.1.3 Pharmacokinetic Variables

Blood for plasma concentrations will be sampled according to the flow chart in section 13. Unless otherwise stated, derivation of pharmacokinetic (PK) parameters will be the responsibility of Early Phase, Clinical PK/Pharmacodynamic, PAREXEL International. The following PK parameters will be determined for Ibuprofen, Pseudoephedrine-HCl, R- and S-ibuprofen in plasma following single dose administration:

Table 1 Pharmacokinetic Parameters after Single Dose Administration

Parameter	Definition
C_{max}	Maximum observed concentration of the analyte in plasma
t_{max}	Time corresponding to occurrence of C_{max}
AUC_{0-tz}	Area under the concentration-time curve (AUC) of the analyte in plasma from 0 hours to the last quantifiable data point
$AUC_{0-\infty}$	AUC from time zero extrapolated to infinity
AUC_{0-tz} S-ibuprofen / AUC_{0-tz} R-ibuprofen	Ratio of S-ibuprofen/ R-ibuprofen as measured by AUC_{0-tz}

8.1.3.1 Pharmacokinetic Parameter Calculation Methods

PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data using WinNonlin Professional (Version 6.3) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
 - If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead.

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- There will be no imputation of missing data.
- All below the limit of quantification (BLQ) values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. All other BLQ values will be set to missing.
- Data may/will be excluded from PK analysis (concentrations listed only) if any of the exclusion criteria from section 8.3.11 are fulfilled.

PK parameters will be estimated according to the following guidelines:

- C_{\max} will be obtained directly from the concentration-time data.

8.2 Analysis Populations

8.2.1 Safety Population

All subjects who received at least one dose of study drug will be included in the safety evaluation (safety population).

8.2.2 Pharmacokinetic Population

The PK analysis population (PKS, PK set) will include all treated subjects that provide observations for both periods for at least one primary endpoint evaluable (AUC_{0-tz} and C_{max}) and without any major protocol deviation thought to interfere with the absorption, distribution, metabolism, and excretion of the compound to be measured. PK parameters for subjects who discontinue after a single treatment will be presented in the listings but will not be used for summary statistics or any statistical analysis.

8.3 Statistical Analysis Methods

8.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed. Data will be described using summary statistics as described in the sections below. Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). All listings will include repeated and unscheduled measurements.

The following rules will apply to any repeated measurements:

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- If the repeated measurement occurs prior to the first dose of study drug then the last obtained value of any repeated measurement will be used in the descriptive statistics.
- If the repeated measurement occurs after the first dose of study drug then the original value of any repeated measurements will be used in the descriptive statistics.

All descriptive statistics will be presented by treatment for measurements obtained during each treatment period. The baseline for all measurements (where applicable) will be the last pre-dose measurement within each period. Descriptive statistics for all data obtained at Screening and follow-up will be presented separately.

8.3.2 Rounding and decimal places

- The following rules will be followed with regard to the number of decimal places and presentation of data in the tables and listings of safety data:
 1. All data will be listed according to the number of decimal places presented in the source data
 2. Mean and median will be tabulated to one more decimal place than the source data
 3. Minimum and maximum values will be tabulated to the same number of decimal places as the source data
 4. Standard deviation (SD) will be tabulated to two more decimal places than the source data
 5. Coefficient of variation (CV)%, if applicable, will be presented to two decimal place
 6. A maximum of three decimal places will apply to all summary statistics.
 7. Percentages will be displayed to two decimal place.
- The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK concentration data:
 1. The individual concentrations will be reported to the same precision as the source data (for example, if the source data is presented to five significant digits, the individual values will be presented to five significant digits)
 2. The mean, SD, geometric mean (gMean) and median will be tabulated to one more significant digit compared to the source data.
 3. Minimum and maximum values will be tabulated to the same precision as the source data.
 4. Geometric CV% will be presented to two decimal places.

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- The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK parameters:
 1. Individual PK parameters will be presented to three significant digits, [REDACTED]. In addition, parameters directly derived from source data (e.g. C_{max}) shall be reported with the same precision as the source data
 2. The mean, gMean, median and SD values will be reported to one more significant digit than the source data, except for CV% which will be presented to two decimal place. [REDACTED]
 3. Geometric least squares means from the statistical analysis will be presented to three significant digits
 4. Estimates and confidence intervals in the form of percentages will be presented to two decimal places

8.3.3 Statistical Significance Level

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated.

8.3.4 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS[®]) Version 9.3 or later. The PK analysis will be performed using WinNonlin Professional Software Version 6.3 or later.

8.3.5 Missing Data

There will be no imputation of missing data.

8.3.6 Interim Analysis

Not applicable.

8.3.7 Protocol Deviations

All protocol deviations will be recorded by the Investigator and will be listed by subject and will include a description of the deviation, the data/time of the deviation (if available), study day of the deviation, time point (if applicable). Protocol deviations will be based on the safety population.

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All protocol deviations will be discussed between PAREXEL (physician, Data Manager, Biostatistician, PK Scientist/Analyst and Medical Writer) and also the Sponsor during the Data Review Meeting (DRM) before database lock. Protocol deviations will be classified as major or minor. Exclusion/inclusion of subjects based on the deviations will be decided upon at the DRM. The classifications and specification will be specified in a separate document, the protocol deviations specification. The main categories for protocol deviations that will be considered are described in Table 2.

Table 2 Protocol Deviations Categories

Code	Category
A	Subject did not meet the inclusion/exclusion criteria
B	Subject received prohibited concomitant medications
C	Subject did not receive the planned dose
D	Deviations from scheduled procedure time outside of the window allowance
E	Procedures not performed due to error or subject availability
F	Deviations regarding sample processing
G	Use of the incorrect ICF, ICF incorrect, etc.
H	Any deviation that does not fit into one of the categories listed above

The window allowance document (WAD, version 2, 24Nov2016) will stipulate the tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

8.3.8 Demographic Data

All demographic data will be presented using the safety population.

8.3.9 Concomitant Medication

All prior and concomitant medication will be listed using the safety population.

8.3.10 Exposure to the Investigational Medicinal Product

Exposure to the investigative product will be shown in a listing.

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8.3.11 Pharmacokinetic Concentrations and Variables

Pharmacokinetic concentration data of all analytes will be shown in a listing including actual sampling times relative to dosing using the safety population.

The analysis of the PK data will be based on the PKS.

Any data excluded will be discussed in the CSR.

Plasma concentrations will be summarized by treatment, analyte and timepoint. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV%), gMean, geometric CV% (calculated as: $gCV\% = \text{SQRT}(e^{s^2} - 1) * 100$; where s is the standard deviation of the natural log-transformed values), median, minimum and maximum values. Summaries will only be presented when at least 2/3 of the subjects have concentrations within the validated concentration range.

Pharmacokinetic parameters will be listed by subject and summarized by treatment. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, CV%, gMean, gCV%, median, minimum and maximum values. [REDACTED]. No descriptive statistics will be determined when fewer than 2/3 individual PK parameters are available.

Individual plasma concentration versus actual times will be plotted by treatment for each analyte in linear and semi-logarithmic scale. Plots of R and S ibuprofen will be combined in one display. Combined individual plasma concentrations including gMean will be plotted by product for each analyte (spaghetti plot). Mean plasma concentrations versus nominal times will also be presented for all analytes in linear and semi-logarithmic scale. R and S-ibuprofen will be overlaid on the same plot.

- Data may be excluded from PK plasma concentration summaries, PK parameter calculations, PK parameter summaries and bioequivalence calculations if any of the following criteria are fulfilled:
 - The pre-dose concentration is greater than 5% of the corresponding C_{\max} in any given treatment period.
 - Subject experienced emesis within 2 x the reported median t_{\max} for the analyte (median t_{\max} is to be determined excluding the subjects experiencing emesis)

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- Concomitant medication, which could render the plasma concentration-time profile unreliable
- Subject has moderate or severe diarrhea within 2 x the reported median t_{max} for the analyte.
- Data excluded in summaries will also be excluded corresponding plots.

8.3.11.1 Handling of Values Below the Limit of Quantification (BLQ) in Concentration Summaries and Listings

Graphical presentation:

For all graphs missing values will be excluded from the calculations. For graphs of arithmetic means all BLQ mean concentrations will be set to missing. Mean values will only be displayed when at least 2/3 of the individual concentrations are available. Graphs of gMeans include only time points with minimum concentration greater than Lower level of quantification (LLOQ). Any arithmetic mean that is BLQ will be excluded from log/linear presentation of arithmetic means. Any BLQ values prior to the last quantifiable concentration will be excluded from both individual linear/linear graphs and individual log/linear graphs. All BLQ values after the last quantifiable concentration will be excluded from individual linear/linear and log/linear graphs.

Handling of values below the limit of quantification (BLQ) in listings and for the calculation of descriptive statistics at each time point:

Concentration below the LLOQ will be indicated by BLQ in the listings, concentration data identified as no sample (NS), not reportable (NR) and Below Limit of Quantification (BLQ) will be labelled as such in the listing.

Missing samples will be excluded from descriptive statistics. Values that are BLQ will be substituted with zero for the calculation of descriptive statistics of concentration by time point. The summary statistics gMean, and gCV% will not be calculated when any BLQ values are used and will be displayed as “not calculable” or NC. Descriptive statistics of concentrations will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range.

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8.3.11.2 Primary analysis: Assessment of Bioequivalence

Bioequivalence will be analyzed using the ratios of the gMeans (test/reference [T/R]) for the C_{max} and AUC_{0-tz} endpoints of ibuprofen and pseudoephedrine-HCL. Additionally, their two sided 90% Confidence Intervals (CI) will be provided. This method corresponds to the two one sided t-tests procedures, each at the 5% significance level.

The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including fixed effects for sequence, subject nested within sequence, period and product. Only subjects who complete the PK sampling in both periods will be included in the analysis for that specific analyte. For each endpoint, the difference between the expected means for the natural log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (LeastSquares Means). Confidence intervals will be calculated based on the residual error from the ANOVA. The differences between the test and reference product and the CIs will be back transformed to the original scale, resulting in point estimates of the T/R gMean ratios and 90% CIs.

The model is described by the following equation

$$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm},$$

where

y_{ijkm} = logarithm of response (AUC or C_{max}) measured on subject m in sequence i receiving treatment k in period j

μ = the overall mean

ζ_i = the i^{th} sequence effect, $i = 1, 2$

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, $m = 1, 2, \dots, 24$

π_j = the j^{th} period effect, $j = 1, 2$

τ_k = the k^{th} treatment effect, $k = 1, 2$

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

The model will be based on the following SAS code:

```
Proc Mixed;
Class treatment period sequence subject;
Model var=treatment sequence period subject(sequence);
/*where "var"=(if doses are different dose
normalized and) log transformed PK parameter*/
Lsmeans treatment / CL alpha=0.05;
Estimate 'Test - Reference' treatment 1 -1 / cl alpha=0.1;
ods output estimates=estim
```

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```
lsmeans=ls_means;  
QUIT;
```

Before the data will be analysed the fixed effect treatment will be numerically coded; Test=1 and Reference=2.

Hypothesis for primary analysis

Bioequivalence is established by using the average bioequivalence method to ensure that the ratio of the primary endpoints of the two treatments (T/R) is contained within a pre-specified acceptance range (see below). This goal is accomplished by testing the below hypothesis on the log scale.

Null hypothesis H_0 (Inequivalence): $\mu_T - \mu_R \leq -\delta$ or $\mu_T - \mu_R \geq \delta$

(i.e. the difference of the population average responses is either less than or equal to the lower bound or greater than or equal to the upper bound of the acceptance range),

Alternative hypothesis H_a (Equivalence): $-\delta < \mu_T - \mu_R < \delta$

(i.e. the difference of the population average responses is both greater than the lower bound and less than the upper bound of the acceptance range), where μ_T and μ_R are the population average responses of the log-transformed measures for the formulations Test and Reference, and δ is the bioequivalence limit that defines the acceptance range for AUC and C_{max} on the logarithmic scale

In this trial, δ is taken to be $\ln(1.25)$. This translates to an acceptance range of 80 to 125% for the gMean of the ratio of the parameters on the original scale.

This hypothesis and its alternative can be decomposed into two one-sided null hypotheses, H_{01} and H_{02} , with their accompanying alternatives:

H_{01} : $\mu_T - \mu_R \leq -\delta$ vs. H_{a1} : $\mu_T - \mu_R > -\delta$

H_{02} : $\mu_T - \mu_R \geq \delta$ vs. H_{a2} : $\mu_T - \mu_R < \delta$

Due to the nature of normal-theory confidence intervals, the test of the null hypothesis at the $\alpha = 0.05$ level is equivalent to carrying out two one-sided tests of the above null hypotheses each at the $\alpha = 0.05$ level of significance. The rejection of both null hypotheses H_{01} and H_{02} at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range.

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Rejection of both null hypotheses H_{01} and H_{02} for both endpoints C_{max} and AUC_{0-tz} of both analytes ibuprofen and pseudoephedrine-HCL will lead to the conclusion of bioequivalence.

8.3.11.3 Secondary analysis

The primary analysis of section 8.3.11.2 will be repeated for $AUC_{0-\infty}$ for ibuprofen and pseudoephedrine-HCL and for C_{max} , AUC_{0-tz} and $AUC_{0-\infty}$ for R-ibuprofen and S-ibuprofen. The same methods will be applied for the S/R-ibuprofen ratio for AUC_{0-tz} .

8.3.12 Safety Analysis

The analysis of the safety variables will be based on the safety set.

8.3.12.1 Adverse Events

The following listings will be produced:

- All pre-treatment AEs and TEAEs.
- Withdrawals due to AEs (if applicable).
- Serious AEs (SAEs) (if applicable).

The following information will be included in the listings: AE number, reported term, System Organ Class (SOC), Preferred Term (PT), start and end date/time, intensity, causality, action taken, outcome, classified as serious and treatment emergence.

Numbers of TEAEs will be summarized by treatment, SOC, PT, and also by treatment, SOC, PT and severity and also by treatment, SOC, PT and causality to treatment. In addition serious TEAEs will be summarized by treatment, SOC and PT.

8.3.12.2 Clinical Safety Laboratory Tests (haematology, biochemistry and urinalysis)

Laboratory values (haematology, biochemistry and urinalysis) will be listed by subject and study time point. The baseline for the laboratory values will be the last pre dose results.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The

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Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs.

Abnormal clinical lab values will be listed separately for clinical chemistry, haematology and urinalysis.

Descriptive statistics (for non-categorical data including haematology and biochemistry) will be presented by treatment and time point for both individual values (N, mean, SD, median, minimum, maximum).

8.3.12.3 Vital Signs

Vital signs data will be listed by subject including changes from baseline. The baseline for the vital signs measurements will be the pre-dose measurement.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by treatment and time point.

8.3.12.4 Twelve-Lead Electrocardiogram

All ECG parameters obtained from the ECG measurement will be listed by subject for each treatment and time point. There will be no change from baseline for ECG.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values will be presented by treatment and time point.

8.3.12.5 Physical Examination

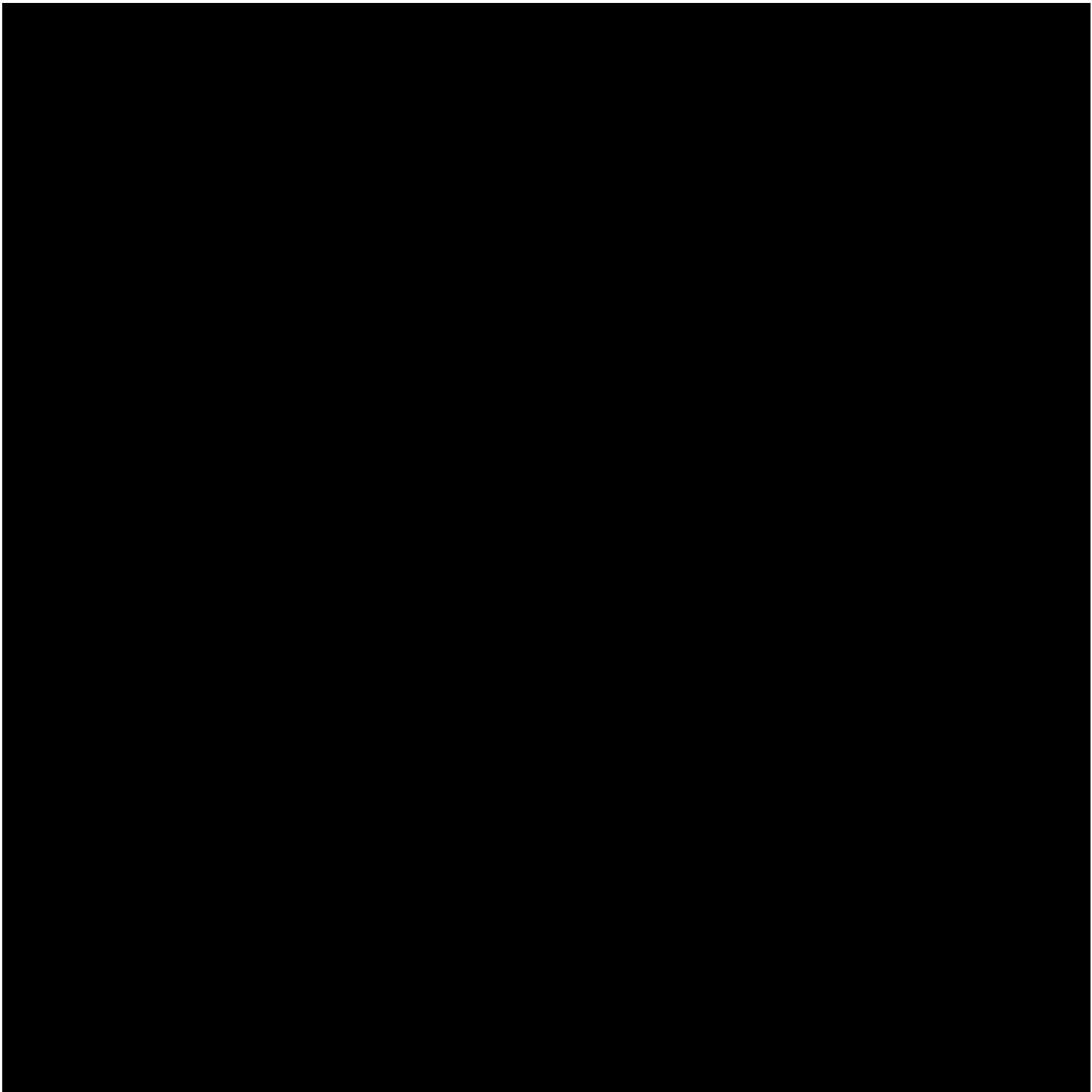
The results of the physical examination will be listed by subject and time-point.

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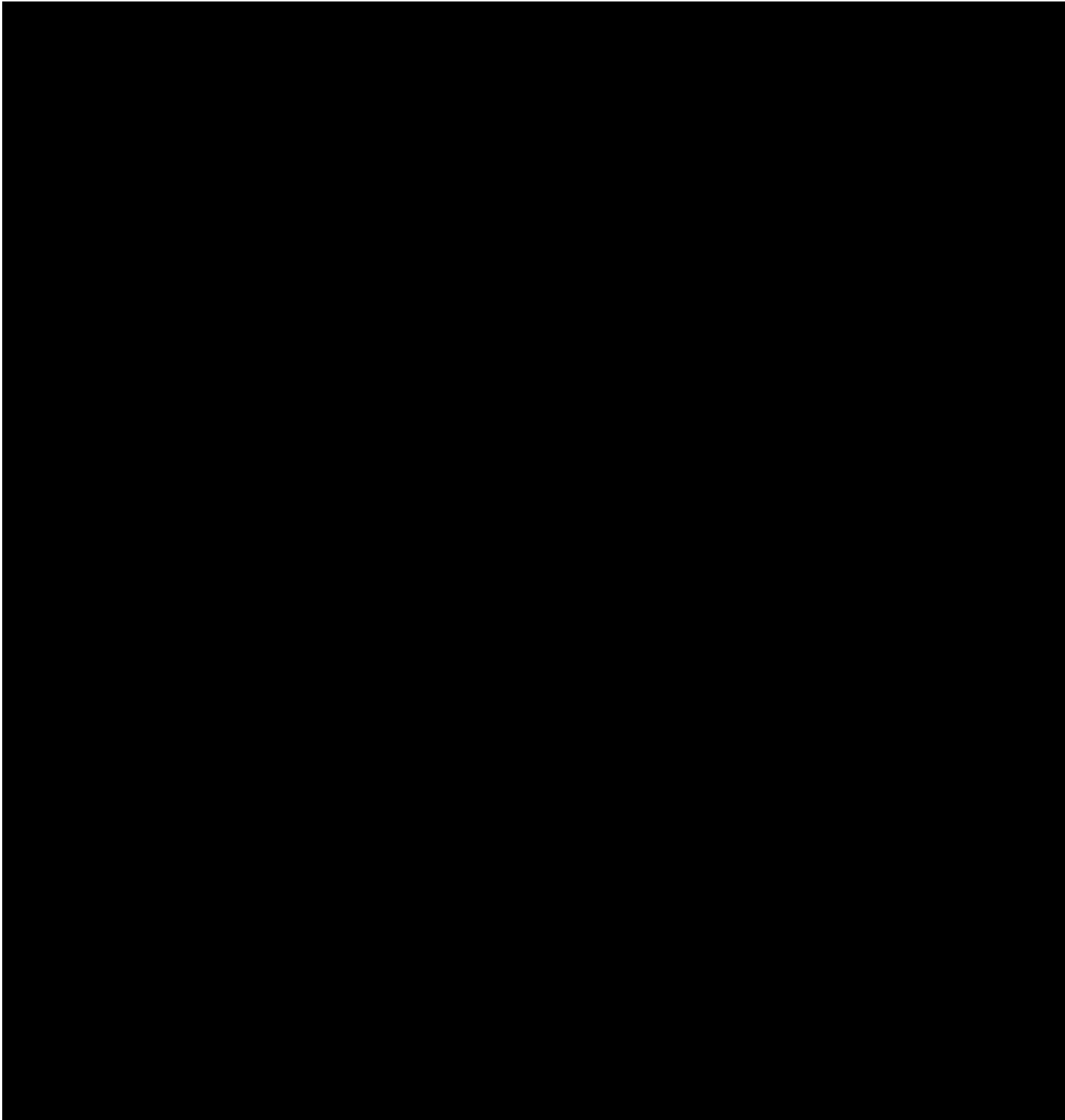
9. REFERENCES

1. SAS[®] Version 9.3 of the SAS System for Personal Computers. Copyright © 2012. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. WinNonlin Professional Software Version 6.3. <http://www.pharsight.com>
3. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, Guideline on the investigation of bioequivalence, London, 20 January 2010.

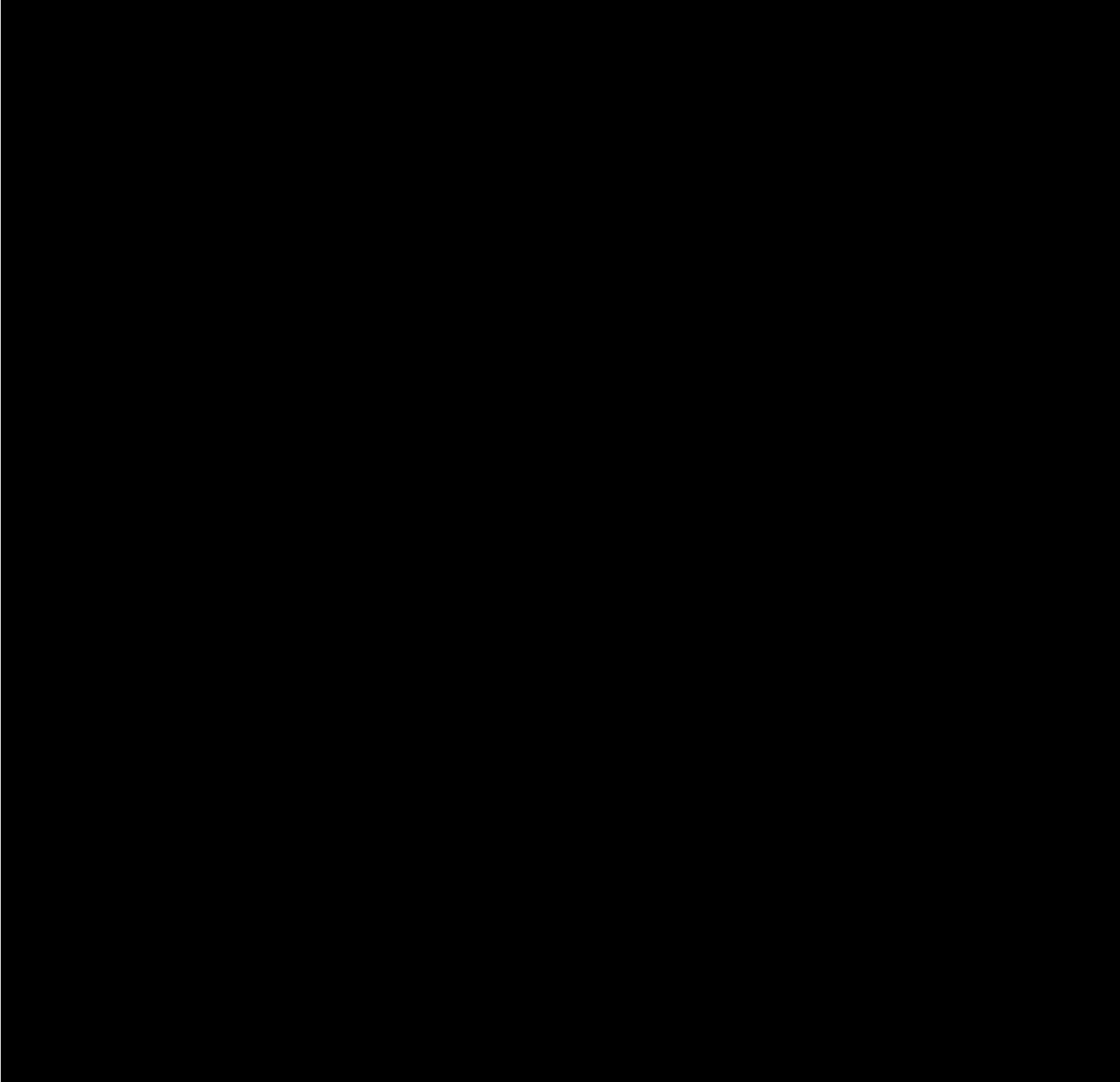
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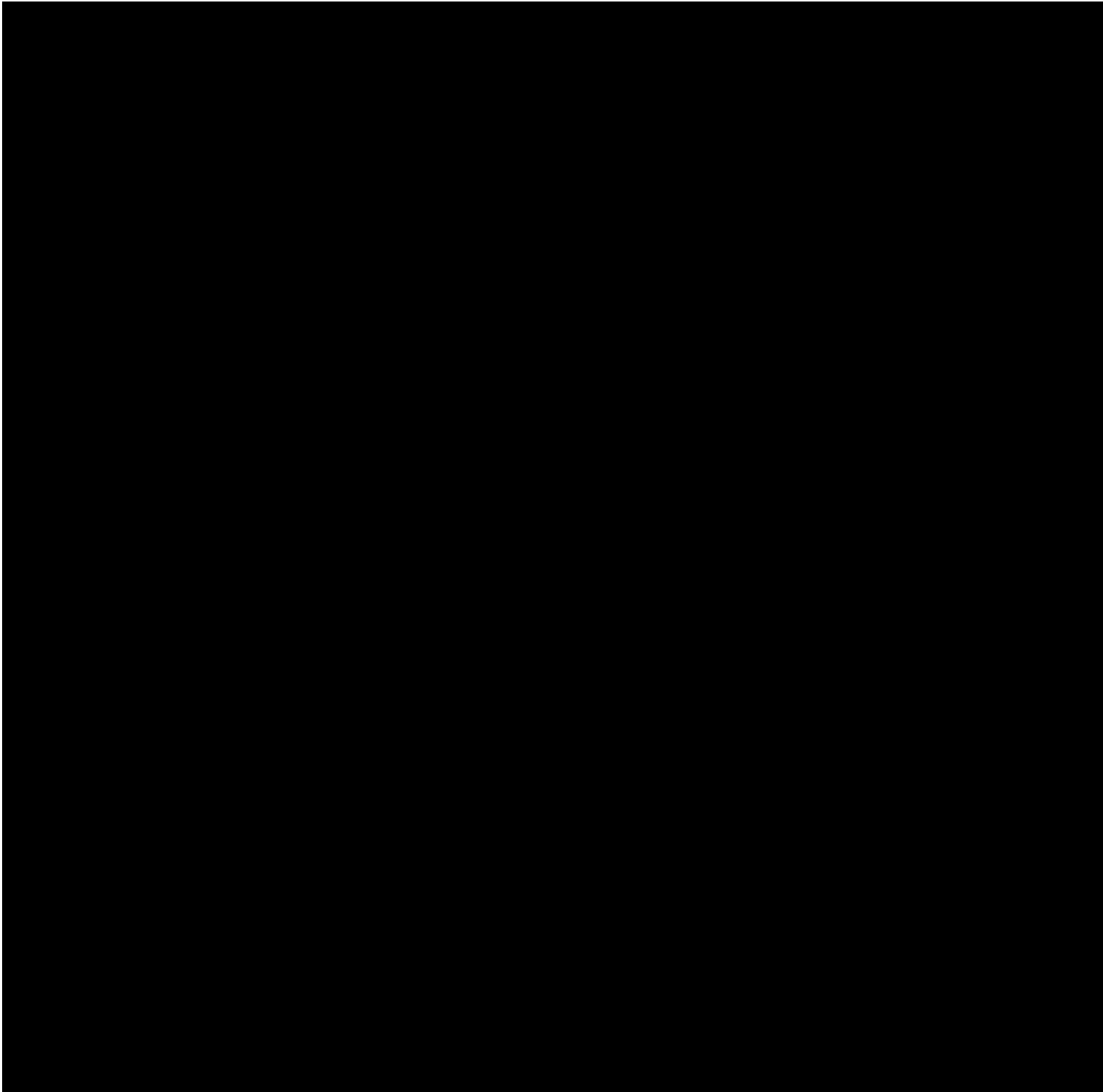
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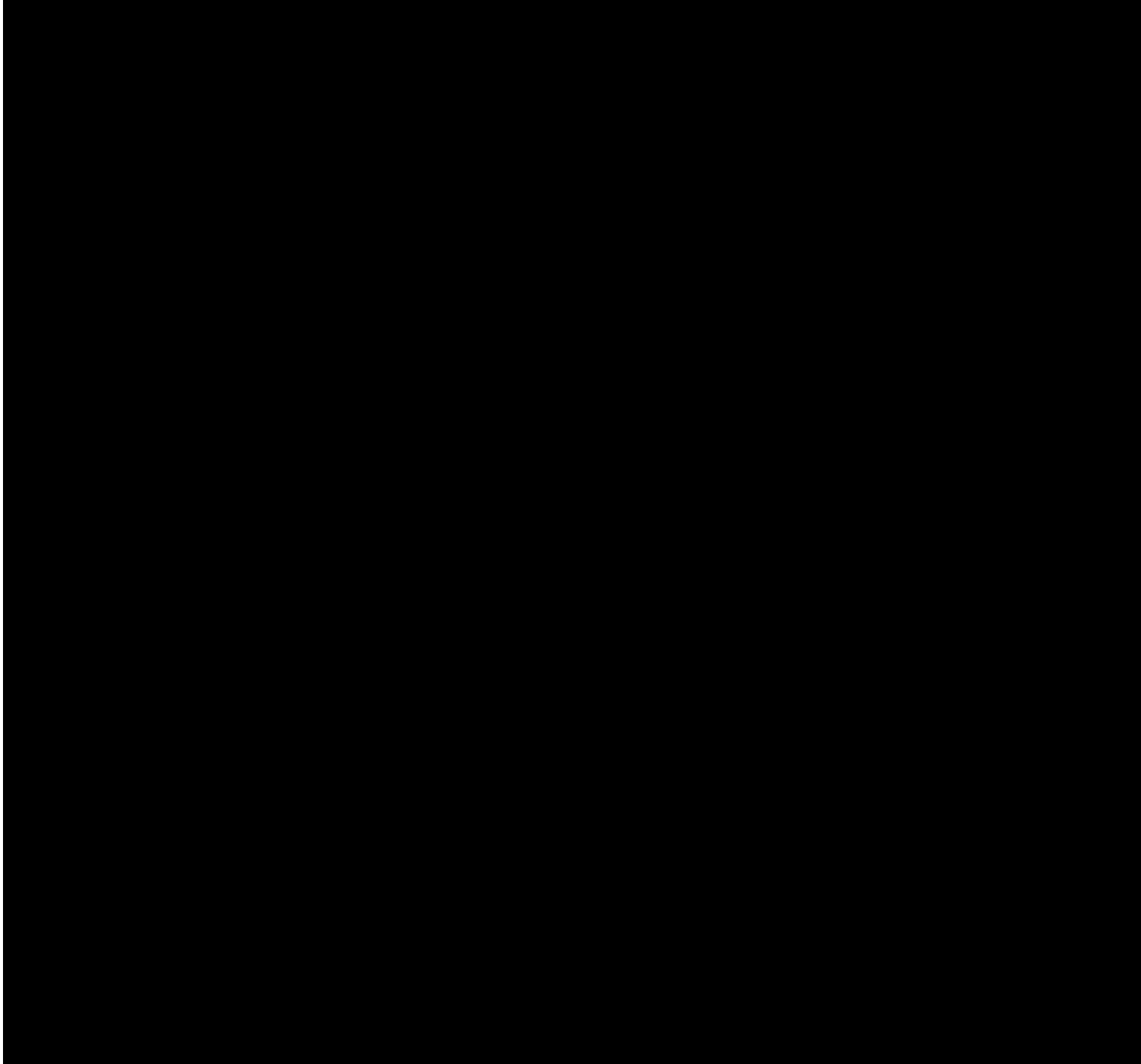
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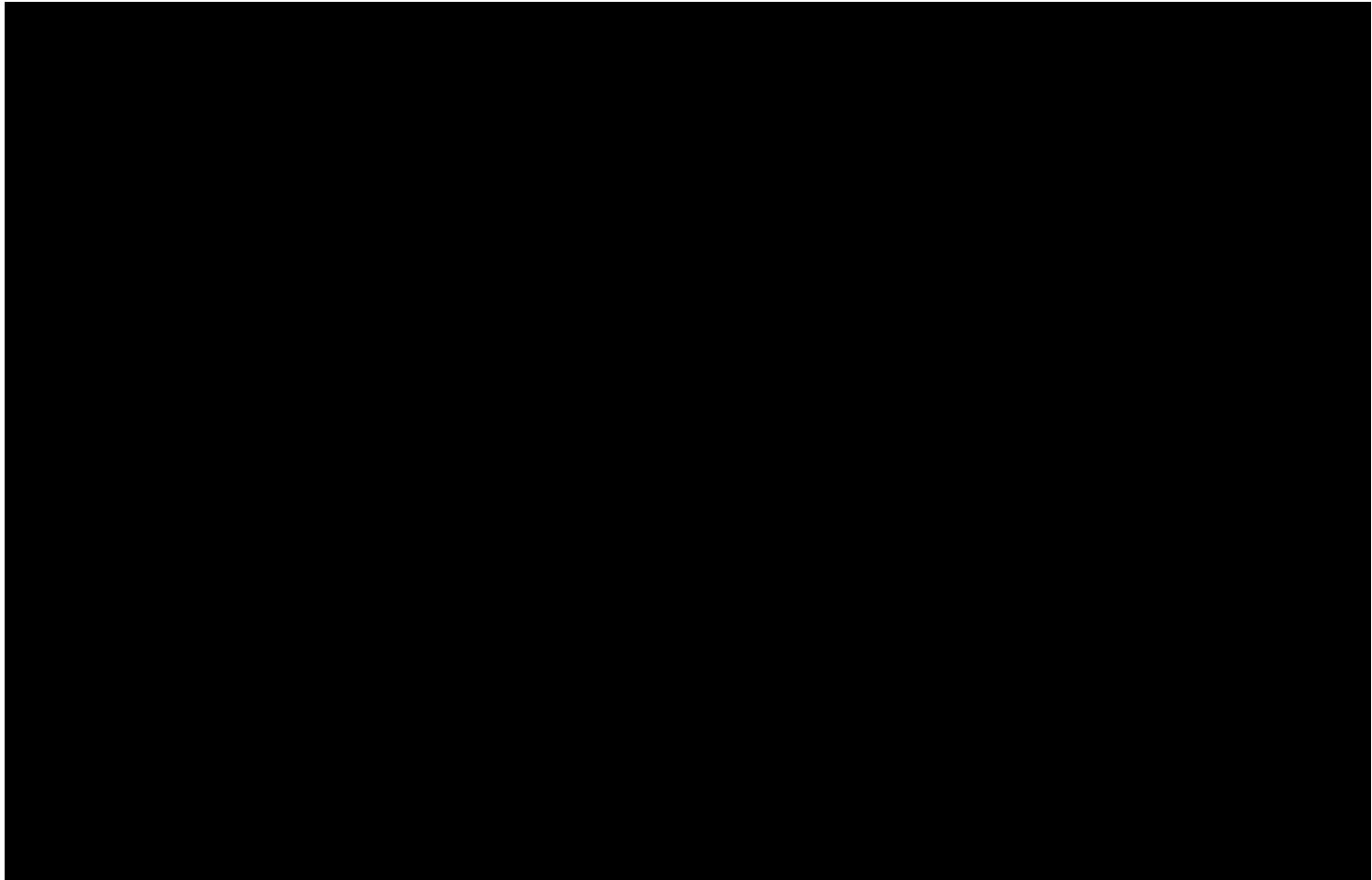
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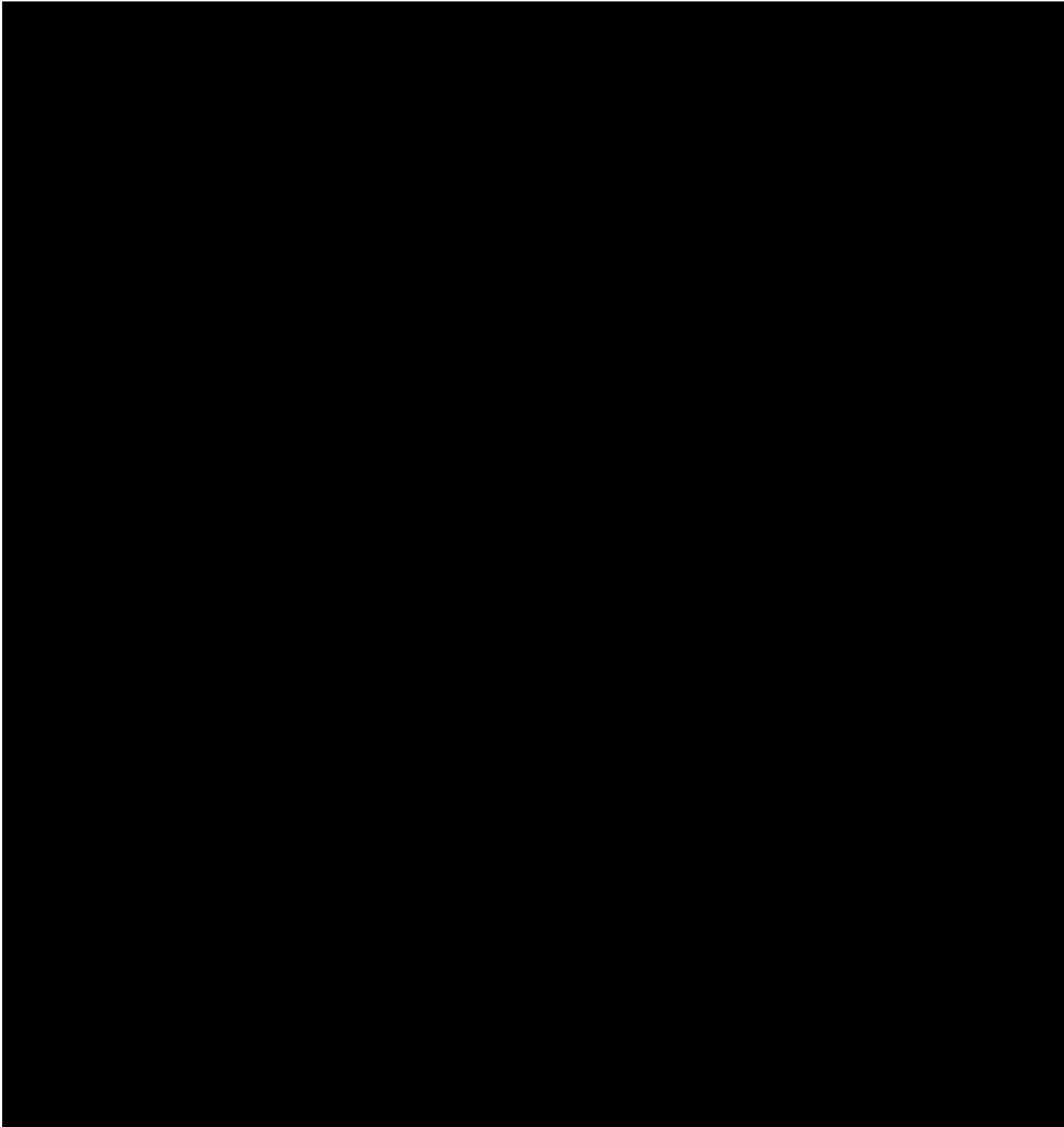
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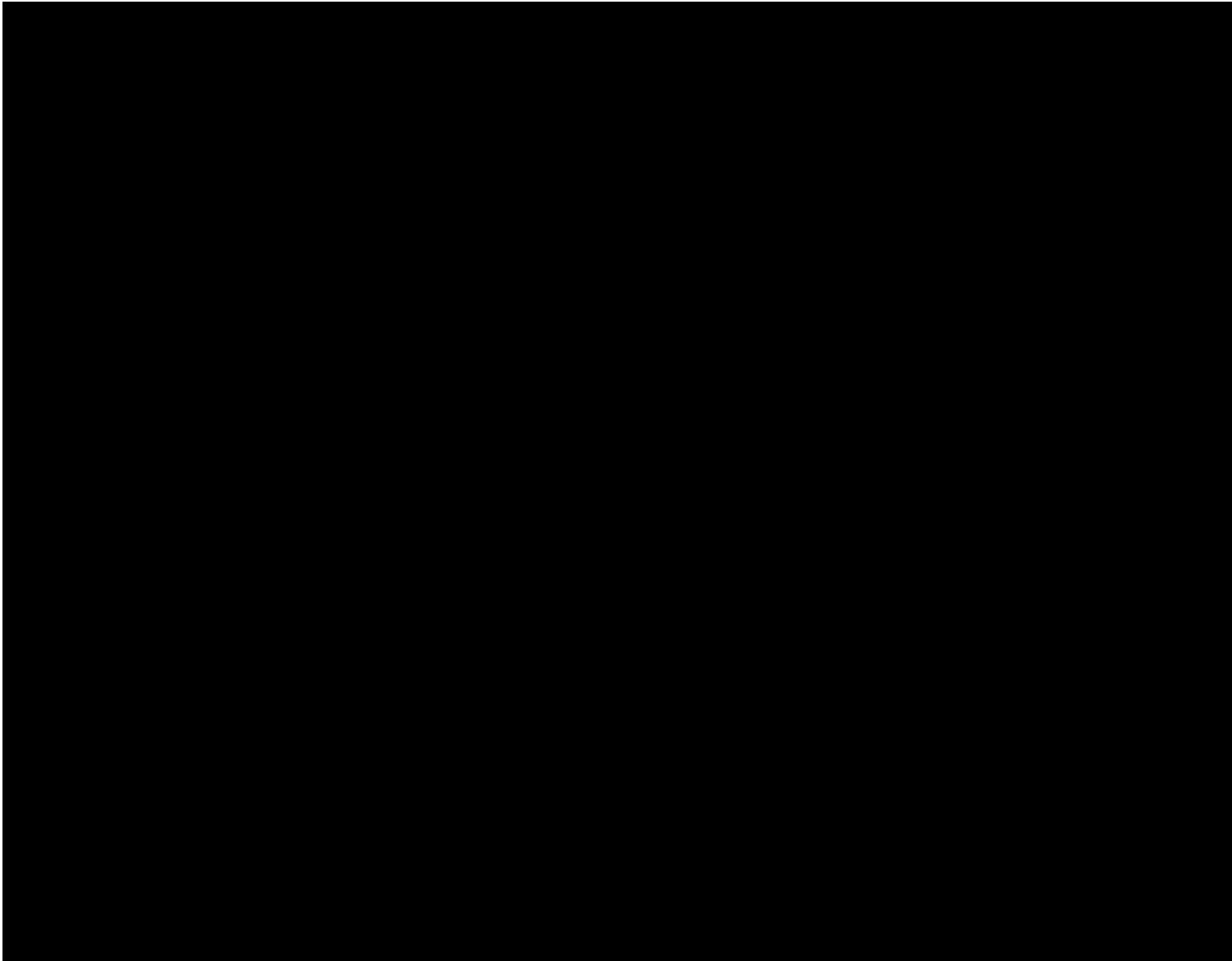
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