

STATISTICAL ANALYSIS PLAN

FOR

ALCON LABORATORIES, INC.  
6201 SOUTH FREEWAY  
FORT WORTH, TX 76134-2099

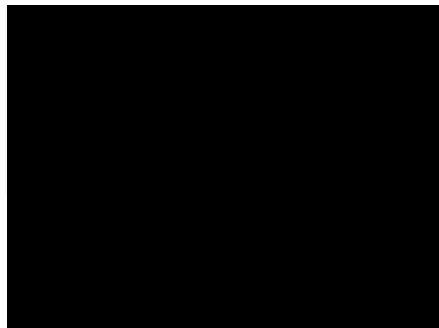
**An Observational Multicenter Clinical Study to Assess the Long-term Safety of the TRANSCEND CYPASS MICRO-STENT Glaucoma Implant in Patients with Primary Open Angle Glaucoma who have Completed Participation in the COMPASS Trial (TMI-09-01)**

**The COMPASS Trial Extension (COMPASS-XT)**

**Protocol TMI-09-01-E / NCT02700984**

Date: 18 February 2018

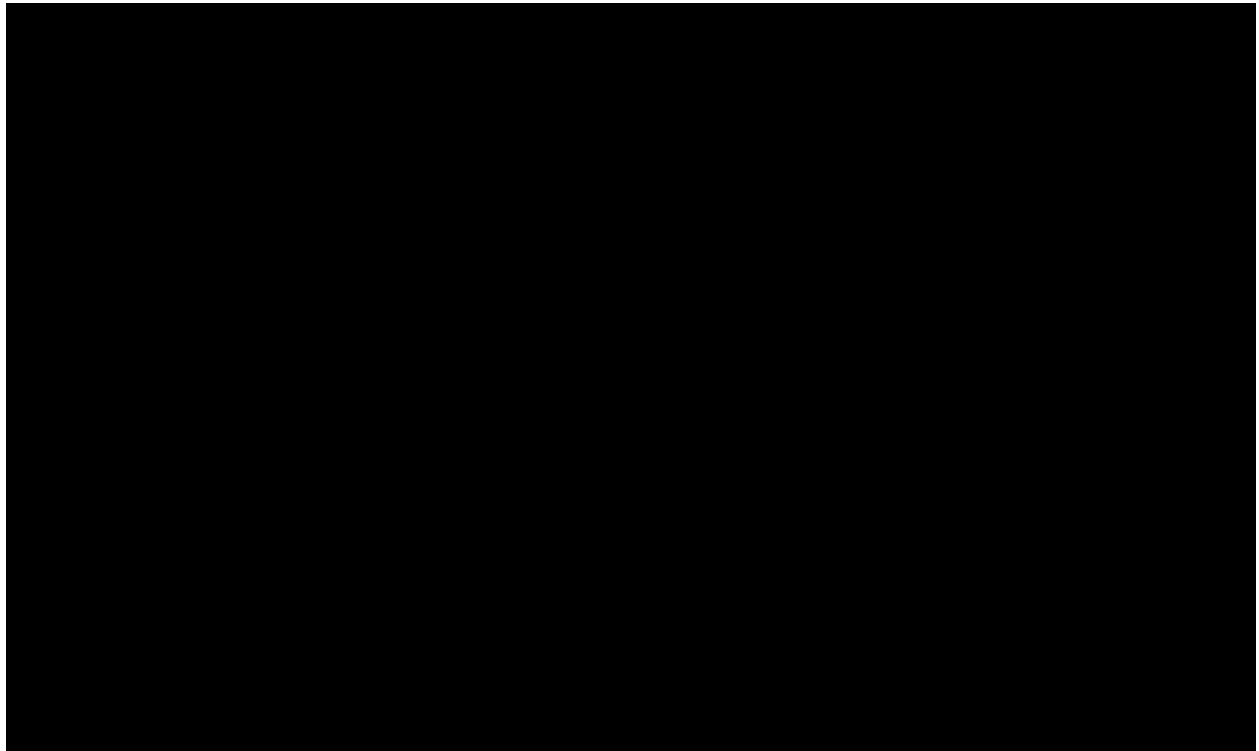
Version Number: 3.0

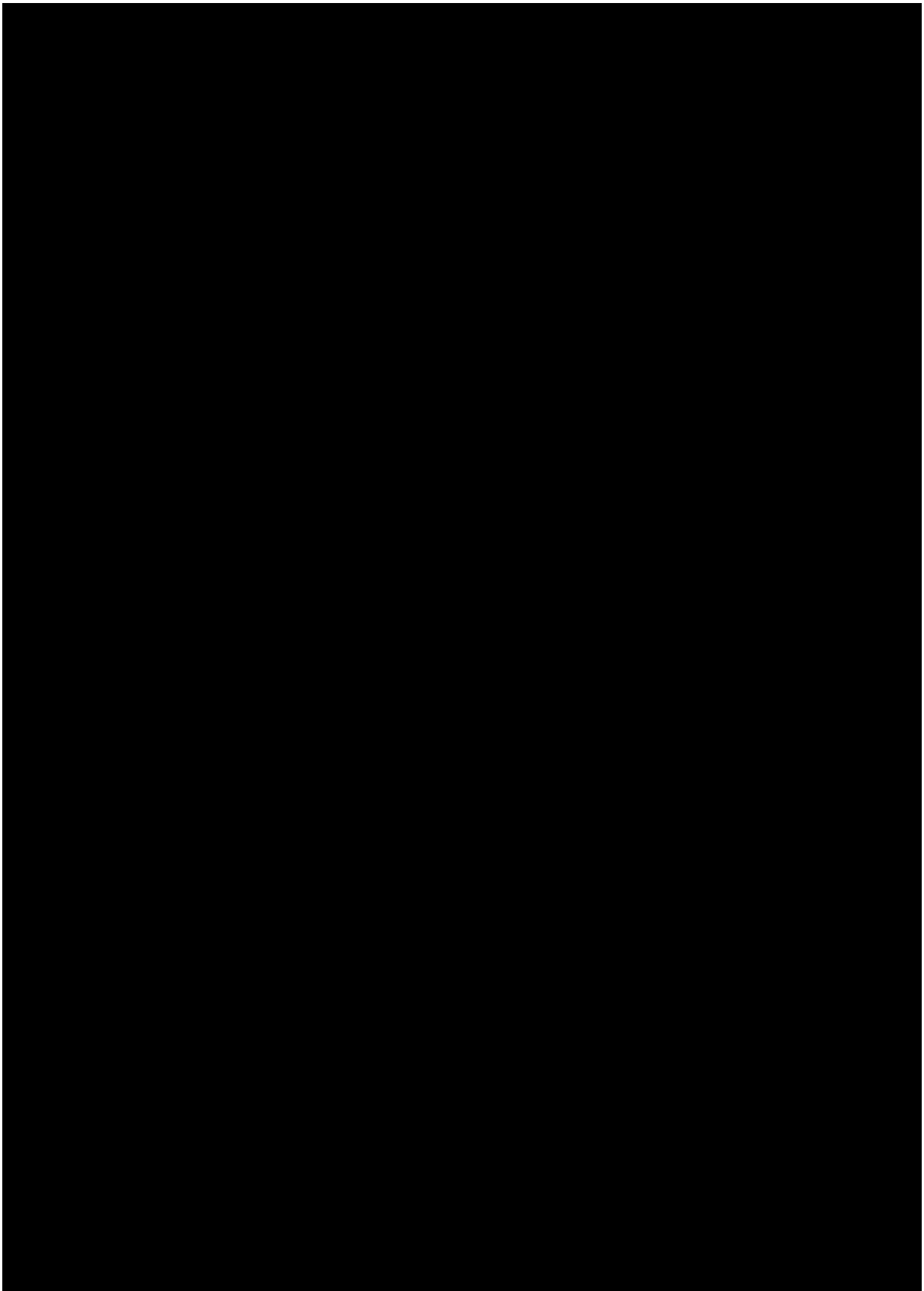


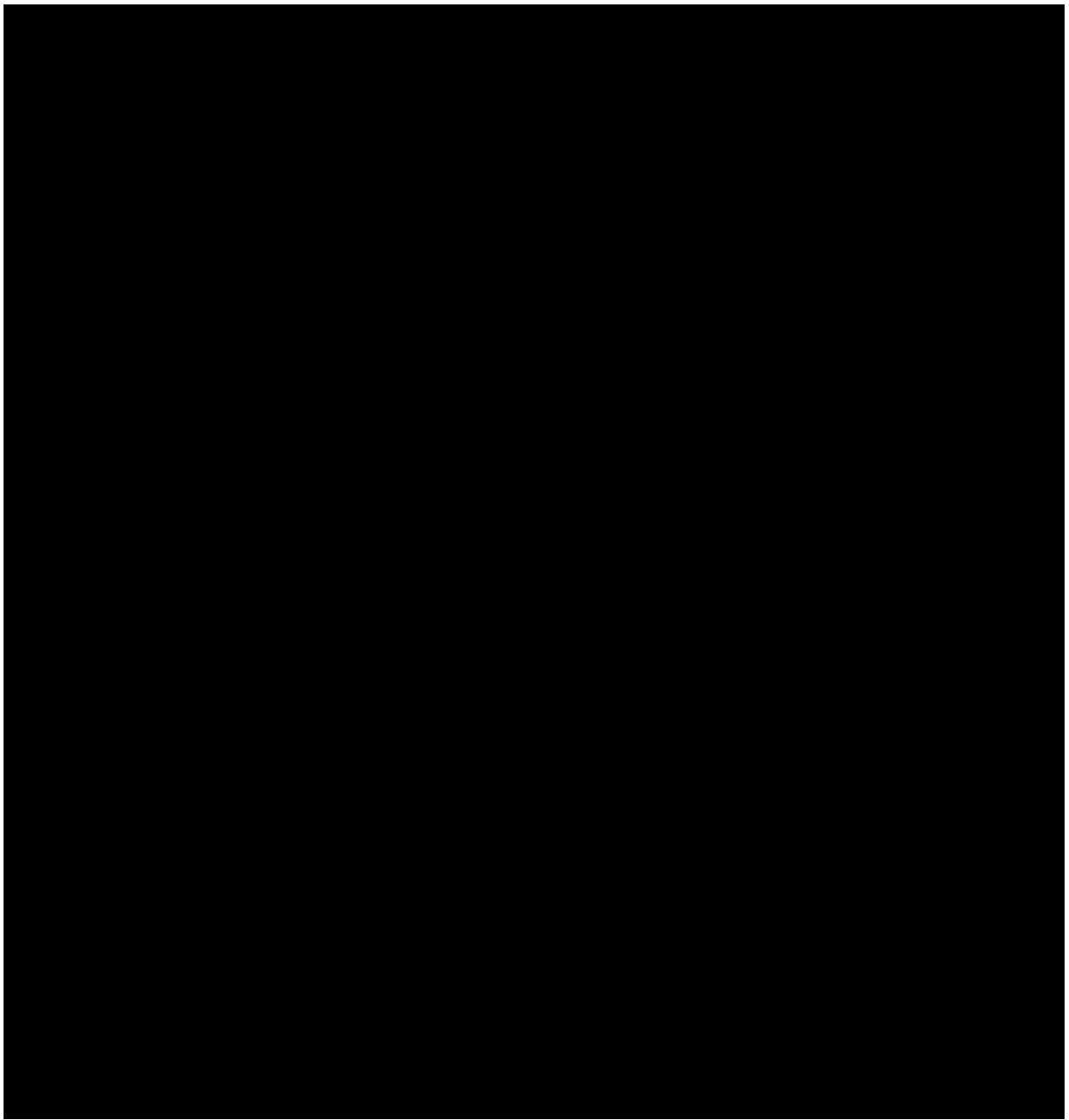
# Statistical Analysis Plan COMPASS-XT

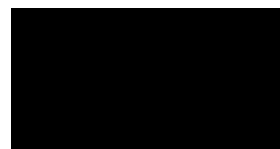
## Table of Contents

<b>1. STUDY DESIGN &amp; OUTCOMES .....</b>	<b>6</b>
<b>2. ASSESSMENT SCHEDULE.....</b>	<b>7</b>
<b>3. ANALYSIS POPULATION .....</b>	<b>7</b>
<b>4. GENERAL STATISTICAL CONSIDERATIONS .....</b>	<b>7</b>
4.1 Subject Accountability .....	8
4.2 Demographic and Baseline Characteristics.....	8
<b>5. STATISTICAL METHODS.....</b>	<b>8</b>
5.1 Sight Threatening Ocular Adverse Events .....	8
5.2 Ocular Adverse Events.....	9
5.3 Central Corneal Thickness (CCT) .....	9
5.4 Central Corneal Endothelial Cell Density .....	10
5.5 Best Corrected Visual Acuity .....	10
5.6 Slit Lamp, Gonioscopy and Fundus Exam Findings .....	10
5.7 Visual Field Loss Mean Deviation .....	11
5.8 Intraocular Pressure .....	11
<b>6. METHODS FOR HANDLING MISSING DATA.....</b>	<b>12</b>



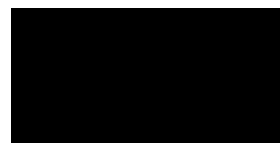






## GLOSSARY

AE	Adverse Event
BCVA	Best Corrected Visual Acuity
CCT	Central Corneal Thickness
ECD	Endothelial Cell Density
ECL	Endothelial Cell Loss
IOP	Intraocular Pressure
MD	Mean Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TLF	Tables, Listings, Figures
TLR	Total Letters Read



## 1. STUDY DESIGN & OUTCOMES

Study Protocol TMI-09-01-E (the COMPASS Trial Extension) is a multicenter observational study. Up to 480 subjects randomized in the Study Protocol TMI-09-01 (the COMPASS Trial) at up to 24 investigational sites may participate. Study data through 5 years post-randomization in the COMPASS Trial will be collected for subjects who consent to participate.

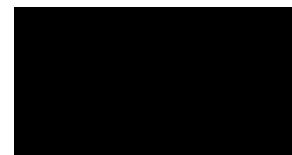
This statistical analysis plan (SAP) presents the details of the statistical methodologies for the analysis of data for Study Protocol TMI-09-01-E (Version G, dated 26 October 2016). The purpose of this research study is to evaluate the long-term safety of the CyPass Micro-Stent in subjects who completed the COMPASS Trial.

### Primary Outcome

- Rate of occurrence of sight-threatening adverse events (AE)

### Secondary Outcomes – Safety

- Best Corrected Visual Acuity (BCVA)
- Rate of occurrence of ocular adverse events (AE)
- Slit lamp, gonioscopy and fundus findings
- Visual field loss mean deviation (MD)
- Central corneal thickness (CCT)
- Central corneal endothelial cell density (ECD)
- Rate of occurrence of CyPass movement, defined as a change by at least 1 in the number of CyPass rings visible (e.g., from 0 rings to 1 ring or from 3 rings to 2 rings) that does not result in clinical sequelae (e.g., secondary surgical intervention to modify device position, corneal endothelial touch by device, corneal edema leading to loss of BCVA > 2 lines at the last postoperative visit in comparison with preoperative BCVA, progressive corneal endothelial cell loss (ECL), erosion of device through sclera, or device obstruction requiring secondary surgical intervention), and that is not attributable to:
  - variations in gonioscopic viewing angle or illumination,
  - changes in angle anatomy due to concomitant findings such as resolution of hyphema,
  - changes in anterior chamber depth, or
  - development of focal peripheral anterior synechiae.



## **Secondary Outcomes – Effectiveness**

- Mean change in intraocular pressure (IOP)
- Proportion of subjects who are not using ocular hypotensive medication with  $\geq 20\%$  reduction in IOP from baseline in the COMPASS Trial
- Proportion of subjects who are not using ocular hypotensive medication with IOP  $\geq 6$  mmHg and  $\leq 18$  mmHg

## **2. ASSESSMENT SCHEDULE**

Subjects are to be evaluated at 36 months ( $1095 \pm 90$  days), 48 months ( $1460 \pm 90$  days) and 60 months ( $1825 \pm 90$  days) post-randomization in study protocol TMI-09-01. Hereafter, the term “XT scheduled follow-up visits” refers to the 36, 48, and 60-month scheduled visits. The examinations required at each scheduled study visit are outlined and summarized in Appendix 1 (Schedule of Events and Procedures) and a description of examination methodology is provided in Appendix 2 (Examination Procedures, Tests, Equipment and Techniques) of the protocol.

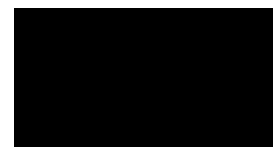
“Baseline” is defined as the Baseline Visit of the COMPASS Trial, unless noted otherwise. Analysis of other visits from the COMPASS Trial (from the 3, 6, 12, and 24-month visits) will include only subjects who enrolled (satisfied study eligibility criteria and signed the informed consent form) in COMPASS-XT.

## **3. ANALYSIS POPULATION**

The analysis population will consist of up to 480 eyes of 480 subjects who completed enrolled in COMPASS-XT

## **4. GENERAL STATISTICAL CONSIDERATIONS**

Unless noted otherwise, continuous variables will be characterized with the number of non-missing values, means, standard deviations, medians, minimums, and maximums while categorical variables will be characterized by frequencies (numerators), denominators, and percentages. There are no hypotheses tested in this study. All confidence intervals will be 95% confidence intervals and will be two sided. Confidence intervals for continuous variables will be based on the t distribution. Confidence intervals for categorical variables be calculated using the exact Clopper-Pearson 95% binomial formula. If there is a special case for a one sided interval, then that interval will be a 97.5% one-sided confidence interval.



All statistical analyses will be conducted using SAS® software, Version 9.4 of the SAS System for Windows or higher.

#### **4.1 Subject Accountability**

Subject accountability by study visit will be summarized based on ANSI Z80.27-2014, modified as necessary for an observational study. A listing of subjects who are screened and considered to be ineligible for study participation will be presented, based on data to be provided by the Alcon monitoring group. This listing will include the reason for subject ineligibility.

In addition, a summary table of protocol deviations will be provided.

#### **4.2 Demographic and Baseline Characteristics**

Demographic and baseline characteristics from the COMPASS Trial for the subjects who are enrolled into this study will be tabulated by treatment group and all subjects (i.e., the total). Age (in years) at consent of the COMPASS Trial will be analyzed as a continuous variable and by the following categories: <60 years, 60 to <70 years, 70 to <80 years, and ≥80 years. Gender, race, ethnicity, and study eye will be analyzed as categorical variables.

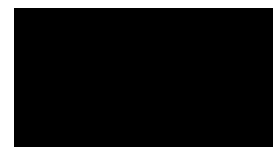
### **5. STATISTICAL METHODS**

The objective of this study is to collect long-term safety data regarding the CyPass Micro-Stent in subjects who completed the COMPASS Trial. The primary outcome is the occurrence of sight threatening AEs. Other study outcomes include the incidence of ocular AEs in the study eye, BCVA, slit lamp, gonioscopy and fundus examination findings, central corneal thickness, central corneal ECD, CyPass movement, and intraocular pressure.

#### **5.1 Sight Threatening Ocular Adverse Events**

Sight-threatening AEs include, but are not limited to, BCVA loss of ≥ 3 lines, endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment and aqueous misdirection. A non-parametric time to event Kaplan-Meier (K-M) analysis for the sight-threatening AE rate at 5 years will be performed, stratified by treatment group. This method accounts for all information that discontinued subjects contribute





to the rate of the primary safety event up to the point at which that subject discontinues (i.e., is censored). The cumulative Kaplan-Meier probability and associated and 95% confidence intervals that a subject experienced a sight-threatening AE will be provided for each treatment group at 5 years.

To aid in the interpretation of the results, the annualized rates (percentages) for each year and over the 5-year period will also be calculated using the LIFETEST procedure. There will be no covariate adjustments in the model as the only factor will be treatment group.

## **5.2 Ocular Adverse Events**

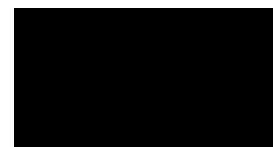
The number of subjects reporting at least one AE of a given type specified in the protocol will be summarized. Ocular AEs not specified in the protocol (i.e., recorded as “other” and written in rather than selected from the list) that occur during the study will coded by MedDRA preferred term and summarized. Each AE will be summarized by incidence (numerator), denominator, percentage and 95% confidence interval. The summarization will be conducted using the FREQ procedure and the count, percent and exact Clopper-Pearson 95% binomial confidence intervals will be reported. Protocol-specified and other AEs will also be provided in separate listings.

## **5.3 Central Corneal Thickness (CCT)**

CCT data collected at baseline, 12 month and 24 month postoperative visits in Protocol TMI-09-01 (the COMPASS trial) and collected in this protocol will be summarized with N, mean, standard deviation, minima, median, and maxima. A 95% confidence interval will be provided for the actual change and percentage change from baseline. Change between 2 consecutive visits will also be summarized.

For the tabulation of actual change and percent change, there will be two sets of tables. The first will use the preoperative CCT from the COMPASS Trial as a baseline value. The second will use the 24-month visit CCT from the COMPASS Trial as the baseline value.

All calculations will be performed using the MEANS procedure and the results will be reported for each of the visits and treatment groups. Descriptive statistics for the changes between consecutive visits will also be calculated using the MEANS procedure.



#### **5.4 Central Corneal Endothelial Cell Density**

Endothelial cell density (ECD) data collected at baseline, 3 month, 6 month, 12 month and 24 month postoperative visits in Protocol TMI-09-01 (the COMPASS trial) and at each XT scheduled follow-up visit will be summarized with N, mean, standard deviation, minima, median, and maxima for each treatment arm. A 95% confidence interval will be provided for the change and percentage change in ECD from baseline. The change between 2 consecutive visits will also be summarized.

All descriptive statistic calculations will be made from the MEANS procedure and the results reported for each of the visits and treatment groups. Descriptive statistics for the changes between consecutive visits will also be calculated using the MEANS procedure.

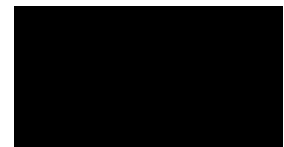
#### **5.5 Best Corrected Visual Acuity**

Best Corrected Visual Acuity (BCVA) data collected at the subject's baseline, 12 month and 24 month postoperative visits in Protocol TMI-09-01 and at each XT scheduled follow-up visit will be summarized as counts (numerators), denominators, and percentages with 95% confidence intervals for subjects who have BCVA 20/20 or better, 20/25 or better, 20/32 or better, 20/40 or better and worse than 20/40. Because BCVA was collected in the COMPASS trial as TLR, TLR values will be converted to Snellen and logMAR Visual Acuity using a conversion table to be approved by Alcon and included in an appendix to the TLFs. Also, shift tables from baseline will be presented with counts (numerators), denominators, percentages, and 95% confidence intervals for Snellen Visual Acuity.

The summarization will be performed via the FREQ procedure and the count, percent, and exact Clopper-Pearson 95% binomial confidence intervals will be reported.

#### **5.6 Slit Lamp, Gonioscopy and Fundus Exam Findings**

Slit lamp, gonioscopy, and fundus examination findings at month 36, 48, and 60 will be tabulated such that the number (numerator), denominator, and percentage of subjects in each category and 95% confidence intervals for the percentages will be summarized by each XT scheduled follow-up visit. The summarization will be performed via the FREQ procedure and the count, percent, and exact Clopper-Pearson 95% binomial confidence intervals will be reported.



In addition, a listing of study subjects with one or more Cypass rings visible at each visit will also be provided.

## **5.7 Visual Field Loss Mean Deviation**

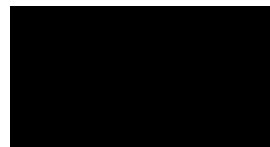
The visual field mean deviation (MD) testing data collected at baseline, 3 month, 6 month, 12 month and 24 month postoperative visits in Protocol TMI-09-01 and in this protocol will be summarized with N, mean, standard deviation, minima, median, and maxima. A 95% confidence interval will be provided for the change and percentage change from baseline.

All calculations will be made from PROC MEANS and the results reported for each of the visits and treatment groups. For the tabulation of change and percent change, there will be two sets of tables, the first will use the baseline from the COMPASS Trial, and the second will use the 24 month visit value from the COMPASS Trial.

## **5.8 Intraocular Pressure**

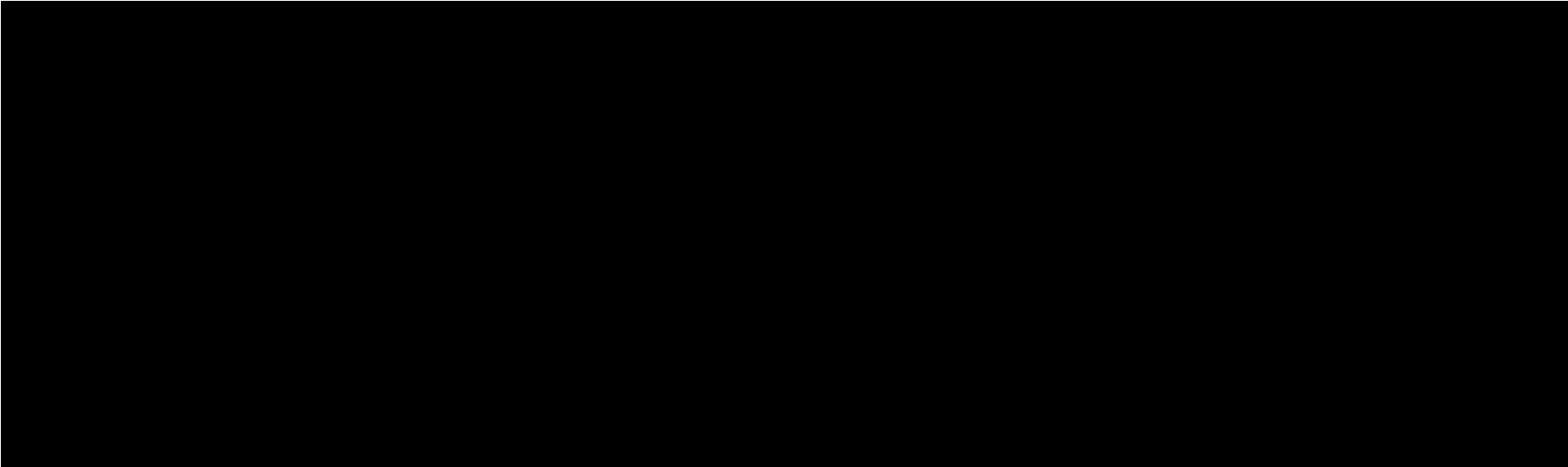
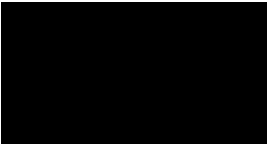
The N, mean, standard deviation, minima, median, and maxima for change in Intraocular Pressure (IOP) from Protocol TMI-09-01 baseline will be obtained by treatment group using the MEANS procedure and presented for each XT scheduled study visit, along with a 95% confidence interval on the mean change.

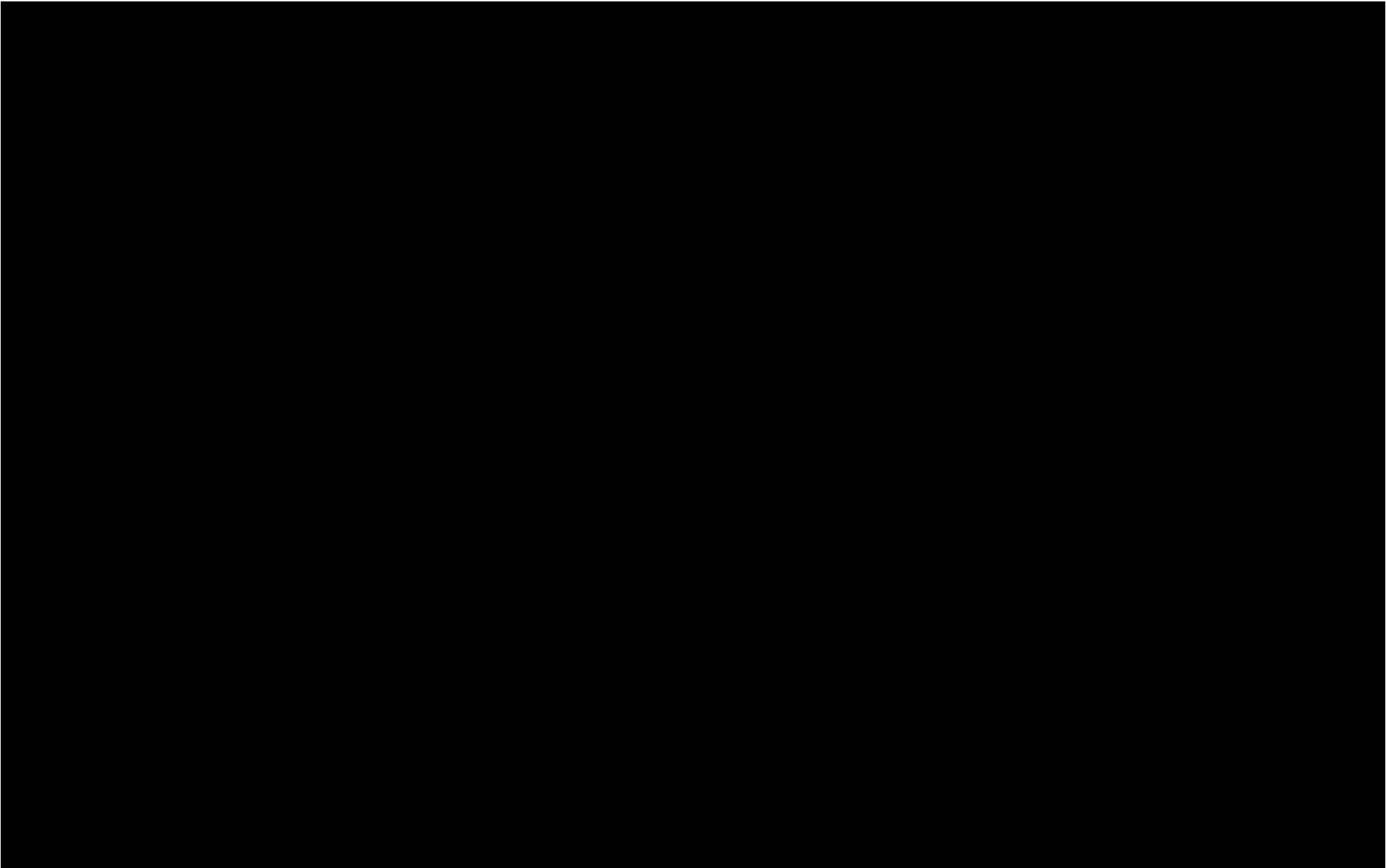
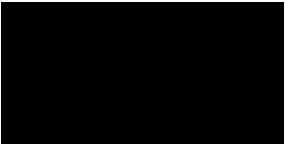
The number and proportion of subjects who are not using ocular hypotensive medication with  $\geq 20\%$  reduction in IOP from baseline in the COMPASS Trial will be summarized by treatment group using the FREQ procedure and also presented at each XT study visit, along with 95% confidence intervals. In order to interpret changes to be reported in the previously described table, the number of ocular hypotensive medications used at Protocol TMI-09-01 screening, 12 month, and 24 month visits, and at each XT scheduled visit, as well as changes from each visit from screening will be summarized by treatment group. Finally, the number and proportion of subjects who are not using ocular hypotensive medication with IOP  $\geq 6$  mmHg and  $\leq 18$  mmHg will be presented at each study visit, along with an exact Clopper-Pearson 95% confidence interval from the FREQ procedure.

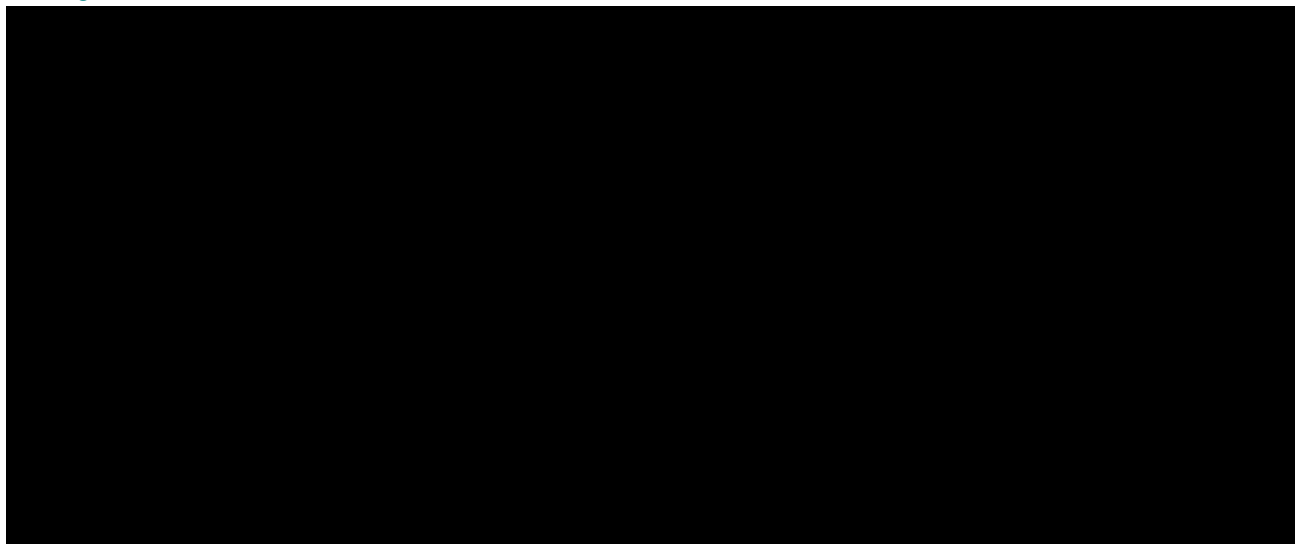
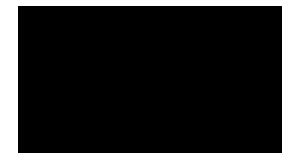


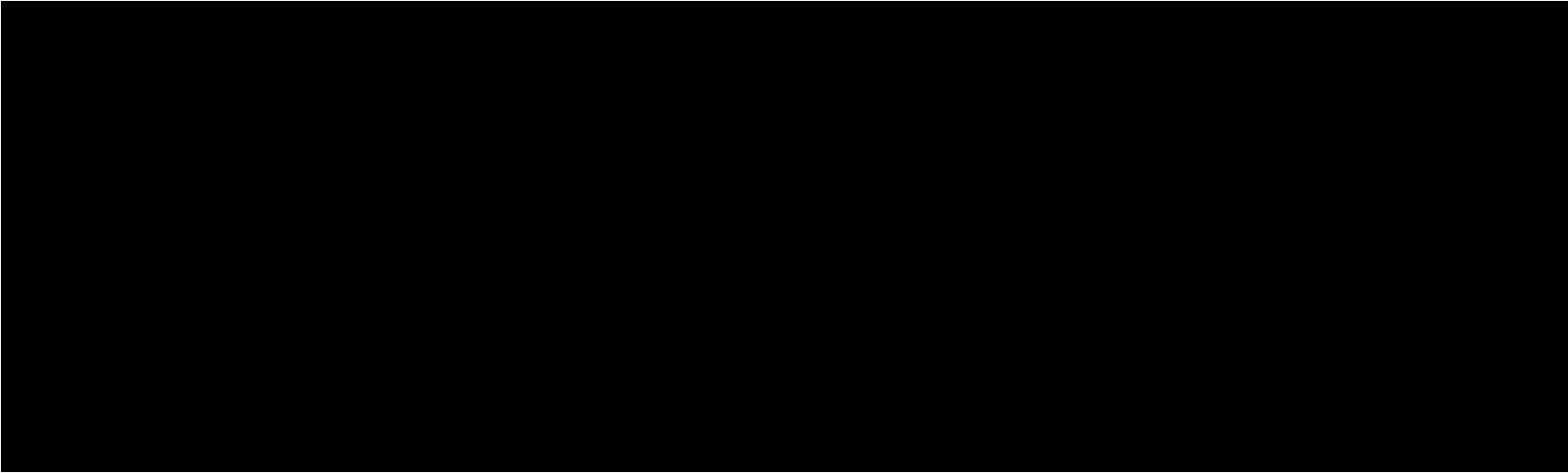
## **6. METHODS FOR HANDLING MISSING DATA**

Since this is a safety observation study, no imputations of the data will be made. All tables and figures will be generated using observed data only.

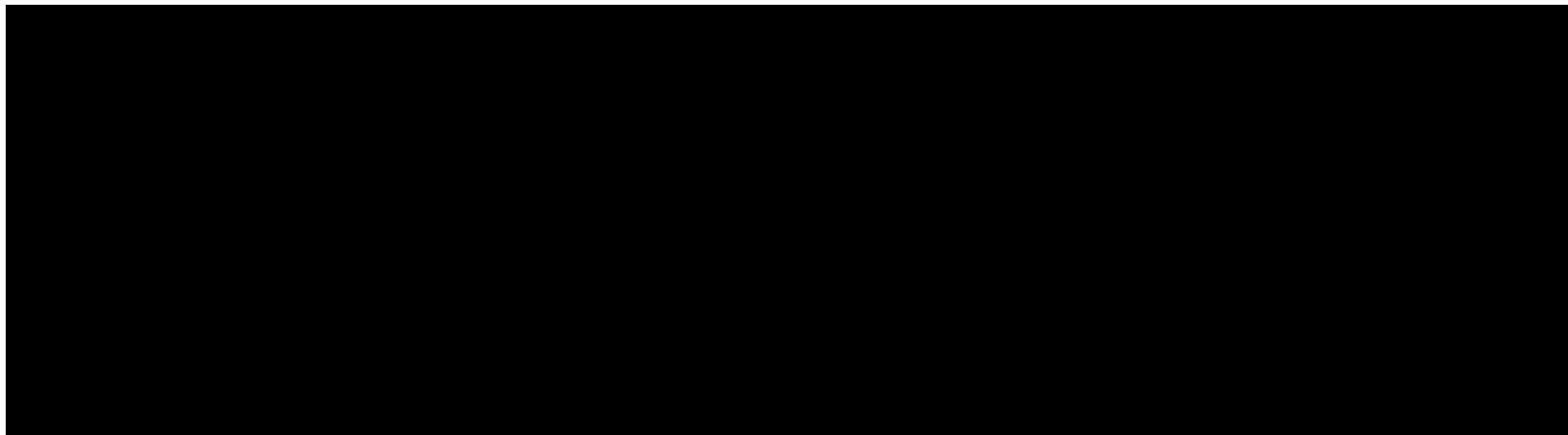
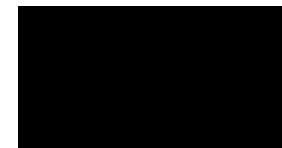


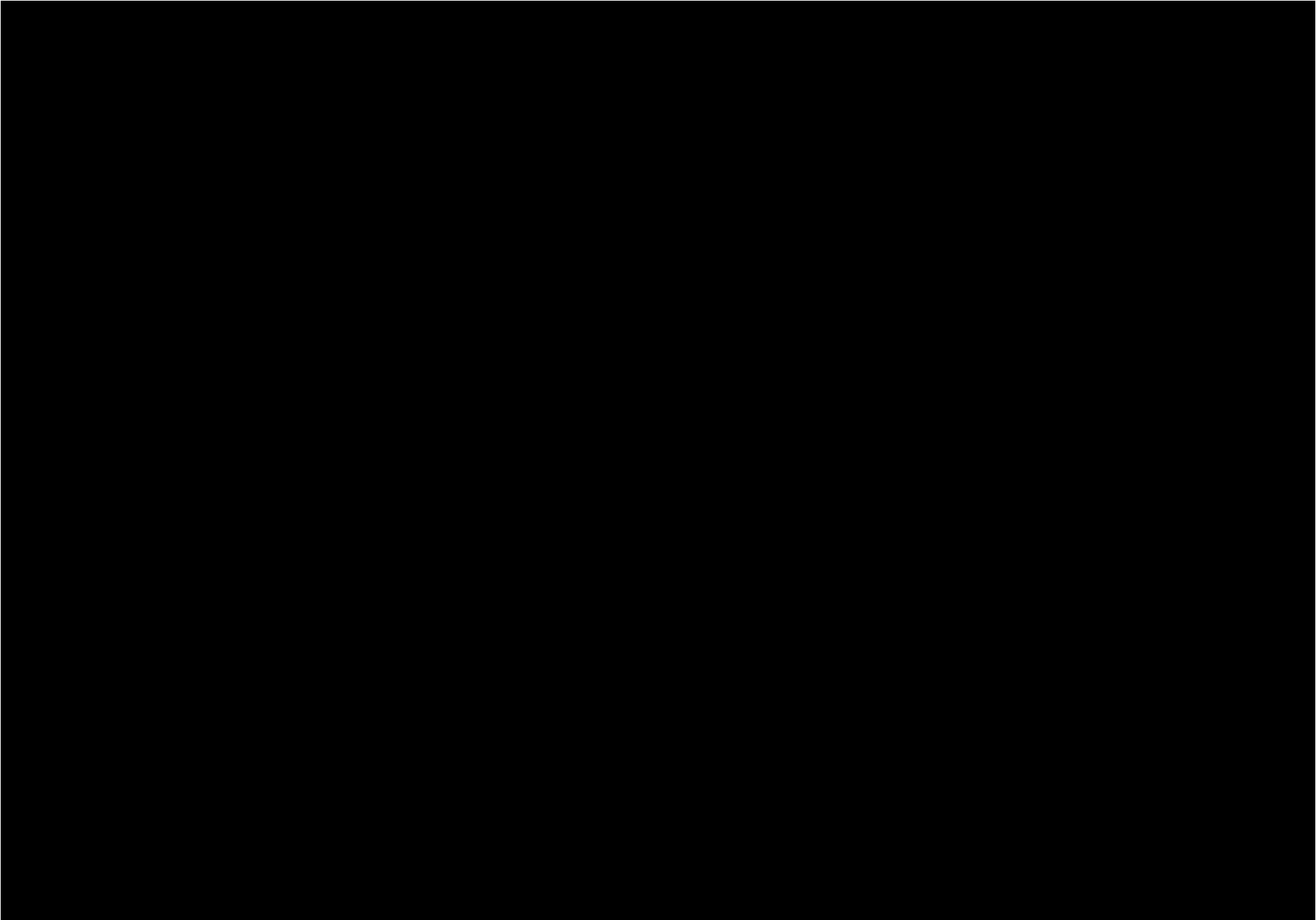




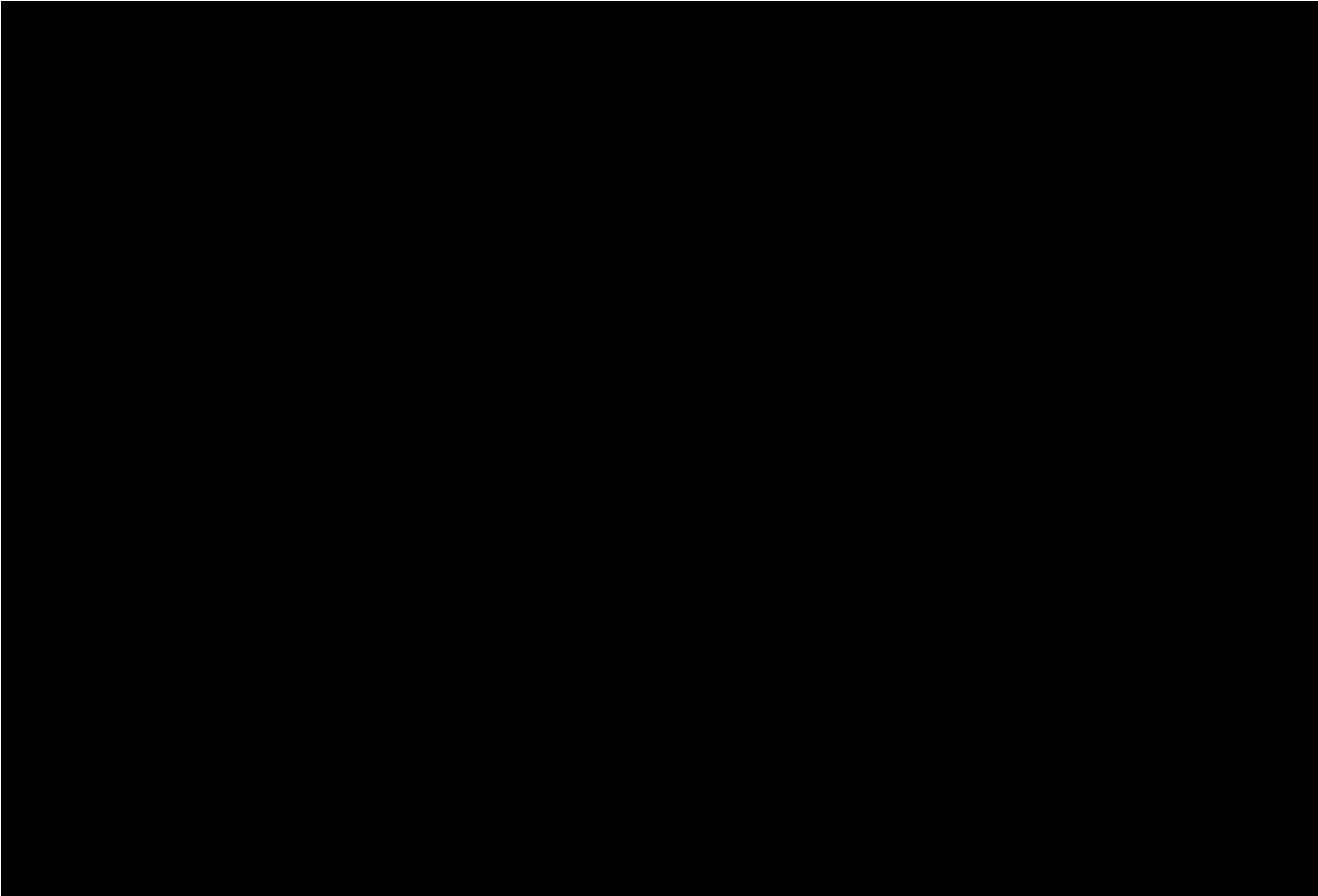
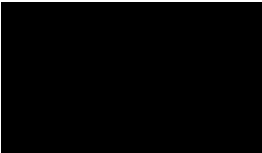


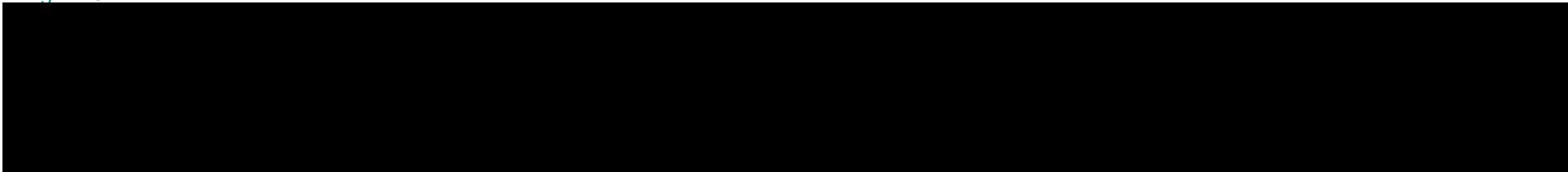


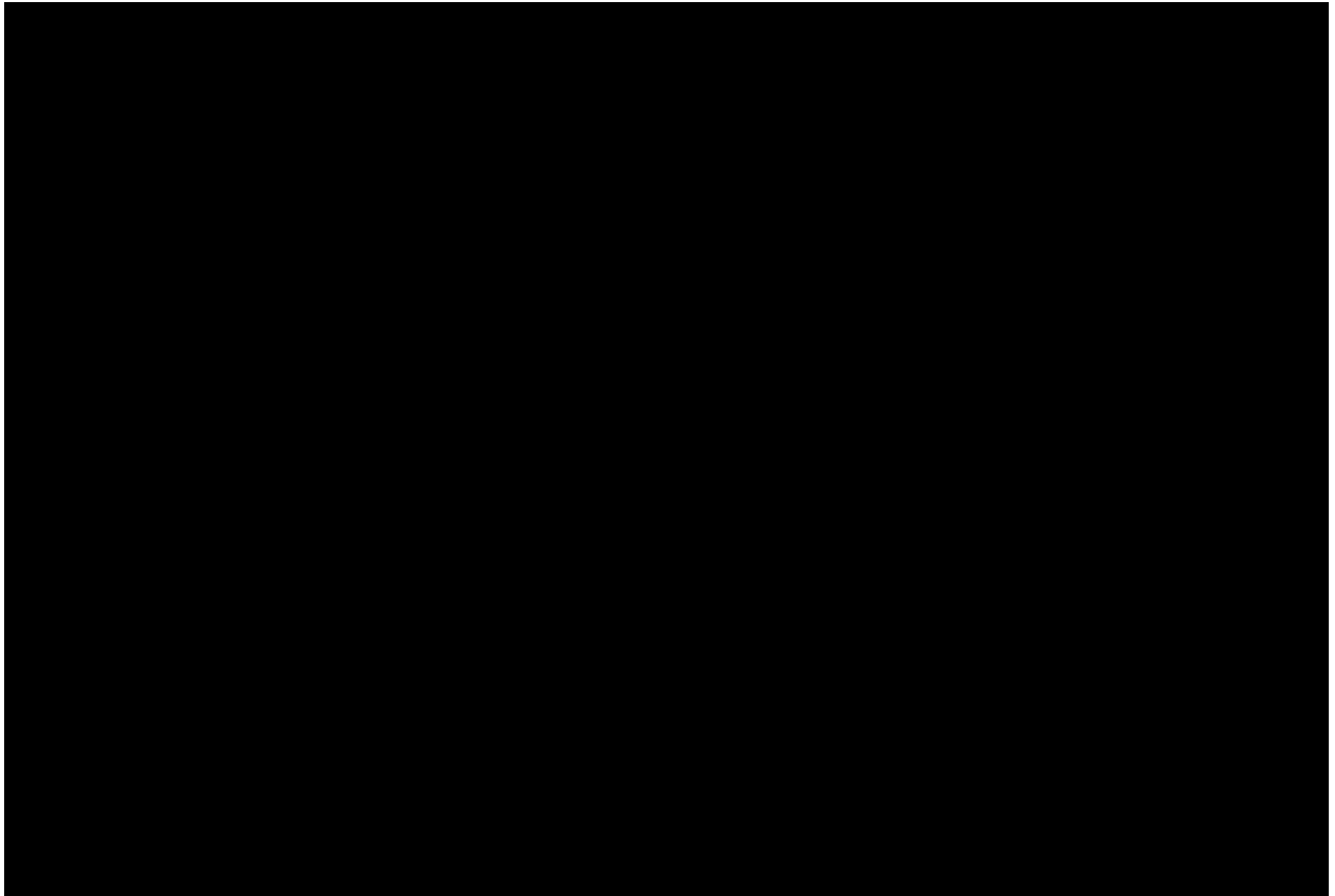




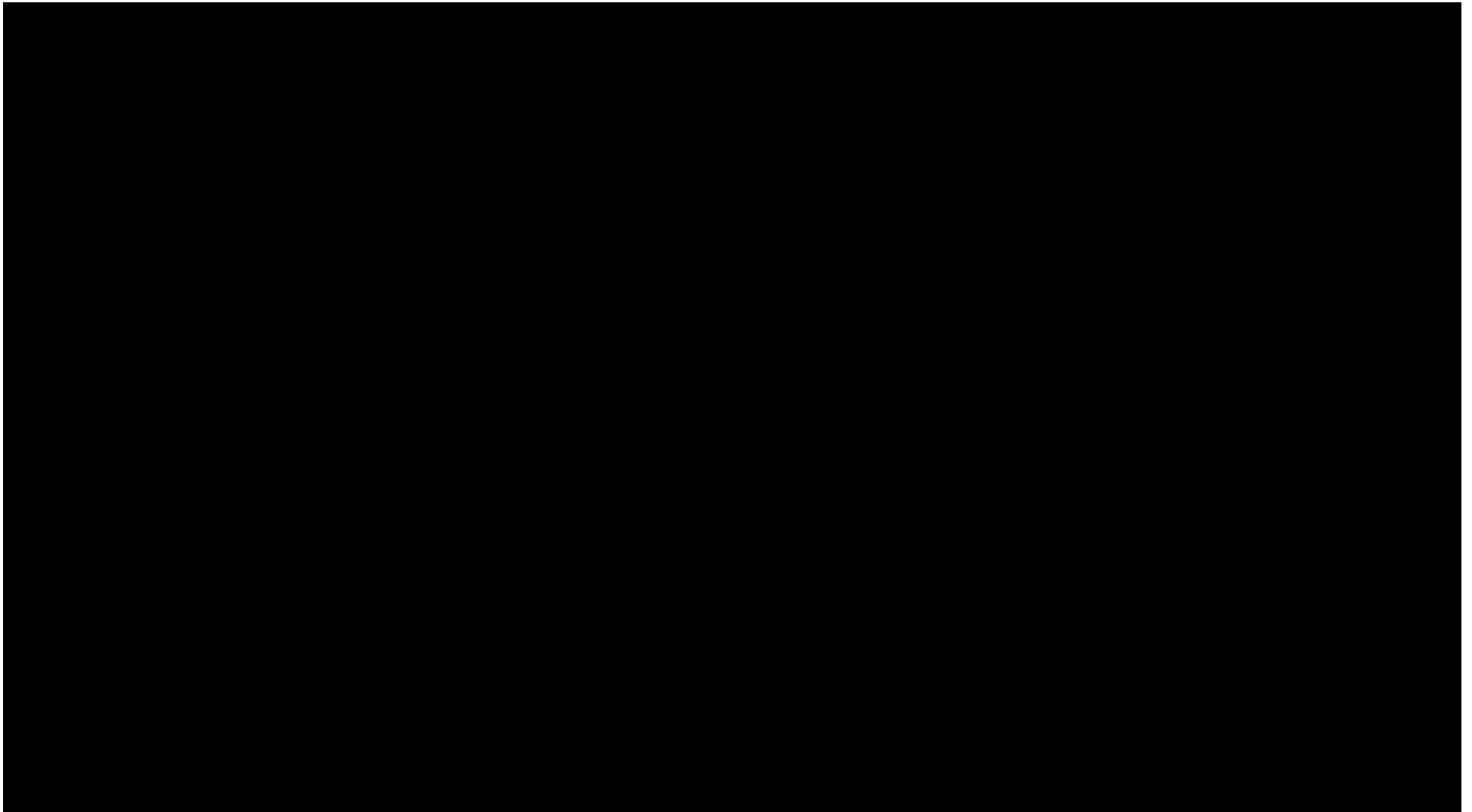




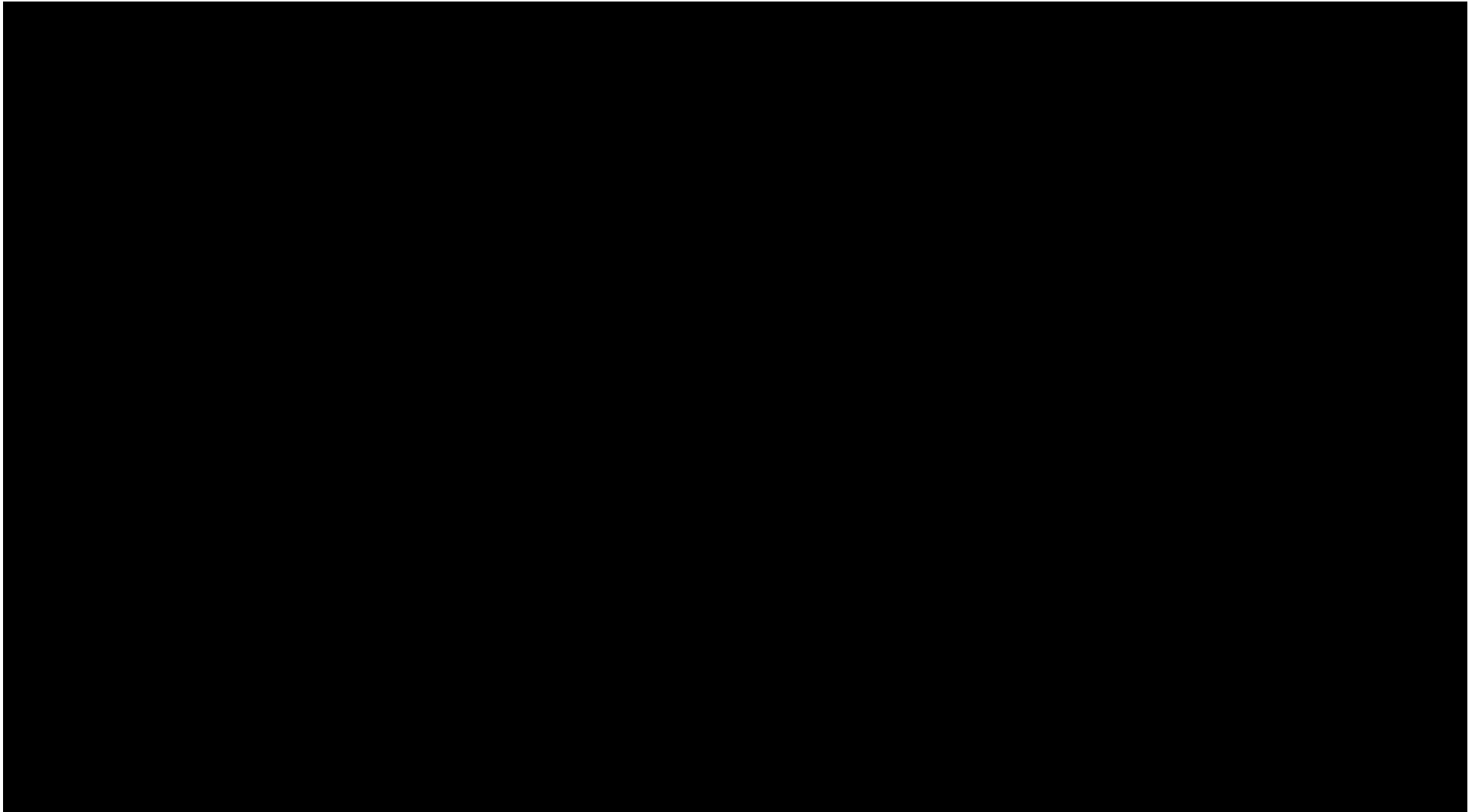


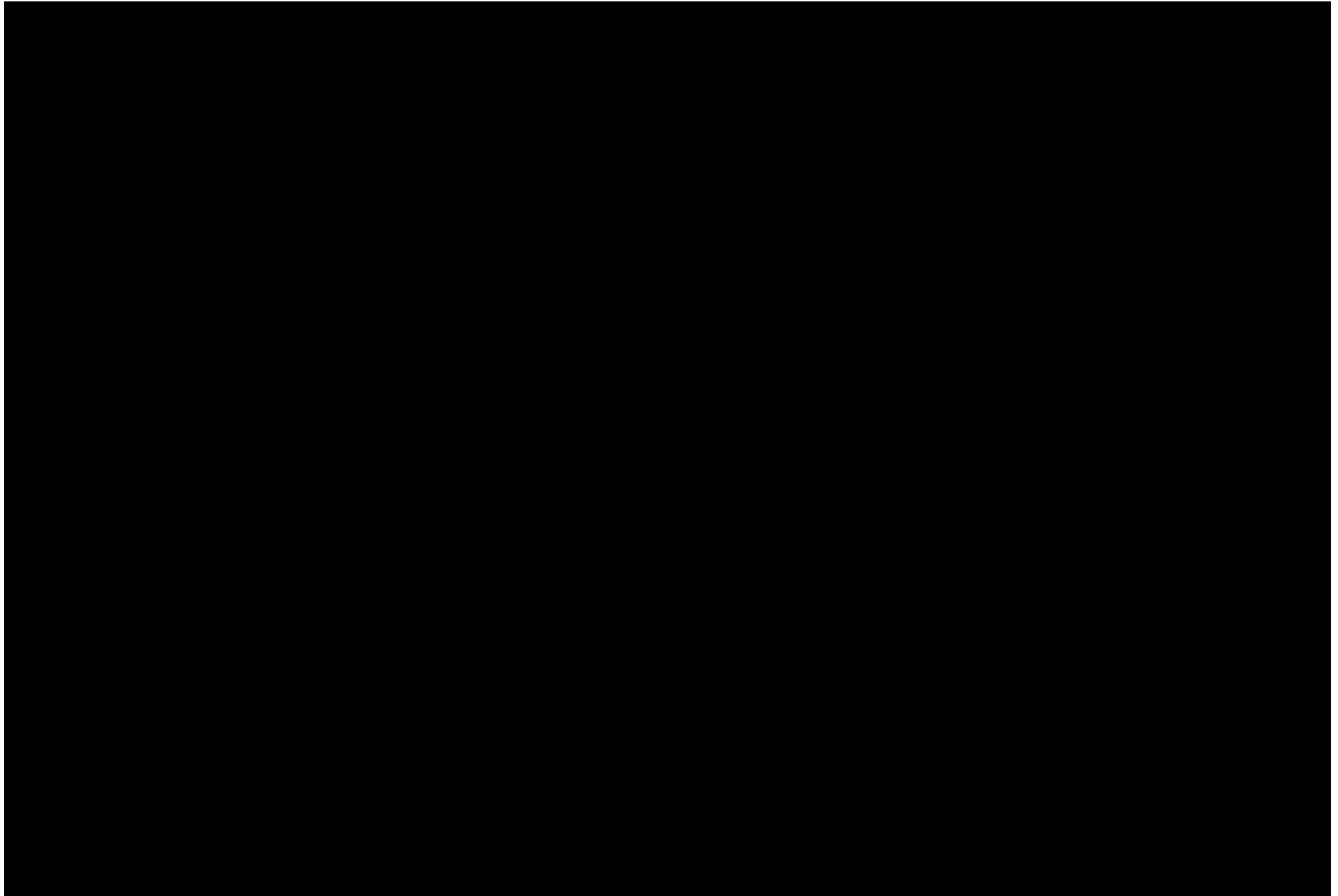


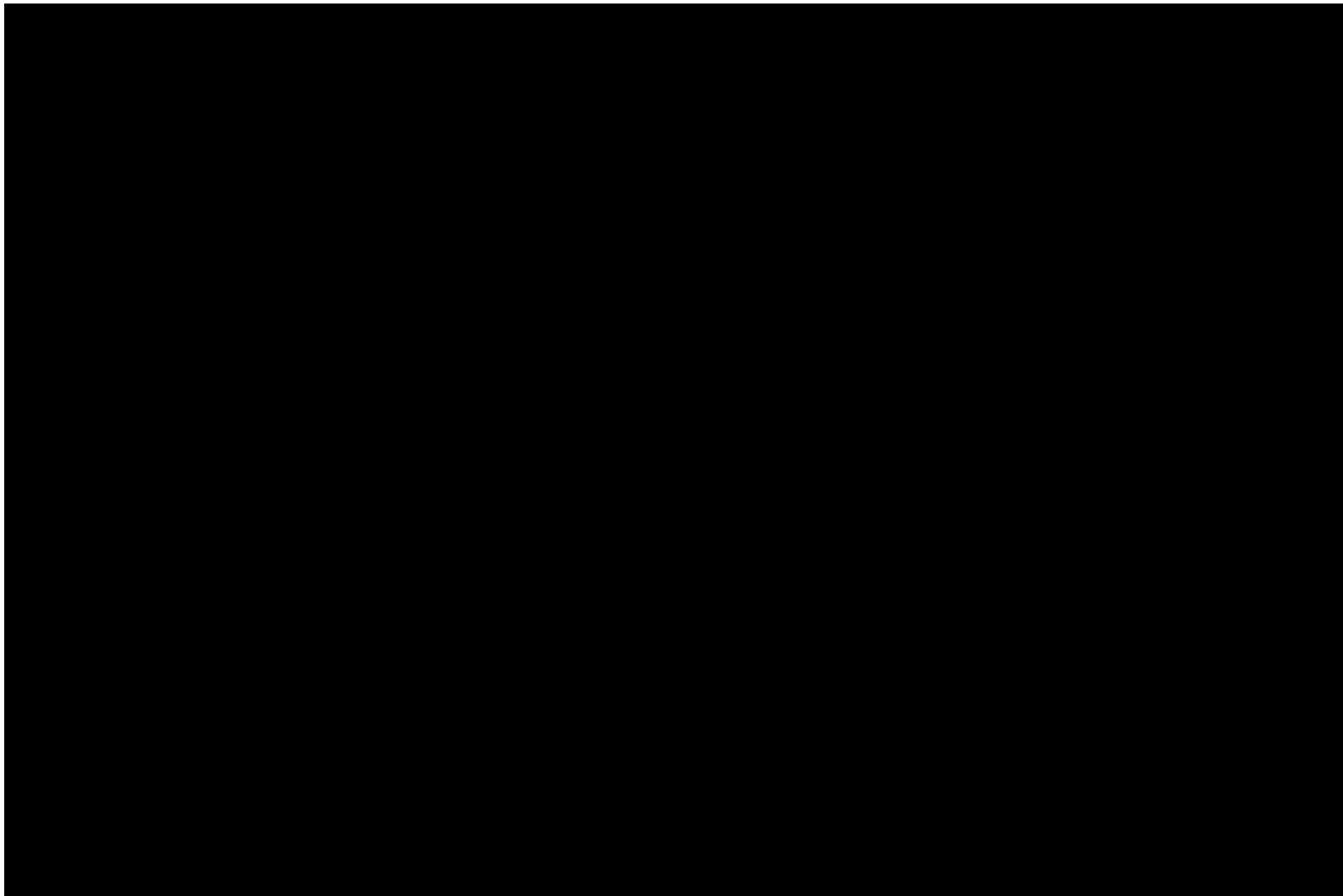
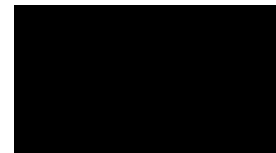


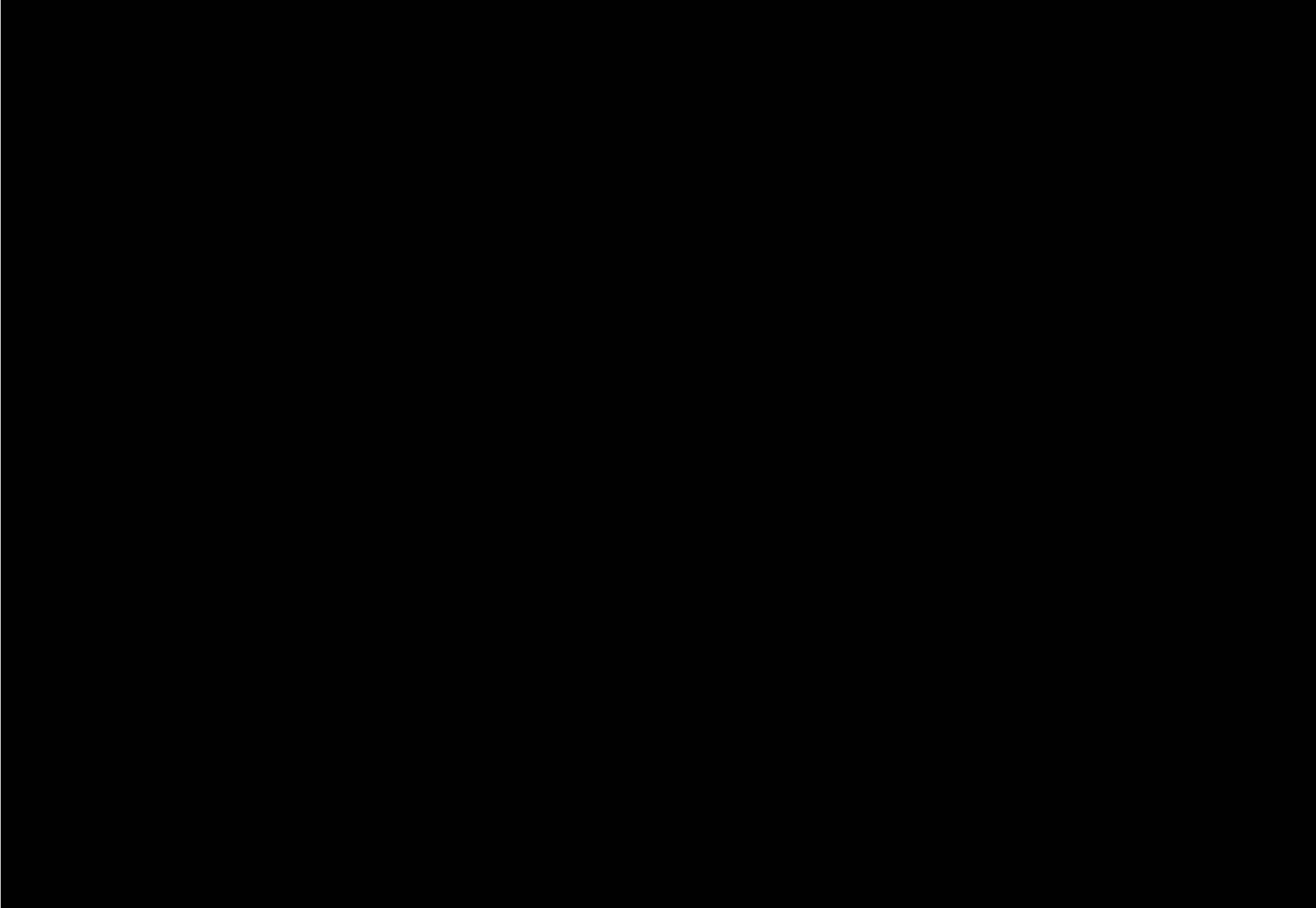
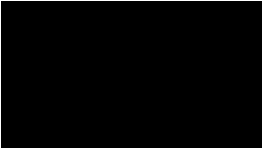


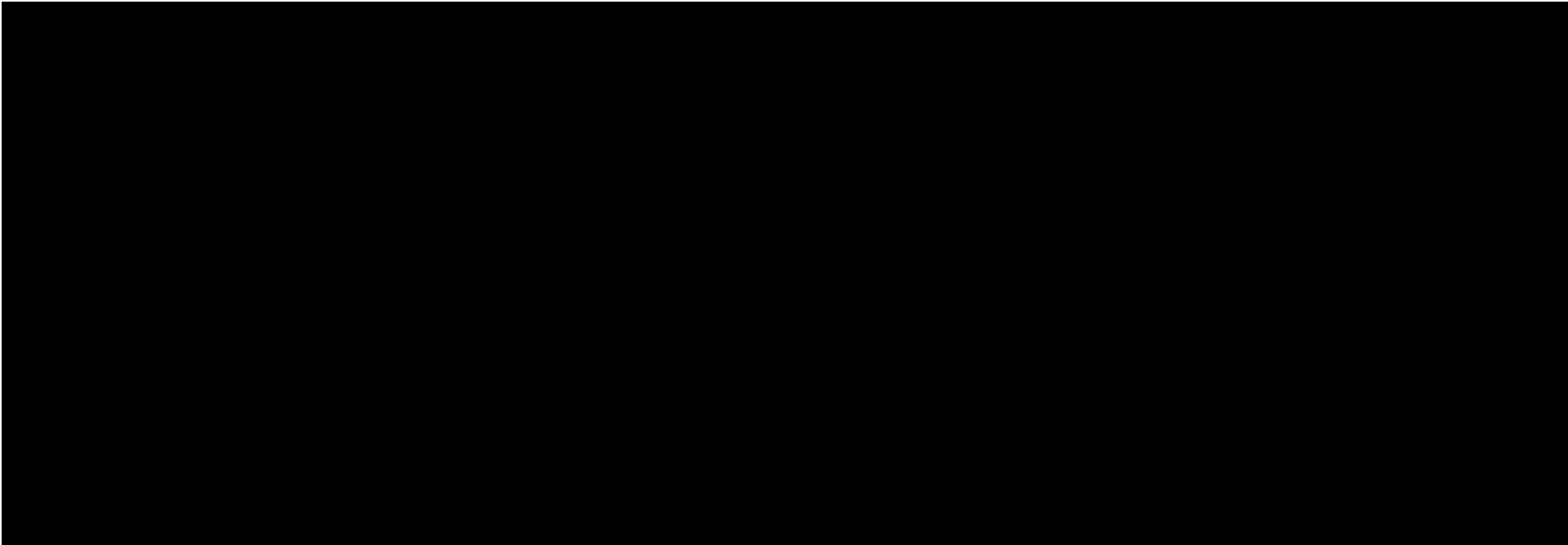
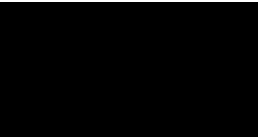


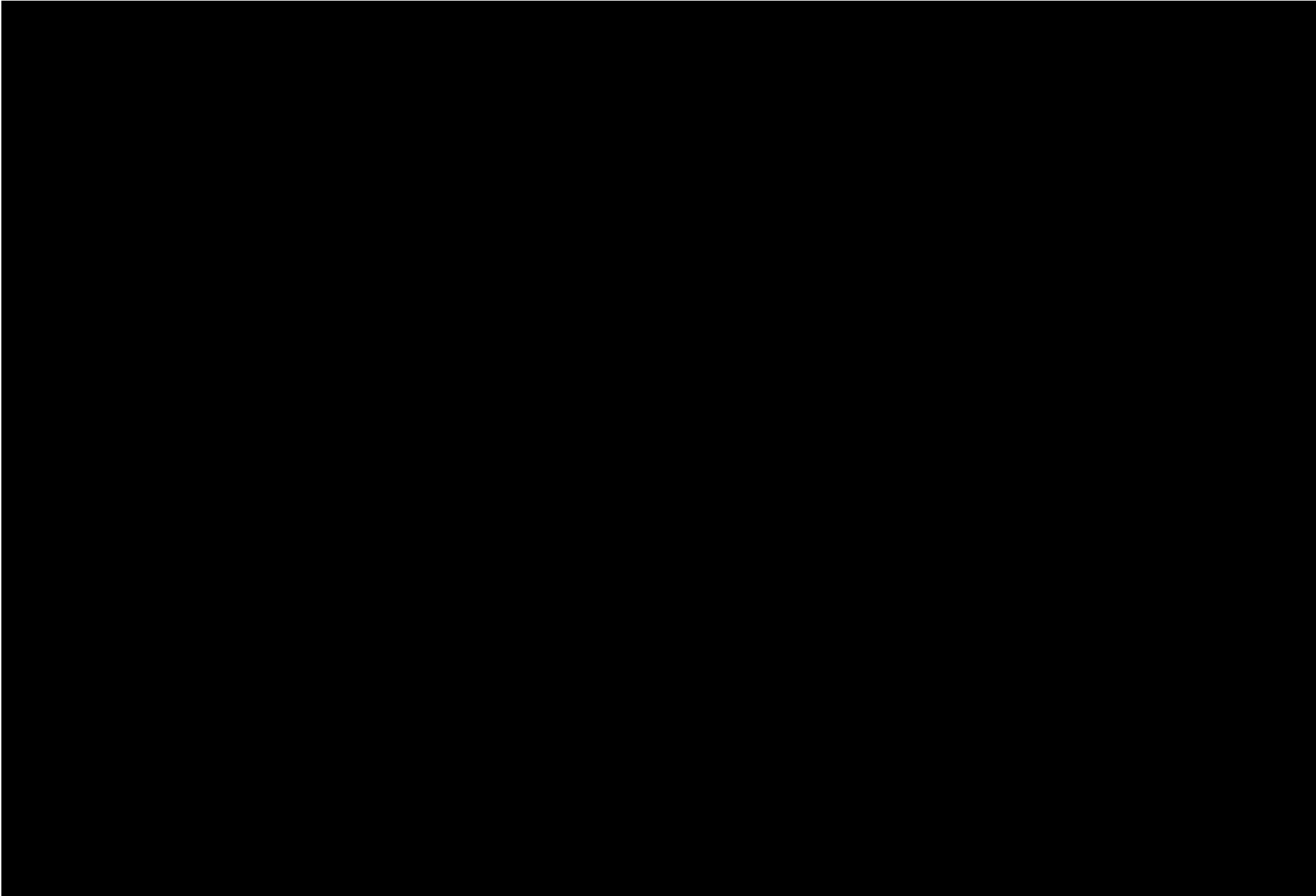
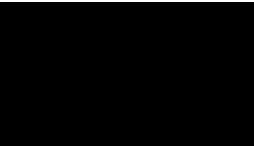


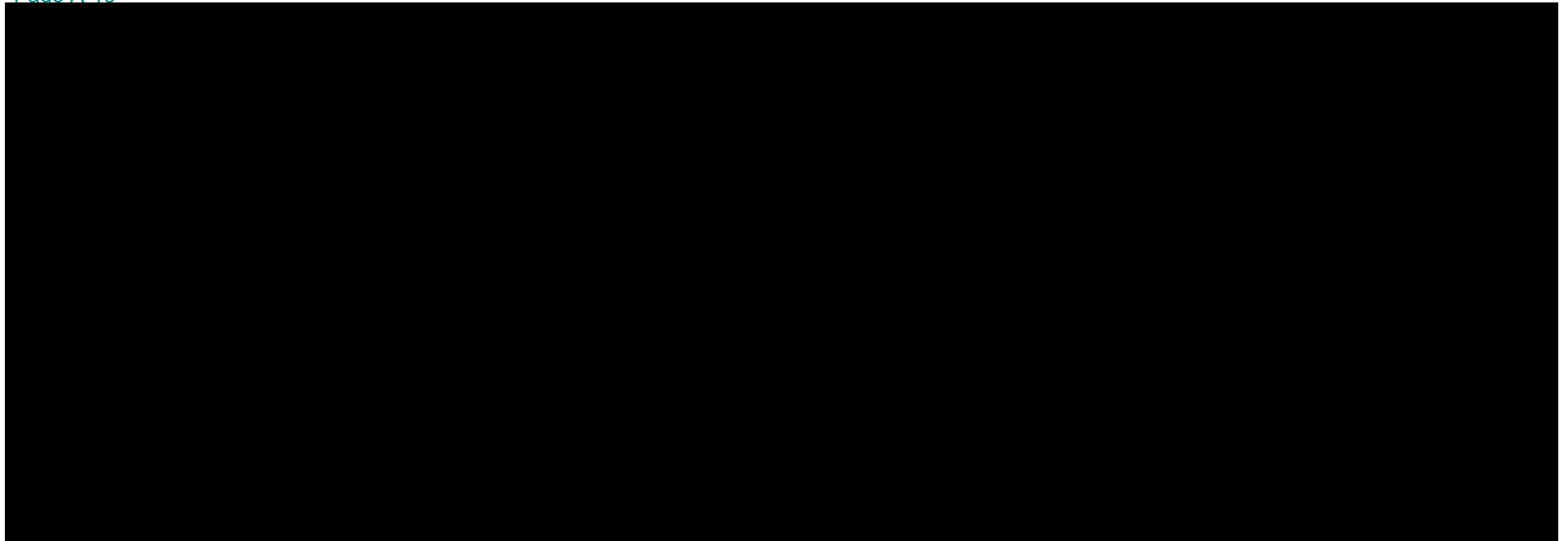


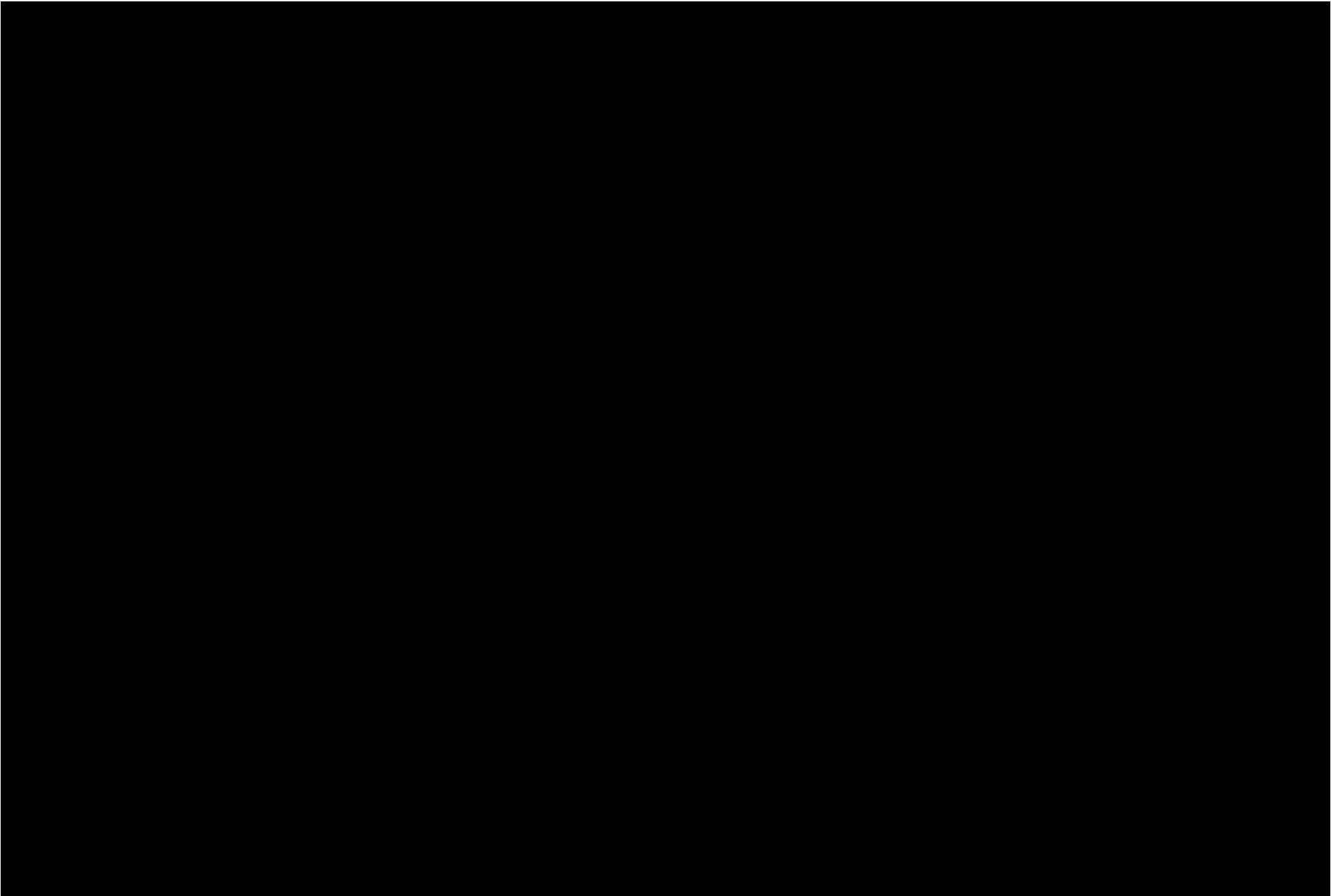
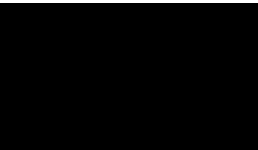




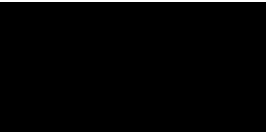


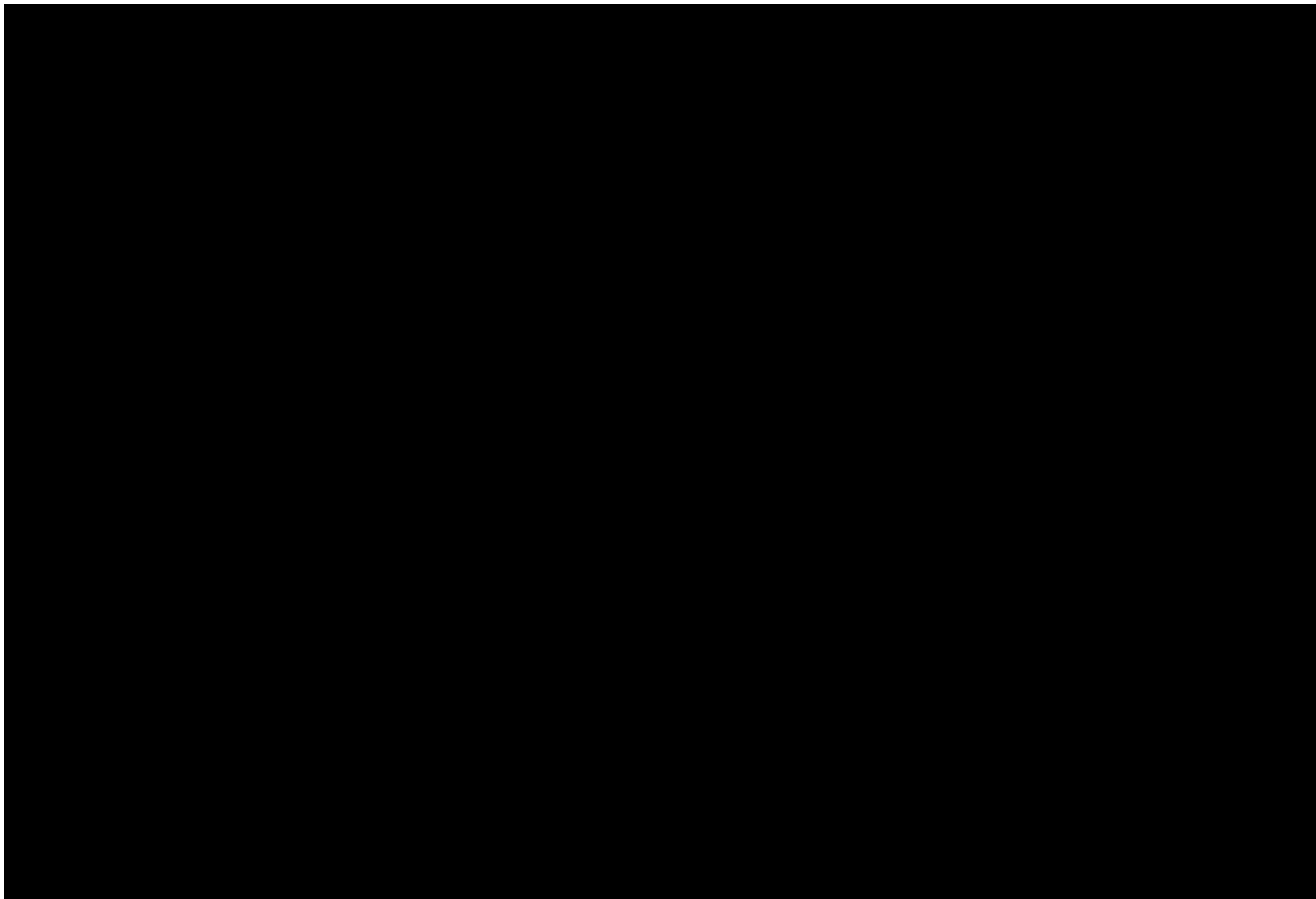
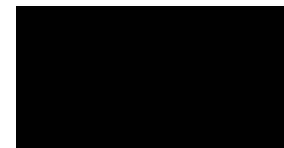


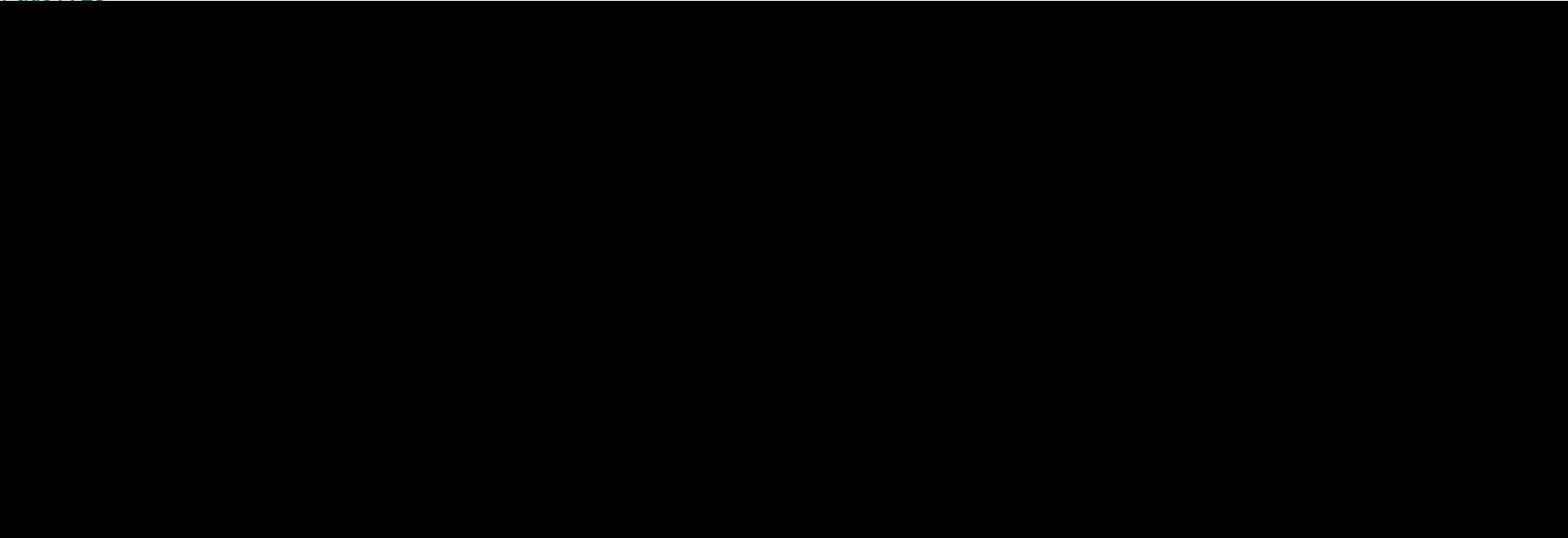
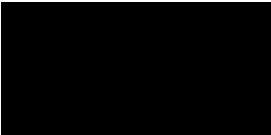


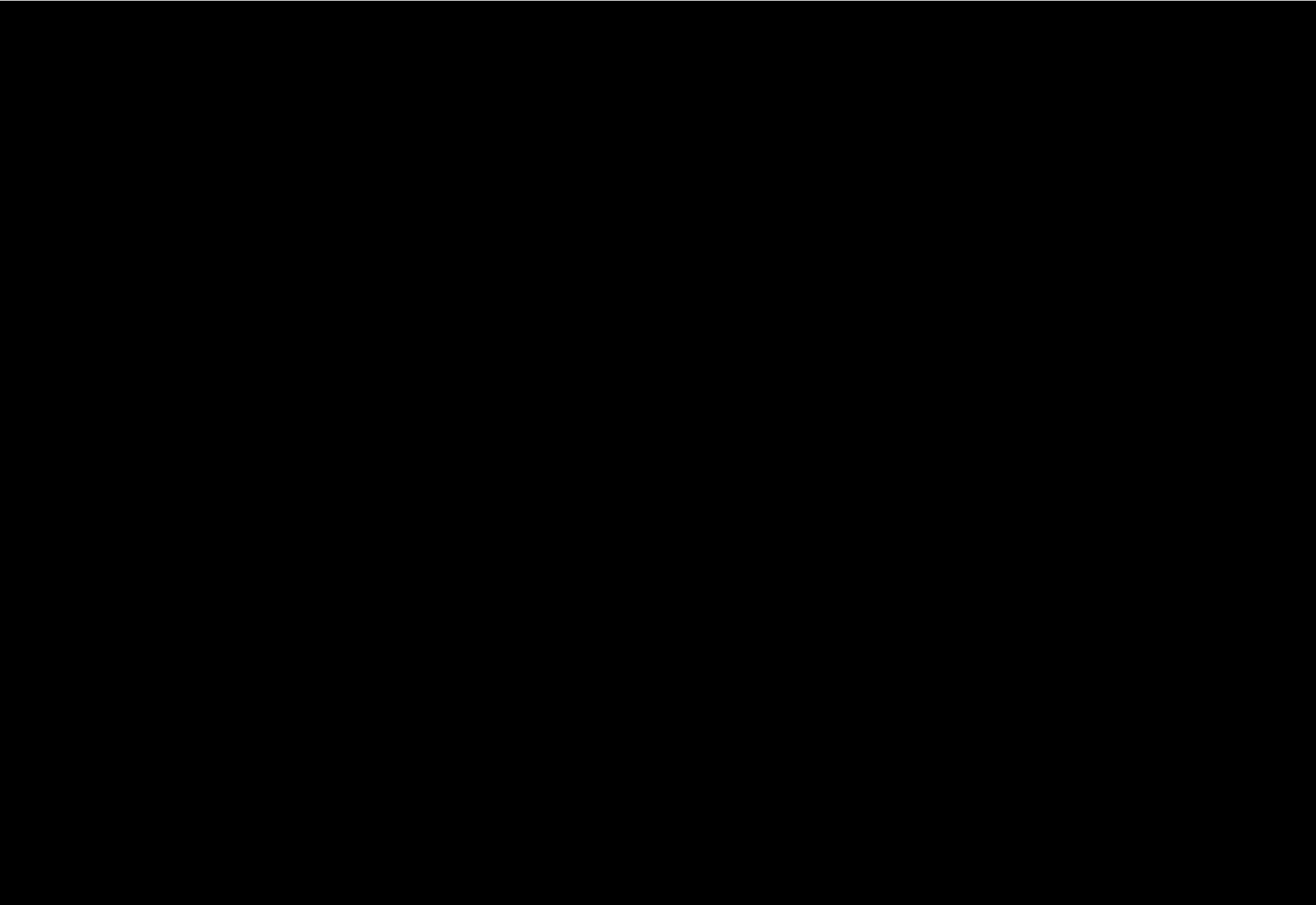
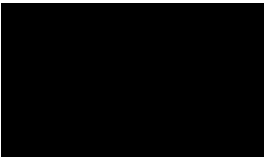


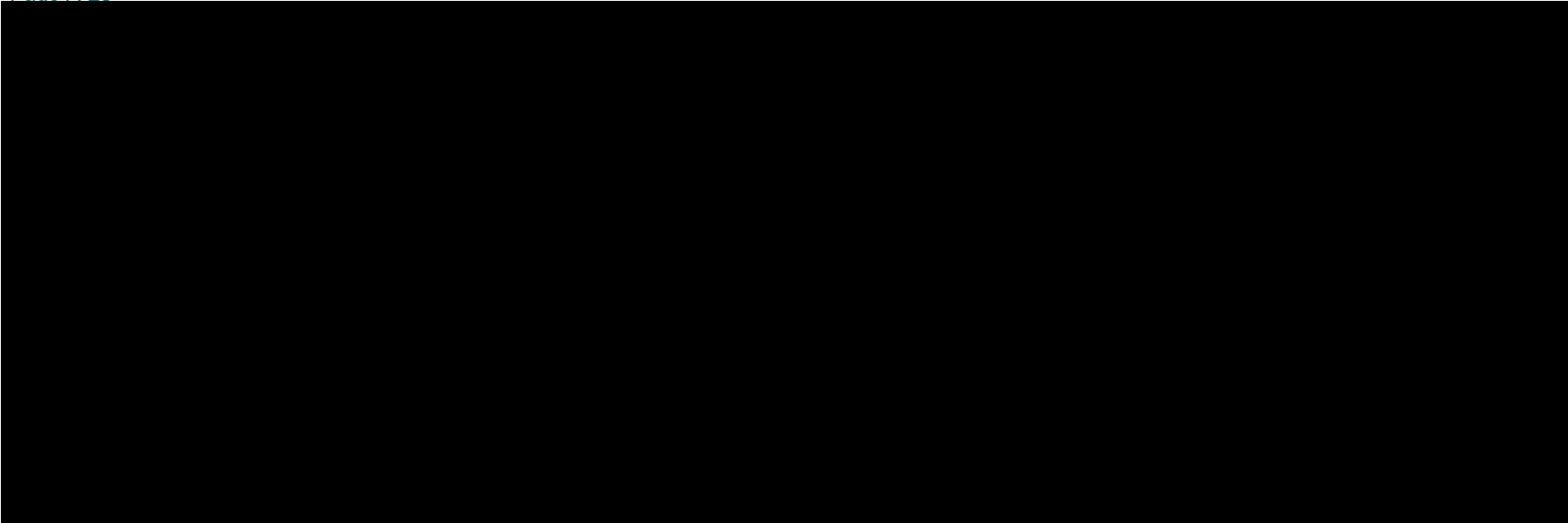


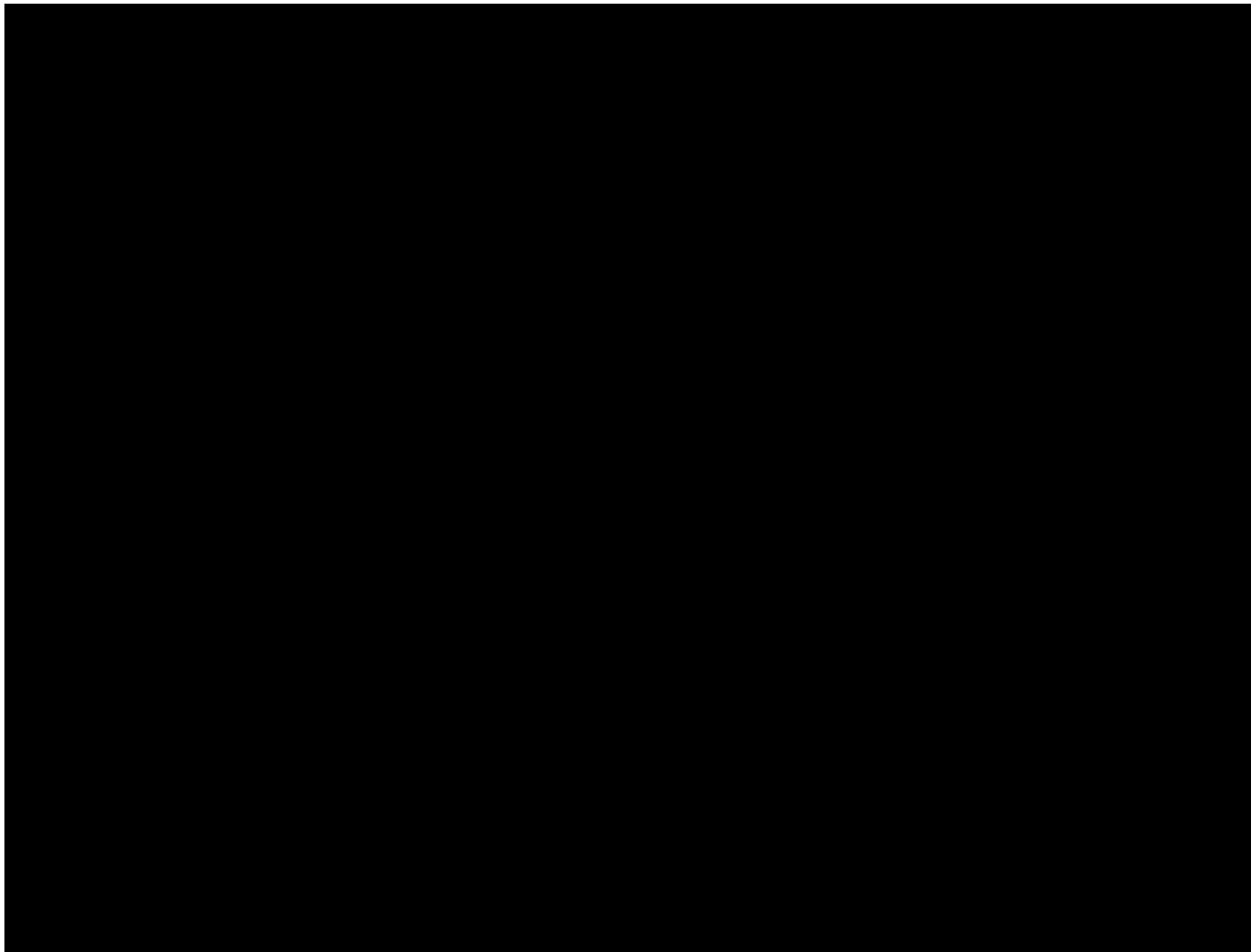
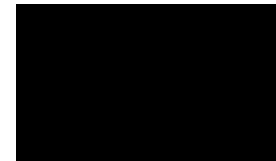


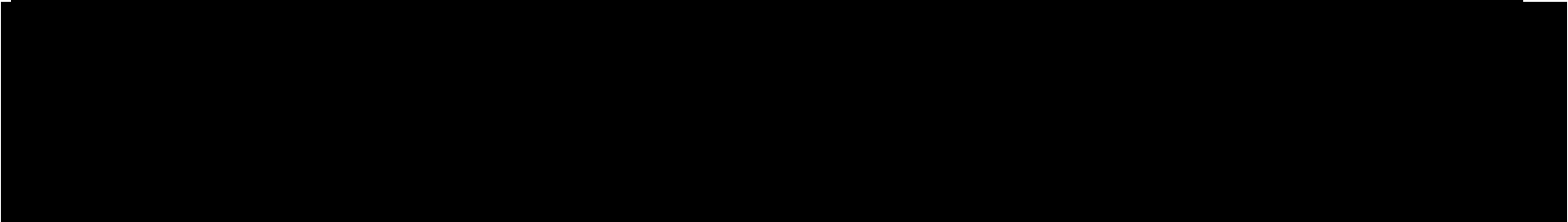


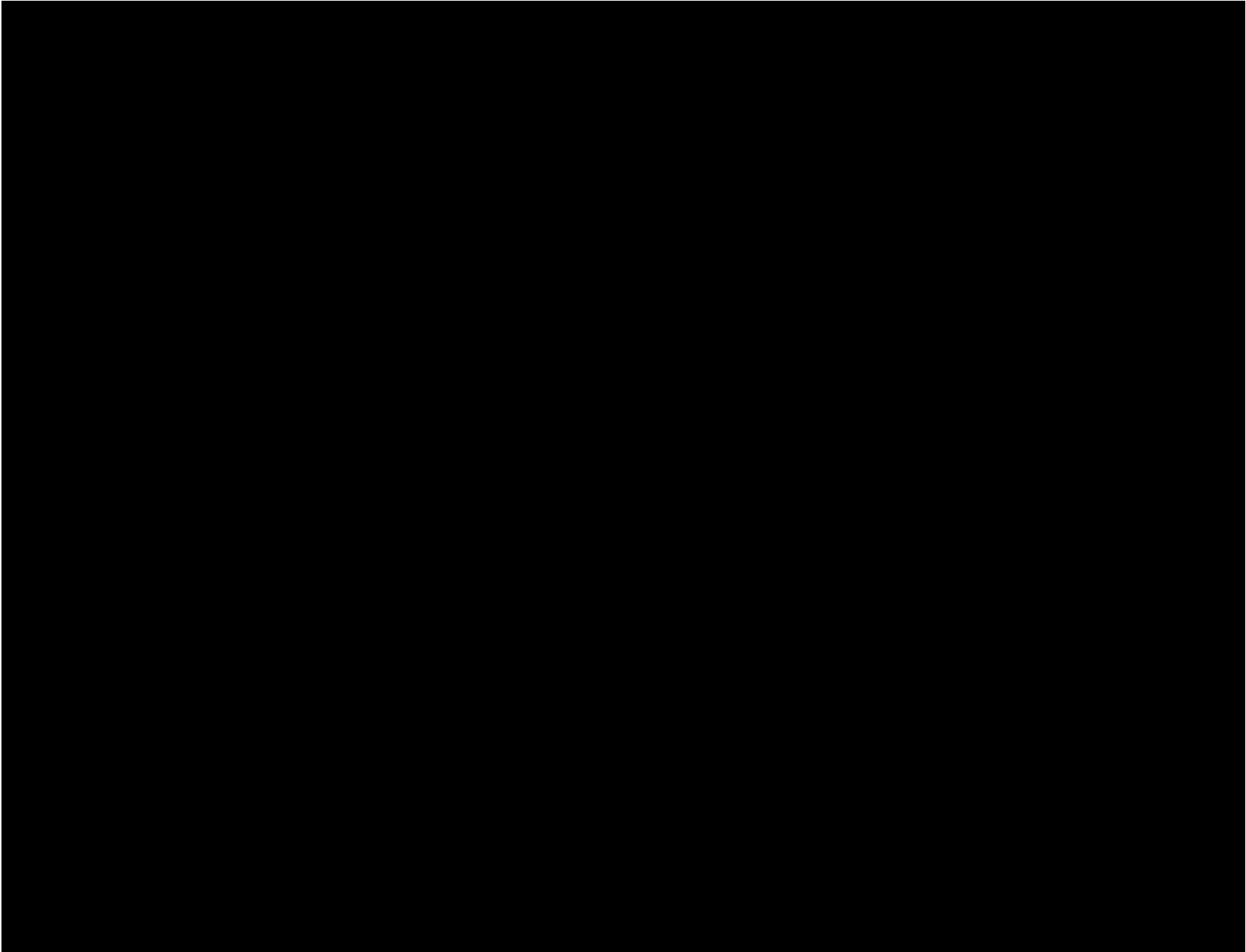
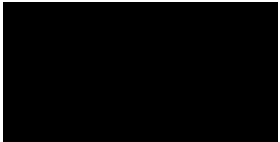














[REDACTED]

