Medtronic

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APPROVALS

NAME	FUNCTIONAL AREA	DATE
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1 OVERVIEW

1.1 Purpose

The Clinical BP (Biostatistical Plan) for the CEP 287 (Multi-Center, Prospective, Observational Study of the TS (Threshold Suspend) Feature with a Sensor-Augmented Pump System in Pediatric Patients with Type 1 Diabetes) study [redacted]

[redacted]

1.2 Scope

The contents of this Biostatistical Plan, written for the the CEP 287 (Multi-Center, Prospective, Observational Study of the TS (Threshold Suspend) Feature with a Sensor-Augmented Pump System in Pediatric Patients with Type 1 Diabetes), apply to the statistical analysis provided by Medtronic Diabetes Biostatistics.

1.3 History

[redacted]

1.4 Initial Review, Approval /Authorized Signatures

[redacted]

1.5 Organizational Overview

[redacted]

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2 Study Conduct

In each study or User Evaluation, Biostatistics tasks are divided into six segments, covering: Study Protocol, CRF Development, Randomization, Statistical Analysis Plan, Statistical Analysis, and Engineering Report.

2.1 Study Protocol

CEP287

2.2 CRF Development

Location of CRF: RAD

2.3 Statistical Analysis Plan

[redacted]

2.4 Statistical Analysis

2.4.1 Actual Randomization Sequence

N/A

2.4.2 Data Extraction, Preparation, and Validation

[redacted]

2.4.3 Statistical Programming

2.4.3.1 Validation

[redacted]

2.4.3.2 Programming code

[redacted]

2.4.4 Output and Final Report

[redacted]

2.4.5 Change from SAP

[redacted]

3 Appendix A

3.1 CLINICAL STATISICAL ANALYSIS PLAN

3.1.1 Synopsis of Study

This study is a longitudinal, multi-center trial that aims to observe the Threshold Suspend (TS) feature with a sensor-augmented insulin pump in patients 2–15 years with Type 1 diabetes. The study will measure the change in A1C from baseline over a period of one year while subjects are wearing the study pump.

The study objective is to demonstrate that home use of Threshold Suspend (TS) is not associated with glycemic deterioration in pediatric patients with type 1 diabetes, as measured by change in A1C.

Up to 300 subjects will be enrolled so that there will be 200 subjects who are eligible to participate in the study.

Up to 20 Investigational centers will be selected across the United States. Selection is based on each Investigator's experience and qualifications, availability of sufficient resources to carry out the required study procedures and the investigator's ability to recruit subjects into the study.

3.1.2 General Statistical Considerations

3.1.2.1 Sample Size, if applicable

3.1.2.1.1 Sample Size for Primary Endpoint

The overall mean change in A1C from baseline to the end of study will be estimated and compared by a non-inferiority test with an A1C margin of 0.4% and a significance level of 0.025 (one-sided). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in A1C is less than 0.4%

The hypothesis is mathematically expressed as:
Ho: $\mu \geq 0.4\%$
Ha: $\mu < 0.4\%$

Where 0.4% is the pre-specified non-inferiority margin, μ is the mean of change in A1C (%).

Assuming the mean of change in A1C from baseline to the 12-month follow-up visit is zero, the standard deviation of change in A1C is 1%, SAS power and sample size calculator shows that a total of 100 subjects will provide over 95% power to detect the non-inferiority with a margin of 0.4% and with one-sided type I error of 0.025.

3.1.2.1.2 Overall Consideration

The above calculations suggest a sample size of 100 subjects who complete the study. For the drop-out rate, a conservative estimate of 20% is adopted (based on STAR3, IDE G060159, the percentage of subjects not completing study in the SAP group is 9.3%); assume 65% of subjects would wear the system most of the time. Then a total of 193 subjects needs to be recruited. In general, a number of 200 will be eligible to participate in the study, with up to 300 subjects enrolled

3.1.2.2 Analysis Datasets, if applicable

Intention to Treat (ITT) Population

The Intention to Treat (ITT) population will include all enrolled subjects.

Completed Case (CC) Population

The Completed Cases (CC) population is all subjects who complete the trial.

Efficacy Population

The primary analysis will be performed on the CC population. Sensitivity analysis will be performed in the ITT population with multiple imputations.

Safety Population

The safety population will be the ITT population (include all enrolled subjects).

3.1.3 Disposition

3.1.3.1 Subject Disposition

The number of subjects enrolled in the study will be presented. The reasons for discontinuing prior to study completion will be summarized.

3.1.3.2 Protocol Deviations

All protocol deviations will be presented in listing.

3.1.4 Baseline Measurements and Demographics

Subject characteristics, including age, gender, race, ethnicity, height, weight, BMI and baseline HbA_1C will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

3.1.5 Study Analysis

3.1.5.1 Analysis of Primary Endpoint

A mixed effects model be used to produce the estimate and confidence interval of the overall mean change in A1C while accounting for inter-site variability: . The 97.5% upper confidence interval of A1C will be calculated and compared to the 0.4% non-inferiority margin. As for endpoint analysis, the proposed mixed effects model using all A1C measurements has more power than the model only using Change in A1C from baseline to one-year visit.

$$Y_{ij} = X_{ij}\beta + B_i + B_{ij} + \varepsilon_{ij}$$

where

$Y_{ij} = (Y_{ij1}, \ldots, Y_{ijn})'$ is the A1C measurement vector for the jth subject in the ith site;

$$X = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 \end{pmatrix}$$ is a the covariate vector for the jth subject in the ith site;

$$\beta = \begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \end{pmatrix}$$ is the coefficient vector, β_0 estimate the mean A1C at baseline, β_4 estimate the mean change of A1C from baseline to one-year visit;

$B_i = (b_{i1}, \ldots, b_{in})'$ is the random effect vector for the ith site;

$B_{ij} = (b_{ij1}, \ldots, b_{ijn})'$ is the random effect vector for the jth subject in the ith site;

$\varepsilon_{ij} = (\varepsilon_{ij1}, \ldots, \varepsilon_{ijn})'$ is the random error term;

"The mean of baseline A1C measurement is estimated by β_0, mean of 3-month A1C measurement estimated by $\beta_0 + \beta_1$, …, mean of 12-month A1C measurement estimated by $\beta_0 + \beta_4$, i.e., β_4 estimate the mean change of A1C from baseline to one-year visit; the 97.5% upper confidence interval of β_4 will be calculated and compared the 0.4% non-inferiority margin."

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3.1.5.4 Analysis of Secondary Endpoint

The mean change in A1C from baseline to 3-month, 6-month, 9-month and 12-month will be summarized individually for each of the three baseline A1C cohorts:

- A1C less than 7.0%;
- A1C between 7.0% to 9.0%;
- A1C greater than 9.0%

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

Questionnaires:

3.1.6 Safety Analysis

All site reported adverse events for enrolled subjects will be summarized. The summary will include all adverse events and adverse events by: Insulin Pump Infusion set; Insulin administration and pump use; Sensor Use; Severe Hypoglycemia; Severe Hyperglycemia; Diabetic Ketoacidosis; Adverse Device Event; Serious Adverse Event and Unanticipated Adverse Device Effect. Adverse Events by Investigator will also be provided. No formal statistical analysis will be carried out.

In addition, data will be collected for a descriptive summary of device disposition; adverse events; device performance and user acceptance. Safety analysis will include a summary of the following:

All adverse events including

- Serious Adverse Events (SAE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe (clinical) Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of Diabetic Ketoacidosis (DKA)

Adverse Events will be stratified by

- **Age**
  - Children age 2-7 years
  - Children age 8-12 years
  - Children age 13-15 years
- **Race**
  - American Indian/Alaska Native
  - Black/African-American
  - White - anticipated maximum 80%
  - Native Hawaiian/Other Pacific Islander
  - Asian
  - Subject Refused
- **Ethnicity**
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
  - Subject Refused

- **Diabetes cohorts based on BMI percentile:**

Weight Status Category	Percentile Range	N=Minimum
Underweight	Less than the 5th percentile	2
Healthy weight	5th percentile to less than the 85th percentile	30
Overweight	85th to less than the 95th percentile	4

Obese	Equal to or greater than the 95th percentile	2

BMI Percentiles according to CDC:
http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html

- **Gender**
  - Male
  - Female
- **Hypoglycemic awareness at Baseline Questionnaire**
  - Patients with intact hypoglycemic awareness (95% confidence interval will be provided)
  - Patients who have impaired hypoglycemic awareness (95% confidence interval will be provided)
- Frequency and average duration of hypoglycemic event (based on two weeks prior to the adverse event)
- The one-sided 95% upper confidence limit of severe adverse event incidence rate (DKA and severe hypoglycemia) will be calculated. Individual one-sided 95% confidence limit for DKA only and severe hypoglycemia only will also be provided.

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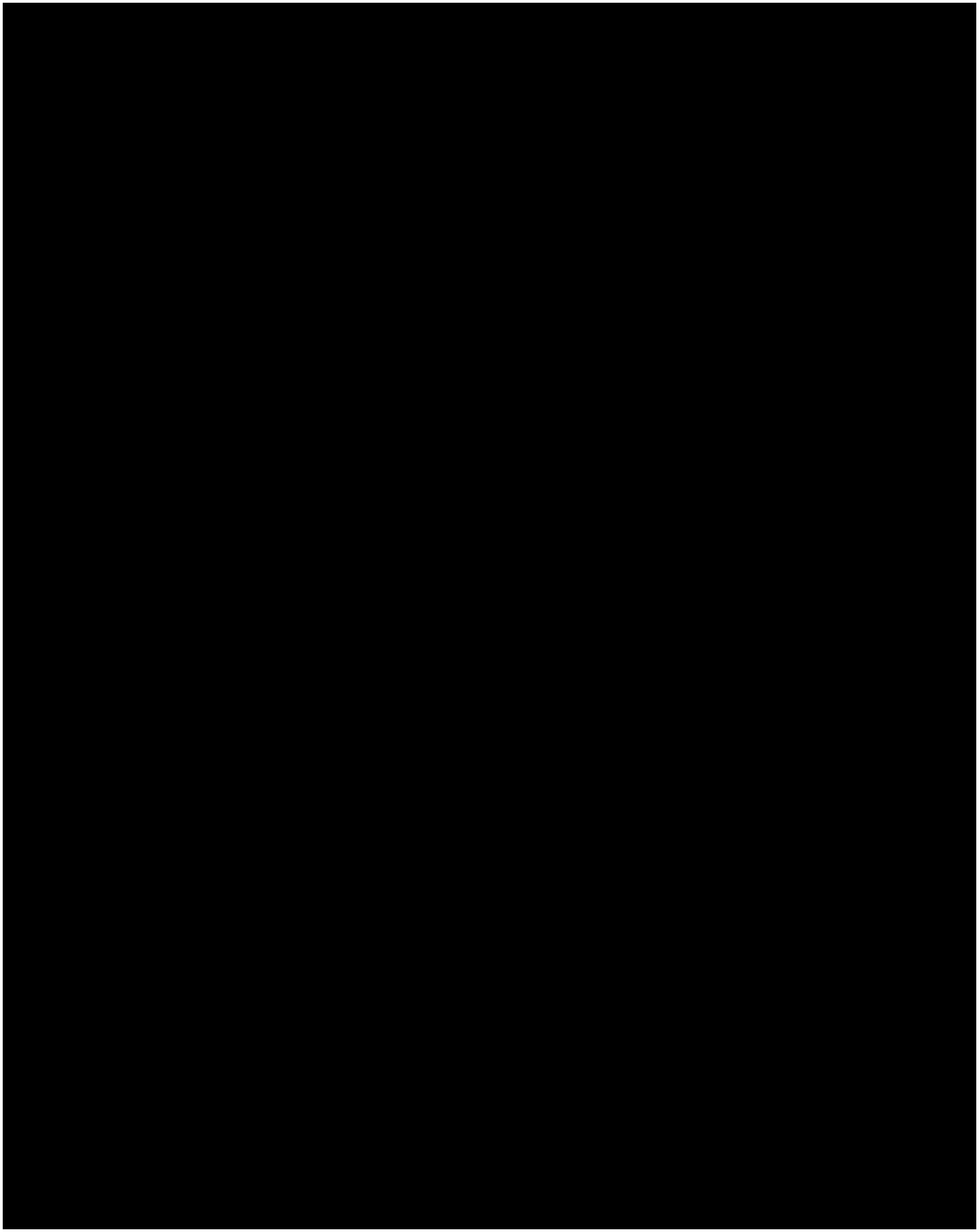

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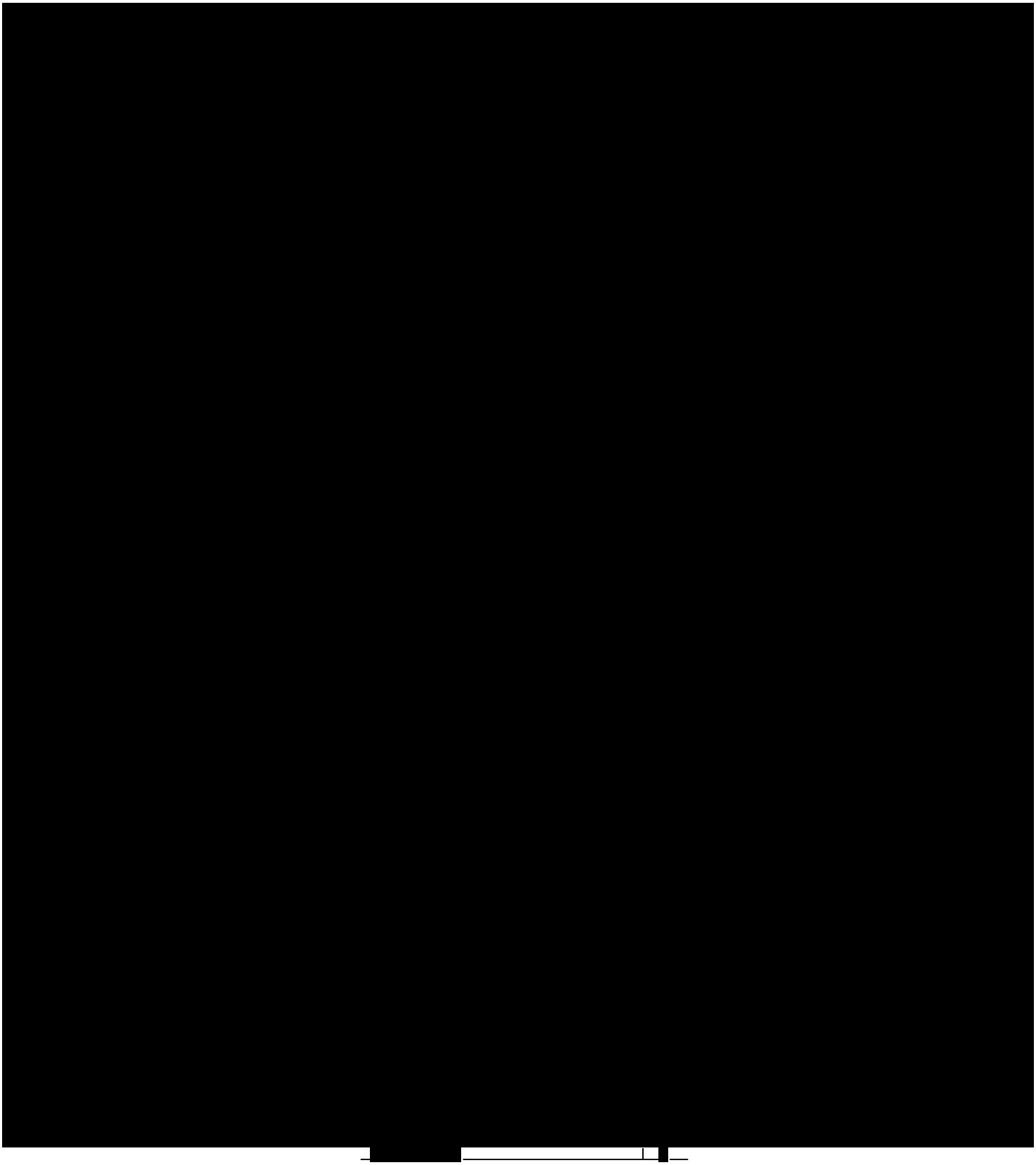

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