Official Title of Study:

A Phase 1/2 Study of TPX-0046, A Novel Oral RET/SRC Inhibitor in Adult Subjects With Advanced/Metastatic Solid Tumors Harboring Oncogenic RET Fusions or Mutations

NCT Number: NCT04161391

Document Date (Date in which document was last revised): December 02, 2022

A PHASE 1/2 STUDY OF TPX-0046, A NOVEL ORAL RET/SRC INHIBITOR IN ADULT SUBJECTS WITH ADVANCED/METASTATIC SOLID TUMORS HARBORING ONCOGENIC *RET* FUSIONS OR MUTATIONS (SWORD-1)

Investigational Product Number:	TPX-0046
Investigational Product Name:	Not Yet Assigned
United States (US) Investigational New Drug (IND) Number:	144490
European Clinical Trials Database (EudraCT) Number:	2020-000781-42
Protocol Number:	TPX-0046-01
Phase:	1/2
Protocol Version:	Version 10.0 (02 December 2022)
Sponsor Name and Address:	Turning Point Therapeutics, Inc. 10628 Science Center Drive, Suite 200 San Diego, CA 92121 USA (a wholly owned subsidiary of Bristol Myers Squibb Company)
Medical Monitor:	[redacted] Turning Point Therapeutics, Inc. 10628 Science Center Drive, Suite 200 San Diego, CA 92121 USA

TURNING POINT THERAPEUTICS APPROVALS

Protocol Number: TPX-0046-01

Version (Date): 10.0 (02 December 2022)

Protocol Title: A Phase 1/2 Study of TPX-0046, a Novel Oral RET/SRC Inhibitor in Adult Subjects with Advanced/Metastatic Solid Tumors Harboring Oncogenic *RET* Fusions or Mutations (SWORD-1)

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 07-Dec-2022 | 17:34 PST
[redacted]

Date: 07-Dec-2022 | 17:34 PST

[redacted]
Turning Point Therapeutics, Inc.

PRINCIPAL INVESTIGATOR STATEMENT OF AGREEMENT

I, the undersigned Principal Investigator, have read and understood the following protocol, TPX-0046-01, Version 10.0, 02 December 2022, and its appendices.

I promise to abide by the International Conference for Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP), the Declaration of Helsinki, and all applicable laws and regulations, and agree that, in all cases, the most restrictive regulation related to a given aspect of research involving protection of human subjects will be followed. If I have a question regarding my obligations during the conduct of this protocol, I have ready access to these aforementioned regulations, as either my personal copy, or available on file from the Chairperson of the Institutional Review Board (IRB)/Ethics Committee (EC) or the Sponsor, via local authorities and, I am authorized to enter into this commitment to conduct the study outlined in this protocol, and my signature below signifies that I agree to conduct the study as outlined herein.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

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ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	adverse event
AKT	protein kinase
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
ATP	adenosine triphosphate
[redacted]	
BICR	Blinded Independent Central Review
BID	twice a day
[redacted]	
CBR	clinical benefit rate
[redacted]	
CLIA	Clinical Laboratory Improvement Amendments
[redacted]	
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
[redacted]	

Term	Definition
ECG	electrocardiogram
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EE	Efficacy Evaluable
EGFR	epidermal growth factor receptor
[redacted]	
EOT	end of treatment
ERK	extracellular signal-regulated kinase
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FGFR	fibroblast growth factor receptor
FIH	first-in-human
[redacted]	
GCP	Good Clinical Practice
[redacted]	
HDPE	high-density polyethylene
[redacted]	
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severe toxic dose
[redacted]	
IC_{50}	half maximal inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IC-ORR	intracranial objective response rate
IRB	Institutional Review Board
JAK	Janus kinase
KIF5B	kinesin family 5B

Term	Definition
LVEF	left ventricular ejection fraction
[redacted]	
MAPK	mitogen-activated protein kinases
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia 2
[redacted]	
MRI	magnetic resonance imaging
[redacted]	
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
[redacted]	
NSCLC	non-small-cell lung cancer
[redacted]	
ORR	objective response rate
[redacted]	
PD	progressive disease
PFS	progression-free survival
[redacted]	
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetics
PR	partial response
[redacted]	
QD	once daily
QOL	quality of life
[redacted]	
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate

Term	Definition
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
[redacted]	
RAS	family of GTPase proteins that are essential components of signaling networks controlling cellular proliferation, differentiation, or survival
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
ROS1	receptor tyrosine kinase encoded by the *ROS1* gene
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
[redacted]	
SOC	standard of care
SRC	tyrosine kinase first identified in avian sarcoma virus
STAT	signal transducer and activator of transcription
STD10	severe toxic dose in 10% of the animals
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
[redacted]	
TRK	tropomyosin receptor kinase
[redacted]	
ULN	upper limit of normal
US	United States
VEGFR	vascular endothelial growth factor receptor
[redacted]	
WOCBP	women of childbearing potential
WT	wild type

1. SYNOPSIS

Name of Sponsor/Company: Turning Point Therapeutics, Inc. (a wholly owned subsidiary of Bristol Myers Squibb Company)
Title of Study: A Phase 1/2 Study of TPX-0046, a Novel Oral RET/SRC Inhibitor in Adult Subjects with Advanced/Metastatic Solid Tumors Harboring Oncogenic *RET* Fusions or Mutations (SWORD-1)
Indication: Treatment of adult patients with advanced/metastatic solid tumors harboring oncogenic rearranged during transfection (*RET*) fusions or mutations.
Name of Investigational Product: TPX-0046
Study Site(s): Fifteen sites are participating in this study globally.
Phase of Development: Phase 1/2
Study Duration: Subjects will remain on study treatment until disease progression, development of unacceptable toxicity, the ability to move to alternative care is identified, or withdrawal of consent. Treatment beyond radiographic or clinical progression will not be allowed. Subjects discontinuing study treatment will have an end of treatment visit within 7 days after the last dose of investigational product. After treatment discontinuation, subjects will have a safety follow-up visit approximately 28 days after the last dose or before any new anticancer treatment is started. The study will close after the final safety follow up is complete.
Study Objectives and Endpoints: Preliminary results from Phase 1 dose escalation indicate that TPX-0046 has a [redacted]. Based on the totality of clinical information available, the Sponsor has decided to discontinue further development of TPX-0046 due to the inability to achieve and optimize a dose that could provide a positive benefit-risk profile in the current treatment landscape for *RET* mutant TKI naïve and pretreated setting. This decision was communicated to study sites on 03 October 2022. As such, no new subjects will be enrolled in this study, which will close after all active subjects have completed treatment. Subjects currently receiving treatment in this study will continue treatment at the discretion of the Investigators until need for discontinuation or the ability to move to alternative care is identified. As such, a synoptic CSR will be generated and submitted to health authorities.

Primary Objectives	Primary Endpoints
Phase 1: • Evaluate the safety and tolerability of TPX-0046 at selected doses • Determine the maximum tolerated dose (MTD) and/or Recommended Phase 2 Dose (RP2D) of TPX-0046	**Phase 1:** • Incidence of first cycle dose-limiting toxicities (DLTs) of TPX-0046 administered orally in a 28-day cycle • MTD and RP2D

Overall Study Design:

This is a Phase 1/2 multi-center, first-in-human (FIH), open-label study designed to evaluate the safety, tolerability, PK, and efficacy of the novel RET/SRC inhibitor TPX-0046 in adult subjects with advanced/metastatic solid tumors harboring oncogenic *RET* fusions or mutations. The global study consists of two portions as shown below in the Study Design schema: 1) Phase 1 Dose Escalation, Food Effect Sub-study, and Dose Expansion in 6 cohorts, and 2) Phase 2 preliminary efficacy evaluation in six defined subject cohorts.

As study enrollment will close prior to completing Phase 1 dose escalation, the Phase 1 food effect substudy, Phase 1 dose expansion, and Phase 2 activities will not take place.

Study Design:

Phase 1 Dose Escalation:

The Phase 1 dose escalation portion will be conducted according to a 3+3 based design. Approximately 60 subjects will be enrolled. Eligible subjects will be adults (≥ 18 years) with advanced/metastatic solid tumors harboring oncogenic *RET* fusions or mutations.

Subjects will be screened for eligibility up to 28 days prior to enrollment (the first day of TPX-0046 administration).

[redacted] Following completion [redacted], subjects will begin once daily (QD) dosing of TPX-0046 in 28-day continuous cycles. es Subjects may receive TPX-0046 until disease progression, unacceptable toxicity, the ability to move to alternative care is identified, or withdrawal of consent. Treatment beyond radiographic or clinical progression will not be allowed. An end of treatment (EOT) visit will be conducted within 7 days of the last dose of TPX-0046. A safety follow-up visit will be conducted within 28 days of the last dose.

Dose Escalation Schema:

The dose escalation schema is illustrated in the table below. No further dose escalation will occur after dose level 9. DLTs will be evaluated independently in any given dosing regimen.

Dose Level	Dose Regimen	Daily Dose (mg/day)	Increment from Previous Daily Dose
1	10 mg QD	10 mg	Not applicable
2	20 mg QD	20 mg	100% increase
3	10 mg BID		
4	30 mg QD	30 mg	50% increase
5	20 mg QD to 30 mg QD	20 mg (1st 14 days), then 30 mg	
6	20 mg BID	40 mg	33% increase
7	20 mg QD to 40 mg QD	20 mg (1st 14 days), then 40 mg	
8	20 mg QD to 20 mg BID	20 mg (1st 14 days), then 40 mg	
9	10 mg QD to 10 mg BID	10 mg (1st 14 days), then 20 mg	50% decrease

Criteria for Defining DLTs:

The AEs described in the table below, excluding toxicities clearly related to disease progression or intercurrent illness, will be considered DLTs during the DLT evaluation period. The DLT evaluation period is defined as 28 days following the first [redacted] dose of the dose regimen administered in Cycle 1 [redacted].

Category	Criteria
Toxicities resulting in an excessive number of missed doses	Inability to deliver at least 75% of the planned dose intensity of TPX-0046 treatment during the DLT evaluation period (ie, at least 21 days of dosing in a 28-day cycle, beginning in Cycle 1) because of toxicity excluding toxicities clearly related to disease progression or intercurrent illness
Hematologic toxicities	• CTCAE grade ≥ 4 neutropenia (absolute neutrophil count [ANC] $< 0.5 \times 10^9$/L) • CTCAE grade ≥ 4 platelet count decrease (platelets $< 25 \times 10^9$/L) or CTCAE grade ≥ 3 ($< 50\times 10^9$/L- 25×10^9/L) associated with clinically significant bleeding or requiring platelet transfusion • CTCAE grade ≥ 4 anemia • CTCAE grade ≥ 3 febrile neutropenia (defined as ANC < 1,000/mm^3 with a single temperature of ≥ 38.3 °C [≥ 101 °F] or a sustained temperature of ≥ 38 °C [≥ 100.4 °F] for > 1 hour)
Renal	• CTCAE grade ≥ 3 creatinine increase (> 3.0 x baseline or > 3-6 × upper limit of normal [ULN])

Hepatic	• CTCAE grade ≥ 3 total bilirubin elevation (> 3 × ULN) • CTCAE grade ≥ 2 total bilirubin elevation (> 1.5 × ULN) **AND** CTCAE grade ≥ 2 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (> 3 × ULN) • CTCAE grade 3 ALT elevation (> 5 × ULN) that does not resolve to at least grade ≤ 1 within 7 days or any grade > 4 ALT elevation • CTCAE grade 3 AST elevation (> 5 × ULN) that does not resolve to at least grade ≤ 1 within 7 days or any grade > 4 AST elevation
Pancreatic	• CTCAE grade 3 serum [redacted] increased with clinical symptoms or any grade ≥ 4 serum [redacted]
Cardiac	• CTCAE grade ≥ 3
Other AEs	• CTCAE grade 3 vomiting or nausea that does not resolve to grade ≤ 1 within 4 days despite optimal anti-emetic therapy or any grade ≥ 4 vomiting • CTCAE grade 3 diarrhea that does not resolve to grade ≤ 1 within 4 days despite optimal anti-diarrhea treatment or any grade ≥ 4 diarrhea • Any CTCAE grade ≥ 3 AE, except for the exclusions noted below • In view of the Investigators and Sponsor, any other unacceptable toxicity encountered
Exceptions to DLT criteria	• CTCAE grade 3 or 4 elevations in alkaline phosphatase (ALP) • CTCAE grade 3 electrolytes abnormalities that are adequately managed by intravenous (IV) or oral (PO) supplementation as evidenced by an improvement to grade ≤ 1 within 3 days • CTCAE grade 3 fatigue which resolves to grade ≤ 1 in ≤ 7 days • CTCAE grade 3 dizziness which resolves to grade ≤ 1 in ≤ 7 days • CTCAE grade 3 ataxia and weakness which resolves to grade ≤ 1 in ≤ 7 days • Isolated grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

In addition, [redacted] in the above criteria may be considered a DLT following review by the Sponsor and study Investigators. [redacted] should represent a [redacted] from baseline.

Subjects are eligible for DLT evaluation if they experience a DLT after at least one dose of the TPX-0046, or do not experience a DLT after taking at least 75% of the doses expected during the DLT evaluation period).

Determination of MTD:

The MTD is defined as the highest dose level of TPX-0046 observed to cause a DLT in fewer than 33% of the treated subjects in the first treatment cycle (ie, Cycle 1, 28 days). If there are 2 subjects who experience DLTs among the first 3 subjects enrolled, or there is a second DLT in up to 6 subjects enrolled at any dose level, the MTD will have been exceeded, and no additional subjects will be enrolled at that dose level. The MTD will then be established at the prior dose level. If the prior dose cohort has only 3 enrolled subjects, the cohort will be expanded up to 6 total subjects.

Safety Review Committee

For the Phase 1 dose escalation, a Safety Review Committee comprised of at minimum the Sponsor Medical Monitor and Study Investigators will review all relevant safety and other relevant clinical data.

Number of subjects (planned):

Phase 1 Dose Escalation: approximately 60 subjects

Inclusion Criteria:

1. Subjects with histological or cytological confirmation of advanced/metastatic solid tumors harboring oncogenic *RET* fusions or mutations, who either have disease progression on or are intolerant to standard therapy; **OR** are ineligible for standard therapy or for whom no standard therapy exists; **OR** are unlikely to tolerate or derive clinical benefit from standard therapy in the opinion of the Investigator **OR** have declined standard therapy.
    - Subjects must have a documented *RET* gene fusion or oncogenic *RET* mutation as determined by local testing in a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited diagnostic lab.

4. Age ≥ 18 years old (or age ≥ 20 as required by local regulation).
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
6. Presence of measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 criteria). For Phase 2 only, **prospectively** confirmed measurable disease according to RECIST v1.1 by Blinded Independent Central Radiology Review (BICR), selected by Sponsor, PRIOR to enrollment.
7. Life expectancy ≥ 12 weeks.
8. Baseline laboratory values fulfilling the following requirements:

Laboratory parameter	[redacted]
ANC	
PLT	
Hgb	
Total bilirubin	
Liver transaminases (ALT/AST)	
ALP	

Creatinine clearance by Cockcroft-Gault formula*	[redacted]

Abbreviations: ALP = alkaline phosphatase; ANC = absolute neutrophil count; AST/ALT = alanine aminotransferase / aspartate aminotransferase; Hgb = hemoglobin; PLT = platelet count; [redacted]

*calculated by Cockcroft-Gault formula: (140 - age [yr]) x body weight [kg] x 1.23 x (0.85 if female) / serum creatinine [µmol/L]. Measured creatine clearance is also acceptable.

9. Subjects with primary CNS tumors or brain metastases who are eligible for the study must meet the following criteria:
   - A minimum of 14 days must have elapsed from the completion of whole brain radiation treatment (WBRT) before the start of treatment with TPX-0046, and all side effects (except for alopecia) from WBRT are resolved to CTCAE version 5.0 grade ≤ 1.
   - A minimum of 7 days must have elapsed from the completion of stereotactic radiosurgery before the start of treatment with TPX-0046, and all side effects (except for alopecia) from stereotactic radiosurgery are resolved to CTCAE version 5.0 grade ≤ 1.
   - Subjects requiring steroids at a stable or decreasing dose (≤ 12 mg/day dexamethasone or equivalent) for at least 14 days are eligible.
   - Subjects on stable doses of levetiracetam (same dose for 14 days) are eligible to be enrolled.
10. For subjects who received prior cytotoxic chemotherapy or prior targeted small molecule therapy at the time of starting treatment with TPX-0046, at least 14 days or five half-lives (whichever is shorter) must have elapsed after discontinuation (or at least 42 days for prior nitrosoureas, mitomycin C, and liposomal doxorubicin; for vandetanib and cabozantinib at least 14 days must have elapsed after discontinuation), and all AEs from prior treatments must have resolved to grade ≤ 1 CTCAE version 5.0 with the exception of alopecia or other AEs that the Investigator does not consider to be a risk to subject safety.
11. Prior radiotherapy is allowed at least 14 days prior to starting treatment with TPX-0046. All AEs from prior treatments must have resolved to grade ≤ 1 CTCAE version 5.0 except for alopecia or other AEs that the Investigator does not consider to be a risk to subject safety.
12. Prior immunotherapy or prior antibody targeted therapies for advanced/metastatic disease is allowed. At least 3 weeks must have elapsed after discontinuation of immunotherapy or therapeutic antibodies and all AEs from prior treatments must have resolved to grade ≤ 1 CTCAE version 5.0 except for alopecia or other AEs that the Investigator does not consider to be a risk to subject safety.
13. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during Screening and be neither breastfeeding nor intending to become pregnant during study participation; and agree to use 2 effective contraceptive methods (combination of any of these options: hormonal, barrier method, or intrauterine device) OR be abstinent OR be surgically sterile prior to study entry OR have a vasectomized partner, for the duration of study participation, and up [redacted] after discontinuation of study treatment. Male subjects or male partners of female subjects of childbearing potential must take appropriate precautions to avoid fathering a child from the time of screening [redacted] after last dose of study treatment and to use appropriate barrier contraception, maintain true abstinence, or have had a vasectomy. Highly effective contraceptive methods are described in Appendix B.
14. Male subjects must refrain from sperm donation from screening through [redacted] after the last dose of study drug.
15. Female subjects must refrain from egg donation from screening through [redacted] after the

last dose of study drug.

16. Ability to complete all study-required procedures and assessments.
17. Provision of written informed consent signed and dated by the subject and the Investigator, before any study interventions are performed.

Exclusion Criteria:

1. Locally advanced/metastatic solid tumor that is a candidate for curative treatment through radical surgery and/or radiotherapy, or chemotherapy.
2. Presence or history of any other active malignancy within 3 years other than a history of adequately treated basal or squamous cell carcinoma of the skin, or any adequately treated in situ carcinoma.
3. Presence of only one measurable tumor lesion that has already been resected or irradiated before enrollment in the study.
4. Known presence of RET gatekeeper mutation(s) (eg, RET V804X) based on most recent applicable molecular testing.
5. Exposure to more than 1 prior selective RET inhibitor (eg, pralsetinib (BLU-667), or selpercatinib (LOXO-292),) unless a subject has discontinued a RET inhibitor treatment due to intolerance in which case Sponsor approval for eligibility is required.
6. Major surgery within 4 weeks of the start of study.
7. Clinically significant cardiovascular disease (either active or within 6 months before enrollment): myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Classification Class ≥ II), cerebrovascular accident or transient ischemic attack, symptomatic bradycardia, requirement for anti-arrhythmic medication. Ongoing cardiac dysrhythmias of CTCAE version 5.0 grade ≥ 2.
8. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (electrocardiogram [ECG] interval measured from the onset of the QRS complex to the end of the T wave) for heart rate (QTcF) > 470 msec obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value
    - For patients with QRS > 120 msec: QTcF > 500
    - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec)
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, congenital long QT syndrome, family history of long QT syndrome, or any concomitant medication known to prolong the QT interval
9. [redacted]
10. [redacted]
11. Known clinically significant active infections not controlled with systemic treatment (bacterial, fungal, viral including human immunodeficiency virus [HIV] positivity). Subjects with chronic HIV must have a CD4+ T cell count ≥ 350 cell/microliter for eligibility. Subjects with chronic hepatitis B virus infection must have an undetectable viral load (and start antiviral therapy if

required according to local or regional guidelines) prior to start of TPX-0046. Subjects with a history of hepatitis C viral infection must have an undetectable viral load.

12. Gastrointestinal disease (eg, Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact drug absorption.
13. Concurrent participation in another therapeutic clinical study.
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or TPX-0046 administration, or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study, or could compromise protocol objectives in the opinion of the Investigator and/or Sponsor.
15. The concomitant use of known strong CYP3A4 inhibitors or inducers is prohibited including their administration within at least 2 weeks prior to the first TPX-0046 dose and throughout the study. Subjects should avoid grapefruit juice or grapefruit/grapefruit-related citrus fruits (Seville oranges, pomelos). See Appendix A for a list of known CYP3A4 inhibitors and inducers.
16. Current or anticipated use of drugs that are known to be sensitive substrates of CYP3A or CYP2B6 is not permitted, including their administration within at least 2 weeks prior to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of sensitive CYP3A or CYP2B6 (eg, bupropion, efavirenz) substrates must be approved by the Sponsor. See Appendix A for a list of known sensitive substrates of CYP3A.
17. Current or anticipated need for drugs that are sensitive CYP2C9 substrates with narrow therapeutic indices, such as celecoxib, phenytoin, or warfarin is not permitted including their administration at least within 2 weeks prior to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of being a CYP2C9 substrate with narrow therapeutic index must be approved by the Sponsor.
18. Current or anticipated use of drugs that are known to be [redacted] is not permitted, including their administration within at least 2 weeks prior to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of [redacted] must be approved by the Sponsor.
19. Known oncogene drivers other than RET including, eg, anaplastic lymphoma kinase [ALK], ROS1 [receptor tyrosine kinase encoded by the *ROS1* gene], or epidermal growth factor receptor [EGFR]) conferring sensitivity to targeted therapies.

Investigational Product/Dosage Formulation:

TPX-0046 drug product is supplied as [redacted] capsules.

Dose Regimen and Route of Administration:

Initially, TPX-0046 will be taken orally QD under fasting conditions (1 hour before, 2 hours after dosing) as follows.

- Phase 1 Dose Escalation: as allocated by dose level. The study will begin with TPX-0046 10 mg QD.

[redacted]

Study Assessments:

Safety observations include physical examinations, body weight, ECOG score, clinical AEs, (hematology, serum chemistries, and urinalysis), ECG, vital signs, [redacted]. As no new subjects will be enrolled in this study, Investigators will follow assessments for subjects currently enrolled as described in the schedule of activities for Phase 1 dose escalation (Table 1). Additional testing considered necessary for safety related to study drug may be performed at the discretion of the Investigator.

Sample Size Determinations:

For the Phase 1 dose escalation, 41 subjects have enrolled across 9 dose levels. Enrollment is closed.

Table 1: Schedule of Activities: Phase 1 Dose Escalation

	Screening (≤28 Days)	[redacted]	Cycle 1 (28 days)				Cycle 2 (28 days)		Cycle 3 (28 days)	Cycle 4 and Beyond (28 days)	End of Treatment	Safety Follow-up
Protocol Activity			**Day 1**	**Day 8**	**Day 14/15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 1**		
Visit Window[a]	NA			±1	±1	±1	±2	±2	±2	±2	+7	+28 days of last dose
Informed Consent[b]	X											
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X
Dispense TPX-0046 and Subject Diary[fg]		X	X		X		X		X	X		
TPX-0046 Compliance			X	X	X	X	X	X	X	X	X	
Laboratory assessments beyond Cycle 3 should be done based on symptomatology and per investigator discretion.												
Complete Blood Count with Differential[c]	X	X	X	X	X	X	X	X	X			
Complete Chemistry Panel[d]	X	X	X	X	X	X	X	X	X			
Coagulation[e]	X	X	X	X	X	X	X		X			
Cardiac Safety Monitoring should be done based on symptomatology and at investigators discretion.												
Tumor Assessment should be done per standard of care.												
Other Clinical Assessments												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications and Non-Drug Supportive Interventions[h]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviation: [redacted]

Note: Regardless of dose interruptions, cycle lengths will remain 28 days and evaluations are to be performed according to the schedules.

a. **Visit Window**: The 28-day screening period starts on the day informed consent is signed by the subject. All study visits (visit date calculations) are based off of the Cycle 1 Day 1 visit date, regardless of dose interruptions; and evaluations are to be performed according to the schedules. The safety follow-up visit should be within 28 days from the last dose of TPX-0046.

b. **Informed Consent**: Must be obtained before undergoing any protocol-specific procedures.

c. **Complete Blood Count with Differential:** White blood cell count, hemoglobin, platelets, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils.

d. **Complete Chemistry Panel:** Sodium, potassium, chloride, bicarbonate, [redacted] blood urea nitrogen or urea, creatinine, magnesium, phosphorus, total calcium, uric acid, total protein, albumin, glucose (non-fasted), lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase.

e. **Coagulation:** Prothrombin time/international normalized ratio (PT/INR), partial thromboplastin time (PTT).

f. **TPX-0046 administration (QD or BID):** TPX-0046 (capsules) will be administered orally as a [redacted]. On Cycle 1 Day 1 TPX-0046 will be administered either QD or BID per the dosing regimen with approximately 8-oz water (240 mL) [redacted] in 28-day continuous cycles. [redacted]

g. **TPX-0046 administration [redacted]:** TPX-0046 (capsules) will be administered orally [redacted] On Cycle 1 Day 1 TPX-0046 will be administered either QD or BID per the dosing regimen with approximately 8-oz water (240 mL) [redacted]. [redacted]

h. **Concomitant Medications and Non-Drug Supportive Interventions:** All concomitant medications and non-drug supportive interventions should be recorded in the CRF.

2. INTRODUCTION

2.1. Mechanism of Action/Indication

TPX-0046 is a RET/SRC kinase inhibitor with a compact three-dimensional macrocyclic structure designed to efficiently target the RET active kinase conformation and to inhibit clinically-relevant RET fusion proteins and mutations. TPX-0046 has demonstrated potent nonclinical activities against RET and clinically-relevant mutant RETs, especially the SFMs which will potentially confer resistance to current investigational RET inhibitors, and approved TKIs that have RET inhibitory activity which represents a potential unmet medical need. TPX-0046 has minimal activity against the gatekeeper mutation family RET V804X, which includes V804M/L/E. TPX-0046 also inhibits SRC and SRC family members that have the potential to reduce bypass resistance and therefore increase its therapeutic effect. Polypharmacological inhibition of RET and SRC is expected to provide strong anti-tumor efficacy for patients with advanced/metastatic solid cancers harboring oncogenic *RET* fusions or mutations, especially patients who have developed resistance from current investigational RET inhibitor treatment. The comprehensive nonclinical pharmacology, pharmacokinetic and toxicology evaluation results strongly support a FIH Phase 1/2 clinical trial with TPX-0046 in adult subjects (≥ 18 years) with advanced/metastatic solid tumors harboring oncogenic RET fusions or mutations.

2.2. Background

The *RET* gene was originally identified as an oncogene in 1985 (Takahashi, 1985) and characterized as a receptor tyrosine kinase (Takahashi, 1987). RET activation regulates multiple signaling pathways (eg, RAS/MAPK/ERK, PI3K/protein kinase [AKT], JAK-STAT) leading to cellular proliferation, migration, and differentiation (Mulligan, 2014). RET plays an essential role in the development and maturation of diverse tissues (Mulligan, 2018). Gain-of-function mutations of *RET* including amplification, activating point mutations or genomic rearrangements lead to ligand-independent kinase activation have been found in heritable and sporadic tumors. Thyroid carcinoma is the most common endocrine malignancy and accounts for 3%–4% of all cancers in the US with an estimated incidence of 57,000 and deaths of 2000 in 2017 (Siegel, 2017). Germline mutations of *RET* are found in multiple endocrine neoplasia 2A (MEN2A), MEN2B, and familial medullary thyroid carcinoma (MTC) (Mulligan, 2018). Mutations in *RET* have been reported in 43% to 71% of sporadic MTC (Moura, 2009). The somatically occurring rearrangements of the *RET* gene have been identified in 20%–40% of papillary thyroid carcinomas (PTCs) and ~1%–2% NSCLCs (Mulligan, 2018). In addition, *RET* fusions have been discovered in Spitzoid tumors (~3%), chronic myelomonocytic leukemia, breast, colon, ovarian, salivary gland and inflammatory myofibroblastic tumors (Mulligan, 2018). *RET* fusions have also been found as a resistance mechanism to EGFR-TKIs in EGFR-mutant NSCLC patients (Bronte, 2019).

2.2.1. RET Targeted Therapies in *RET*+ Disease and Drug Resistance

Multi-kinase inhibitors with activity against RET have been approved for the treatment of a variety of solid and hematological malignancies, such as cabozantinib, vandetanib, lenvatinib, sorafenib for thyroid cancers and ponatinib, alectinib, sunitinib, nintedanib, and regorafenib for

other indications. Multi-kinase inhibitors with moderate activity against RET can achieve confirmed responses in certain patients with *RET*-rearranged or *RET*-mutant cancers but the ORR and DOR are significantly lower than those observed in other oncogene-driven, advanced-stage tumors with matched targeted therapies (Drilon, 2018a). The potent and selective RET inhibitors with minimal off-target activities are likely required for achieving long lasting anti-tumor activity in patients with advanced/metastatic solid tumors harboring an abnormal *RET* gene. Two selective RET inhibitors, pralsetinib (BLU-667) and selpercatinib (LOXO-292) have achieved marked anti-tumor activity in both NSCLC and thyroid cancers (Drilon, 2018b and Subbiah, 2018). Accordingly, selpercatinib was approved by the US Food and Drug Administration (FDA) for adult patients with metastatic *RET* fusion positive NSCLC and adult and pediatric patients 12 years of age and older with *RET* mutant MTC or *RET* fusion positive thyroid cancer refractory to radioactive iodine therapy (Retevmo™ USPI, 2020).

Multiple resistance mutations to vandetanib and cabozantinib, including gatekeeper mutations V804X and SFMs G810X have been reported from preclinical studies (Liu, 2018). The development of RET solvent front mutations have also been reported as resistance mechanisms following treatment with selective RET inhibitors (Solomon, 2020). In RET-rearranged NSCLC, the type of upstream RET fusion partner produced different sensitivity to multi-kinase inhibitors. Lower ORR and shorter median PFS in patients with kinesin family 5B (*KIF5B)-RE*T+ NSCLC treated with multi-kinase drugs were observed relative to other RET rearrangements (Yoh, 2017; Drilon, 2017). KIF5B-RET leads to a substantial increased *RET* transcription (Kohno, 2012) and strongly activate a RET-SRC-EGFR-FGFR signaling hub (Das, 2017). Inhibition of SRC kinase may interrupt recruitment of multiple receptor tyrosine kinases (RTKs). SRC family tyrosine kinases are known to regulate MTC cellular proliferation in vitro (Liu, 2004). Therefore, a dual inhibitor of both RET and SRC represents a highly-desired therapeutic intervention to maximally target abnormal RET signaling in cancers.

2.3. Nonclinical Overview

2.3.1. Nonclinical Pharmacology

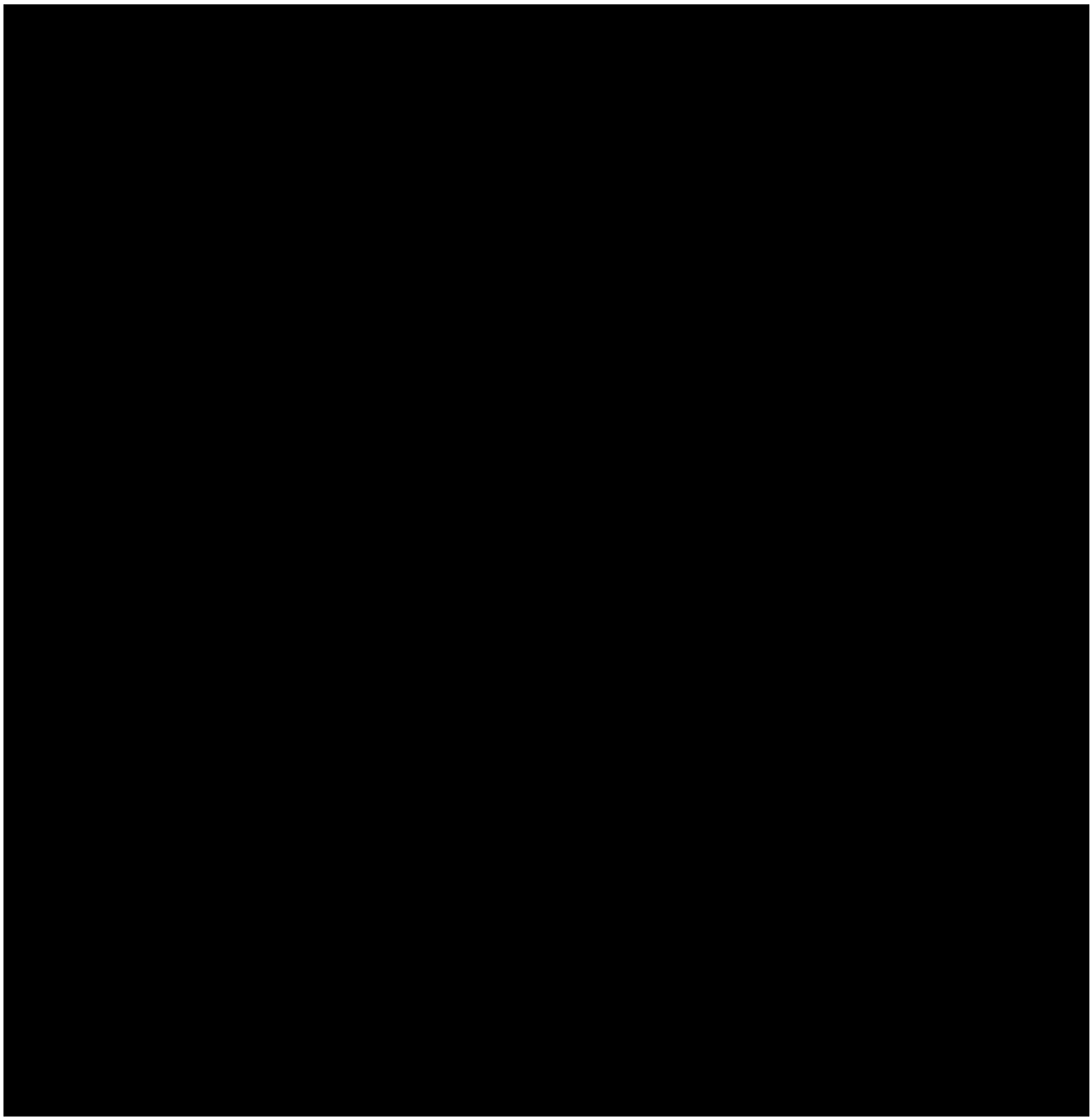
A comprehensive program, including in vitro and in vivo assessments, was conducted on TPX-0046 to evaluate its primary and secondary pharmacodynamic properties, as well as the safety pharmacology to support a FIH Phase 1/2 clinical trial with TPX-0046 in patients with advanced solid tumors harboring genetic alternations in RET. Primary pharmacodynamics of TPX-0046 began with biochemical potency assessments via inhibition of the catalytic activities for multiple recombinant kinases, including the oncogenic RET fusion proteins and mutants as shown [redacted]. In cellular assays, the effect of TPX-0046 on RET autophosphorylation, downstream signal effectors, and cell proliferation in human primary cancer cell lines and engineered stable cell lines expressing the targeted fusion RET oncogenes was evaluated as shown in Table 3. Target human plasma exposure to be associated with pharmacological activity for TPX-0046 is [redacted], the calculated IC_{90} value of KIF5B-*RET* solvent front mutation G810R determined in in vitro cell proliferation assays. The in vivo assessment of TPX-0046 on the efficacy of tumor growth inhibition and pharmacodynamic target modulation were performed in a series of mouse xenograft tumor models – both cell line and patient-derived as shown in Figure 1.

[redacted]

Table 3: Summary of TPX-0046 Activities against RET in Cellular Assays

	Cell Line	TPX-0046
Cell Proliferation IC_{50} (nM)	[redacted]	
[redacted]		

[redacted]



In the secondary pharmacodynamic studies, TPX-0046 was screened in biochemical assays at 100 nM in two kinase panels: 374 recombinant protein kinases (Reaction Biology) and 157 recombinant kinases (Eurofins). Kinases inhibited by TPX-0046 greater than 90% in either panel were followed up by determining half maximal inhibitory concentration (IC_{50}) values along with selected RTKs which are often inhibited by multi-kinase RET inhibitors [redacted]. Kinases inhibited in biochemical assays with IC_{50} < 10 nM were subjected to further testing in cellular assays that measure either cell proliferation or target engagement [redacted] TPX-0046 is highly selective with only [redacted] kinases of the [redacted] kinases inhibited with less than [redacted] selectivity over WT RET potency.

[redacted]

[redacted] Kinases inhibited in biochemical assays with IC_{50} < 10 nM were subjected to further testing in cellular assays that measure either cell proliferation or target engagement [redacted]. Many kinases with IC_{50} values < 10 nM in biochemical assays did not translate to potency in cellular assays likely due to either the artificial nature of the recombinant kinase protein or the low concentration of the competitive ligand ([redacted] ATP in biochemical assay, > 1 mM in cells). [redacted]. SRC family kinases were evaluated in nanoBRET assays and found to have IC_{50} > [redacted] but the assays may have flaws. [redacted] states "for the [redacted] SRC assay, a luciferase (NanoLuc) is fused to the C-terminal tail of SRC which has an autoinhibitory phosphorylation site at Tyr530. This construct design might affect the regulation of SRC kinase conformation". As such, [redacted] potency from SRC, SRC family kinases, and janus kinases are not reported. There were kinases inhibited by TPX-0046 in cellular assays within 100-fold of TPX-0046 potency toward RET [redacted]: FGFR1/2, TRKA/B/C, ROS1, and TXK. TPX-0046 inhibits fibroblast growth factor (FGF) receptors with [redacted] in biochemical assays as determined in multiple studies (in the presence of [redacted] ATP). These results were confirmed in [redacted] cellular assays with IC_{50} values of [redacted] for FGFR1, FGFR2 and FGFR3, respectively. In biochemical assays, [redacted] In TRK-dependent cell proliferation assays, TPX-0046 has IC_{50} values of [redacted] in [redacted] cells with TPM3-TRKA, [redacted] in Ba/F3 cells with TEL-TRKB, and [redacted] in Ba/F3 cells with TEL-TRKC. ROS1 had an IC_{50} of [redacted] in a biochemical assay and [redacted] in a cell proliferation assay. For TXK, TPX-0046 had a biochemical IC_{50} = [redacted] and a cellular IC_{50} = [redacted]. Kinases inhibited by TPX-0046 with IC_{50} < 10 nM that have only biochemical potency (SRC family kinases, PEAK1, TIE2) may not all have potent cellular potency. Pseudopodium enriched atypical kinase 1 (PEAK1) is a pseudokinase with controversial non-receptor tyrosine kinase activity and has not been reported to be an oncogenic driver as its function is as a molecular scaffold (O'Rourke, 2018). Taken together, TPX-0046 is highly potent for TPX-0046 with only one kinase (TRKA) displaying cellular potency within 10-fold of RET cellular potency.

In additional secondary pharmacodynamic studies of 44 purified receptors, ion channels, transporters, and enzymes, TPX-0046 at [redacted] only inhibited [redacted] and [redacted] with IC_{50} values of [redacted], respectively. TPX-0046 had minimal effects on human ion channels of hNav1.5 ([redacted] HEK293 cells) and human L-type $C_{av}1.2$ (IC_{50} [redacted], HEK293 cells), and moderate effect on human ether-à-go-go-related gene (hERG) ([redacted], CHO cells).

Taken together, TPX-0046 has demonstrated potent nonclinical activities against RET and clinically-relevant mutant RETs, especially the SFMs which will likely confer resistance to any therapy that has RET inhibitory activity, including investigational selective RET inhibitors, which represents a potential unmet medical need. TPX-0046 is an inhibitor of SRC tyrosine kinase in in vitro assays. Aberrant activation of SRC signaling contributes to diverse aspects of tumor development and treatment resistance. The inhibition of the SRC kinase has the potential to reduce the recruitment of multiple RTKs involved in bypass resistance and therefore increase the therapeutic effect of TPX-0046. Therefore, pharmacological inhibition by TPX-0046 of a broad range of oncogenic *RET* mutations and fusion proteins is expected to provide anti-tumor efficacy for *RET*+ cancer patients, especially patients who have developed resistance. These

comprehensive in vitro and in vivo evaluation results strongly support a FIH Phase 1/2 clinical trial with TPX-0046 in adult patients with advanced solid tumors harboring an oncogenic *RET* fusion or mutation.

2.3.2. Nonclinical Pharmacokinetics

The absorption, distribution, metabolism, excretion (ADME) properties as well as drug-drug interaction profile of TPX-0046 were characterized in various animal and human in vitro and in vivo systems.

Oral bioavailability was [redacted] (at [redacted]) and [redacted] (at [redacted]) following single administration of TPX-0046 in a suspension. A new formulation of the TPX-0046 capsule was developed to improve consistency across batches. In a study in monkeys to assess the comparability of pharmacokinetic profiles of batches, the new TPX-0046 capsule formulations exhibited similar exposures compared to the original clinical formulation. TPX-0046 has a predicted human CL of [redacted], a V_{ss} of [redacted], an effective $t_{½}$ of [redacted] hours, and an oral bioavailability of [redacted].

TPX-0046 equally distributed into plasma and red blood cells. Binding to plasma proteins was [redacted] animal species and humans.

Reaction phenotyping studies using human recombinant cytochrome P450 (CYP) enzymes suggested that [redacted]

These in vitro drug-drug interaction assessments suggest TPX-0046 may [redacted]

Overall, the nonclinical ADME, and drug-drug interaction assessments of TPX-0046 support the advancement for clinical evaluation.

2.3.3. Nonclinical Toxicology

A comprehensive IND-enabling nonclinical safety assessment program has been conducted consistent with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline, “Nonclinical Evaluation for Anticancer Pharmaceuticals (S9),” and is comprised of single- and repeat-dose exploratory toxicology

studies and definitive 28-day toxicology studies conducted in two mammalian species (rat and monkey), selected based on comparable metabolite profiles in humans, using the clinically-relevant route (oral) and schedule (once daily) of administration (ICH Guidance: S9, 2009). The pivotal 28-day repeat dose toxicity studies in rats and cynomolgus monkeys demonstrated evidence of inflammatory stimulation, effects on growing bone physes, and soft tissue mineralization, with adequate exposure margins for the adult patient population.

2.4. Basis of Clinical Starting Dose of TPX-0046-01 FIH Study

For the recommended starting dose of TPX-0046-01 FIH study, an integrated approach in accordance with regulatory guidance, scientifically justified using all available nonclinical data including PK, pharmacodynamics, and toxicity was applied. Based on the projected human PK at the proposed starting dose of 10 mg QD, the exposure-based margins relative to the toxicokinetic parameters at STD10 or highest non-severe toxic dose (HNSTD) are summarized [redacted].

[redacted]

3. STUDY OBJECTIVES AND ENDPOINTS

Preliminary results from Phase 1 dose escalation indicate that TPX-0046 has a [redacted]. Based on the totality of clinical information available, the Sponsor has decided to discontinue further development of TPX-0046 due to the inability to achieve and optimize a dose that could provide a positive benefit-risk profile in the current treatment landscape for *RET* mutant TKI naïve and pretreated setting. This decision was communicated to study sites on 03 October 2022. As such, no new subjects will be enrolled in this study, which will close after all active subjects have completed treatment. Subjects currently receiving treatment in this study will continue treatment at the discretion of the Investigators until need for discontinuation (Section 8.7) or ability to move to alternative care is identified. As such, a synoptic CSR will be generated and submitted to health authorities.

Primary Objectives	Primary Endpoints
Phase 1: • Evaluate the safety and tolerability of TPX-0046 at selected doses • Determine the maximum tolerated dose (MTD) and/or Recommended Phase 2 Dose (RP2D) of TPX-0046	**Phase 1:** • Incidence of first cycle dose-limiting toxicities (DLTs) of TPX-0046 administered orally in a 28-day cycle • MTD and RP2D

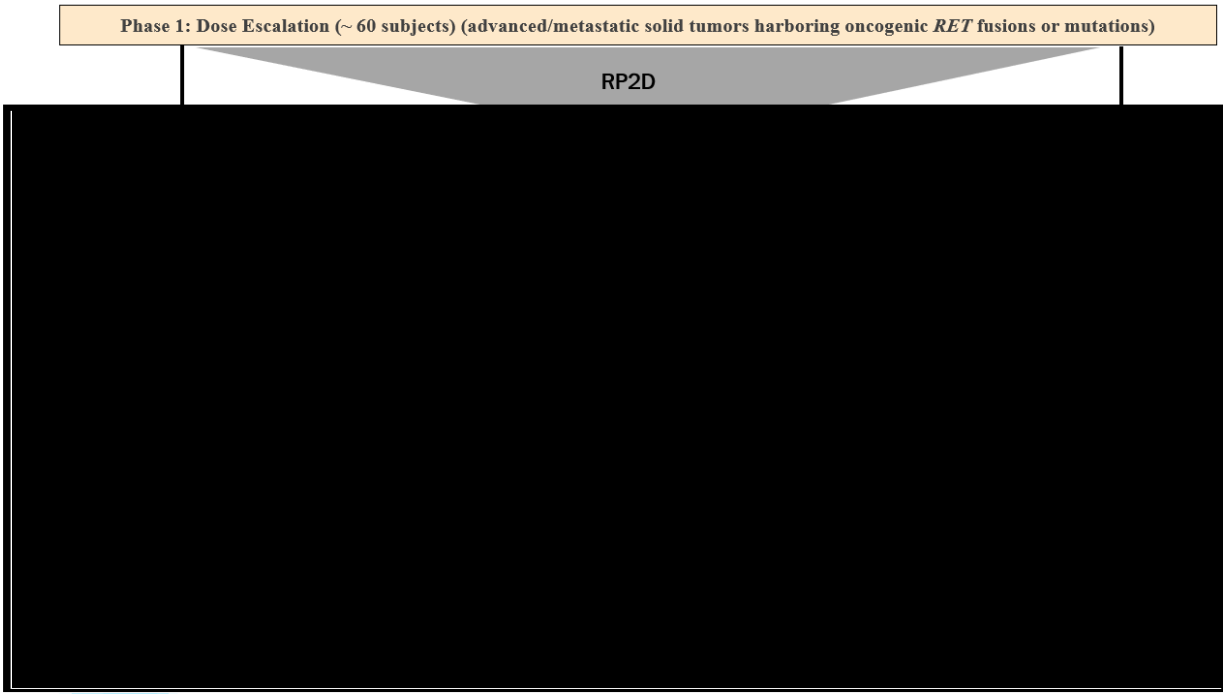
4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase 1/2 multi-center, first-in-human (FIH), open-label study designed to evaluate the safety, tolerability, PK, and efficacy of the novel RET/SRC inhibitor TPX-0046 in adult subjects with advanced/metastatic solid tumors harboring oncogenic *RET* fusions or mutations. The global study consists of two portions as shown in Figure 2: 1) Phase 1 Dose Escalation, Food Effect Sub-study, and Dose Expansion in 6 cohorts, and 2) Phase 2 preliminary efficacy evaluation in six defined subject cohorts.

As the study enrollment will close prior to completing Phase 1 dose escalation, the Phase 1 food effect substudy, Phase 1 dose expansion, and Phase 2 activities will not take place.

Figure 2: Study Design



4.1.1. Phase 1 Dose Escalation

The Phase 1 dose escalation portion will be conducted according to a 3+3 based design. Approximately 60 subjects will be enrolled. Eligible subjects will be adults (≥ 18 years) with advanced/metastatic solid tumors harboring oncogenic *RET* fusions or mutations.

Subjects will be screened for eligibility up to 28 days prior to enrollment (the first day of TPX-0046 administration). On [redacted] subjects will receive a [redacted] post-dose to evaluate [redacted] TPX-0046 [redacted] Following completion of the [redacted], subjects will begin QD dosing of TPX-0046 in 28-day continuous cycles. Dose escalation levels are presented in Table 5). Subjects may receive TPX-0046 until disease progression, unacceptable toxicity, the ability to move to alternative care is identified, or withdrawal of consent,. Treatment beyond radiographic or clinical progression will not be allowed.

An EOT visit will be conducted within 7 days of the last dose of TPX-0046. A safety follow-up visit will be conducted within 28 days of last dose.

Table 5: TPX-0046 Dose Escalation Levels and Regimens

Dose Level	Dose Regimen	Daily Dose (mg/day)	Increment from Previous Daily Dose
1	10 mg QD	10 mg	Not applicable
2	20 mg QD	20 mg	100% increase
3	10 mg BID		
4	30 mg QD	30 mg	50% increase
5	20 mg QD to 30 mg QD	20 mg (1st 14 days), then 30 mg	
6	20 mg BID	40 mg	33% increase
7	20 mg QD to 40 mg QD	20 mg (1st 14 days), then 40 mg	
8	20 mg QD to 20 mg BID	20 mg (1st 14 days), then 40 mg	
9	10 mg QD to 10 mg BID	10 mg (1st 14 days), then 20 mg	50% decrease

Abbreviations: BID = twice daily; QD = once daily.

[redacted]

4.1.1.1. Dose Escalation Schema

The dose escalation schema is illustrated in Table 5. No further dose escalation will occur; dose level 9 was the last to enroll subjects prior to closing study enrollment. DLTs will be evaluated independently in any given dosing regimen.

4.1.1.2. Dose-Limiting Toxicity

Subjects are eligible for DLT evaluation if they experience a DLT after at least one dose of the TPX-0046, or do not experience a DLT after taking at least 75% of the doses expected during the DLT evaluation period. Subjects who do not fulfill these requirements and who discontinue study participation before completing the DLT evaluation period will not be replaced. The DLT evaluation period is defined as 28 days following the first [redacted] dose of the dose regimen administered in Cycle 1 [redacted]

The following AEs, excluding toxicities clearly related to disease progression or intercurrent illness, will be considered DLTs (Table 6).

Table 6: Criteria for Defining Dose-Limiting Toxicities

Category	Criteria
Toxicities resulting in an excessive number of missed doses	Inability to deliver at least 75% of the planned dose intensity of TPX-0046 treatment during the DLT evaluation period (ie, at least 21 days of dosing in a 28-day cycle, beginning in Cycle 1) because of toxicity excluding toxicities clearly related to disease progression or intercurrent illness
Hematologic toxicities	• CTCAE grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 0.5×10^9/L) • CTCAE grade ≥ 4 platelet count decrease (platelets < 25×10^9/L) or CTCAE grade ≥ 3 (< 50×10^9/L- 25×10^9/L) associated with clinically significant bleeding or requiring platelet transfusion • CTCAE grade ≥ 4 anemia • CTCAE grade ≥ 3 febrile neutropenia (defined as ANC < 1,000/mm^3 with a single temperature of ≥ 38.3 °C [≥ 101 °F] or a sustained temperature of ≥ 38 °C [≥ 100.4 °F] for > 1 hour)
Renal	• CTCAE grade ≥ 3 creatinine increase (> 3.0 x baseline or > 3-6 × upper limit of normal [ULN])
Hepatic	• CTCAE grade ≥ 3 total bilirubin elevation (> 3 × ULN) • CTCAE grade ≥ 2 total bilirubin elevation (> 1.5 × ULN) **AND** CTCAE grade ≥ 2 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (> 3 × ULN) • CTCAE grade 3 ALT elevation (> 5 × ULN) that does not resolve to at least grade ≤ 1 within 7 days or any grade > 4 ALT elevation • CTCAE grade 3 AST elevation (> 5 × ULN) that does not resolve to at least grade ≤ 1 within 7 days or any grade > 4 AST elevation
Pancreatic	• CTCAE grade 3 serum [redacted] increased with clinical symptoms or any grade ≥ serum [redacted]
Cardiac	• CTCAE grade ≥ 3
Other AEs	• CTCAE grade 3 vomiting or nausea that does not resolve to grade ≤ 1 within 4 days despite optimal anti-emetic therapy or any grade ≥ 4 vomiting • CTCAE grade 3 diarrhea that does not resolve to grade ≤ 1 within 4 days despite optimal anti-diarrhea treatment or any grade ≥ 4 diarrhea • Any CTCAE grade ≥ 3 AE, except for the exclusions noted below • In view of the Investigators and Sponsor, any other unacceptable toxicity encountered
Exceptions to DLT criteria	• CTCAE grade 3 or 4 elevations in ALP • CTCAE grade 3 electrolytes abnormalities that are adequately managed by IV or PO supplementation as evidenced by an improvement to grade ≤ within 3 days • CTCAE grade 3 fatigue which resolves to grade ≤ 1 in ≤ 7 days • CTCAE grade 3 dizziness which resolves to grade ≤ 1 in ≤ 7 days • CTCAE grade 3 ataxia and weakness which resolves to grade ≤ 1 in ≤ 7 days • Isolated grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; IV = intravenous; PO = per os (by mouth); ULN = upper limit of normal.

In addition, [redacted] not included in the above criteria may be considered a DLT following review by the Sponsor and study Investigators. [redacted] should represent a [redacted].

To fully characterize the safety of TPX-0046, subjects who are discontinued from treatment before completing the DLT evaluation period (28 days, beginning in Cycle 1) due to disease progression or other events unrelated to TPX-0046 will be replaced.

[redacted] for subjects experiencing a DLT

Subjects who experience a DLT are [redacted]. The treatment of these subjects will be evaluated on a case by case basis in consultation with the Investigator and Medical Monitor.

Subjects who experience a DLT [redacted] (if applicable) once adequate recovery is achieved and in the opinion of the Investigator and Medical Monitor the subject is benefiting from therapy.

4.1.1.3. Maximum Tolerated Dose

The MTD is defined as the highest dose level of TPX-0046 observed to cause a DLT in fewer than 33% of the treated subjects in the first treatment cycle (ie, Cycle 1, 28 days). If there are 2 subjects who experience DLTs among the first 3 subjects enrolled, or there is a second DLT in up to 6 subjects enrolled at any dose level, the MTD will have been exceeded, and no additional subjects will be enrolled at that dose level. The MTD will then be established at the prior dose level. If the prior dose cohort has only 3 enrolled subjects, the cohort will be expanded in up to 6 total subjects.

4.1.1.4. Safety Review Committee

For Phase 1 dose escalation of the study, a Safety Review Committee comprised of at minimum the Sponsor Medical Monitor and study Investigators will review all relevant safety and other relevant clinical data (including DLTs).

4.2. Recommended Dose Modifications

Every effort should be made to administer TPX-0046 on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Subjects are to be instructed to notify the Investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery, and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

4.2.1. Dose Interruptions

Dose interruptions may occur in the event of a treatment-related toxicity or a non-treatment-related issue (eg, elective surgery).

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in the dose modification table (see Table 7).

Doses may be held as needed until toxicity resolution. Depending on when the AE is resolved, a treatment interruption may lead to the subject missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle. Subjects not recovering from TPX-0046-related toxicity to grade ≤ 1 [redacted] since the last dose must discontinue TPX-0046 treatment.

If the AE that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Table 7 unless otherwise agreed to following discussion between the Investigator and the Medical Monitor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting [redacted], treatment resumption must be discussed with the Medical Monitor.

Every effort should be made to maintain the tumor assessments and visit scheduling as described in the Schedules of Activities.: Regardless of dose interruptions, cycle lengths will remain 28 days and evaluations are to be performed according to the schedules.

4.2.2. Dose Delays

Re-treatment following treatment interruption for treatment-related toxicity may not occur until the event has resolved to grade ≤ 1 or baseline [redacted] of the event.

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant laboratory assessments may be increased as clinically indicated.

Refer to the Dose Reductions section for AEs requiring dose reduction at the time of treatment resumption (Section 4.2.3).

If subjects require discontinuation of TPX-0046 for [redacted] at any time during the study, then study treatment should be permanently discontinued, unless the Investigator's benefit/risk assessment suggests otherwise after discussion with the Medical Monitor.

Regardless of dose interruptions, cycle lengths will remain 28 days and evaluations are to be performed according to the schedules.

4.2.3. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the TPX-0046 dose may need to be reduced when treatment is resumed. No further dose reduction for the remaining subjects will be allowed.

Dose reduction of TPX-0046 by one and, if needed, 2 dose levels (Table 7) will be allowed depending on the type and severity of toxicity encountered. As a guide, subjects currently being treated at 30 mg QD should reduce one dose level to 20 mg QD. If a subject is being treated at 40 mg QD and requires dose reduction, they should dose reduce to 30 mg QD initially and then 20 mg QD if needed.

For subjects who undergo a dose reduction for an AE other than a protocol-defined DLT, a subsequent re-escalation of the dose may be considered appropriate if deemed safe by the Investigator and after consultation with the Sponsor's Medical Monitor. Subjects requiring more than 2 dose reductions will be discontinued from the treatment and entered in the follow-up phase, unless otherwise agreed between the Investigator and Medical Monitor. All dose modifications/adjustments must be clearly documented in the subject's source notes and case report form (CRF).

All dose reduction cases should be discussed with the Medical Monitor unless specifically outlined in the protocol. In cases where no specific dose adjustment requirements for CTCAE version 5.0 grade 2 treatment-related toxicity exist, Investigators should always manage their subjects according to their medical judgment, which may include dose reduction or interruption based on the particular clinical circumstances in consultation with the Medical Monitor.

[redacted] **for subjects with DLTs is not allowed in the Phase 1 study. Subjects experiencing a DLT** [redacted] **(if applicable) once adequate recovery is achieved.**

Recommended dose reductions are described in Table 7.

Table 7: Dose Modifications for Adverse Events (CTCAE version 5.0)

Toxicity	CTCAE Grade 1*	CTCAE Grade 2*	CTCAE Grade 3	CTCAE Grade 4
Hematologic	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is grade ≤ 2, or has returned to baseline, then resume treatment at the same dose level or reduce by one dose level as per the Investigator's discretion. Grade 3 lymphopenia without other dose- limiting events (eg, opportunistic infection) may continue study treatment without interruption.	Discontinue treatment permanently.
Non-Hematologic	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then reduce by one dose level and resume treatment.	Discontinue treatment permanently.
Pneumonitis (occurred in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Asymptomatic, radiographic findings only: No need for dose adjustment. Initiate appropriate monitoring. Symptomatic: Withhold current dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume treatment at the same dose. Discontinue permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment.	Withhold current dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume treatment at one dose level lower. Discontinue permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment.	Discontinue treatment permanently.	Discontinue treatment permanently.

Toxicity	CTCAE Grade 1*	CTCAE Grade 2*	CTCAE Grade 3	CTCAE Grade 4
AST or ALT elevation	Continue at same dose level.	Continue at same dose level. Withhold current dose if concurrent CTCAE grade ≥ 2 total bilirubin elevation (> 1.5 x ULN).	Withhold current dose until resolves to grade ≤ 1.	Discontinue treatment permanently.
Prolonged QTc	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue at the same dose level.	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue at the same dose level.	Withhold dose. Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Upon recovery to grade ≤ 1: if no other cause for QTc prolongation is found or is considered drug-related resume treatment at 1 dose level lower.	Discontinue treatment permanently.
Dizziness ataxia, or weakness	Continue at same dose level	Withhold current dose until toxicity is grade ≤1 or has returned to baseline	Withhold dose until toxicity is grade ≤1 or has returned to baseline	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then reduce by 1 dose level and resume treatment; or discontinue treatment as per the Investigator's discretion after discussion with Medical Monitor

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; ULN = upper limit of normal

*Cycle will not be extended to cover for the missing doses. In cases where no specific dose adjustments for CTCAE grade 1 or grade 2 treatment-related toxicity are provided, Investigators should always manage their subjects according to their medical judgment, which may include dose reduction or interruption based on the particular clinical circumstances.

4.2.4. Dose Modifications:

In all subjects, treatment options for mitigating should be discussed with the Medical Monitor. Additional dosing guidelines for are provided in Table 8.

Table 8: Recommended Dose Modification Guidelines

	TPX-0046 Dose Modification[a]

[a]Dose reduction or interruption should be implemented upon consultation with the Medical Monitor.

4.2.5. Dose Modifications:

exams including will be conducted per the Schedules of Activities For adverse reactions follow the dose modification guidelines provided in Table 9.

Table 9: Dose Modification Guidelines

CTCAE Grade *	Parameters	TPX-0046 Dose Modification
1	Asymptomatic; clinical or diagnostic observations only	Withhold current dose until toxicity has returned to baseline. If resolves within 4 weeks, resume . Then, consider re-escalation if no recurrence for 4 weeks. If stable for 2 consecutive exams but not resolved, resume
2	Symptomatic; moderate decrease in and or less decreased from known baseline)	Withhold current dose until toxicity has returned to baseline. If resolves within 4 weeks, may resume
3	Symptomatic with marked decrease in or more than of decreased from known baseline,	Withhold current dose until toxicity has returned to baseline. If resolves within 4 weeks, may resume
4	Best corrected or worse in the	Discontinue treatment permanently

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

5. SUBJECT ELIGIBILITY CRITERIA

Each subject must meet all of the following inclusion criteria and none of the exclusion criteria to be enrolled in the study.

5.1. Inclusion Criteria

1. Subjects with histological or cytological confirmation of advanced/metastatic solid tumors harboring oncogenic *RET* fusions or mutations, who either have disease progression on or are intolerant to standard therapy; **OR** are ineligible for standard therapy or for whom no standard therapy exists; **OR** are unlikely to tolerate or derive clinical benefit from standard therapy in the opinion of the Investigator **OR** have declined standard therapy.

    - Subjects must have a documented *RET* gene fusion or oncogenic *RET* mutation as determined by local testing in a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited diagnostic lab.

4. Age ≥ 18 years old (or age ≥ 20 as required by local regulation).
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
6. Presence of measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 criteria). For Phase 2 only, **prospectively** confirmed measurable disease according to RECIST v1.1 by Blinded Independent Central Radiology Review (BICR), selected by Sponsor, PRIOR to enrollment.
7. Life expectancy ≥ 12 weeks.

8. Baseline laboratory values fulfilling the following requirements:

Laboratory Parameter	Result
ANC	[redacted]
PLT	
Hgb	
Total bilirubin	
Liver transaminases (ALT/AST)	
ALP	
Creatinine clearance by Cockcroft-Gault formula*	

Abbreviations: ALP = alkaline phosphatase; ANC = absolute neutrophil count; AST/ALT = alanine aminotransferase / aspartate aminotransferase; Hgb = hemoglobin; PLT = platelet count; [redacted]
*calculated by Cockcroft-Gault formula: (140 - age [yr]) x body weight [Kg] x 1.23 x (0.85 if female) / serum creatinine [µmol/L]. Measured creatine clearance is also acceptable.

9. Subjects with primary CNS tumors or brain metastases who are eligible for the study must meet the following criteria.

   - A minimum of 14 days must have elapsed from the completion of whole brain radiation treatment (WBRT) before the start of treatment with TPX-0046, and all side effects (except for alopecia) from WBRT are resolved to CTCAE version 5.0 grade ≤1.
   - A minimum of 7 days must have elapsed from the completion of stereotactic radiosurgery before the start of treatment with TPX-0046, and all side effects (except for alopecia) from stereotactic radiosurgery are resolved to CTCAE version 5.0 grade ≤1.
   - Subjects requiring steroids at a stable or decreasing dose (≤12 mg/day dexamethasone or equivalent) for at least 14 days are eligible.
   - Subjects on stable doses of levetiracetam (same dose for 14 days) are eligible to be enrolled.

10. For subjects who received prior cytotoxic chemotherapy or prior targeted small molecule therapy at the time of starting treatment with TPX-0046, at least 14 days or five half-lives (whichever is shorter) must have elapsed after discontinuation (or at least 42 days for prior nitrosoureas, mitomycin C, and liposomal doxorubicin; for vandetanib and cabozantinib at least 14 days must have elapsed after discontinuation), and all AEs from prior treatments must have resolved to grade ≤1 CTCAE version 5.0 with the exception of alopecia or other AEs that the Investigator does not consider to be a risk to subject safety.

11. Prior radiotherapy is allowed at least 14 days prior to starting treatment with TPX-0046. All AEs from prior treatments must have resolved to grade ≤1 CTCAE version 5.0 except for alopecia or other AEs that the Investigator does not consider to be a risk to subject safety.

12. Prior immunotherapy or prior antibody targeted therapies for advanced/metastatic disease is allowed. At least 3 weeks must have elapsed after discontinuation of immunotherapy or therapeutic antibodies and all AEs from prior treatments must have resolved to grade ≤1 CTCAE version 5.0 except for alopecia or other AEs that the Investigator does not consider to be a risk to subject safety.
13. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during Screening and be neither breastfeeding nor intending to become pregnant during study participation; and agree to use 2 effective contraceptive methods (combination of any of these options: hormonal, barrier method, or intrauterine device) OR be abstinent OR be surgically sterile prior to study entry OR have a vasectomized partner, for the duration of study participation, and [redacted] after discontinuation of study treatment. Male subjects or male partners of female subjects of childbearing potential must take appropriate precautions to avoid fathering a child from the time of screening [redacted] after last dose of study treatment and to use appropriate barrier contraception, maintain true abstinence, or have had a vasectomy. Highly effective contraceptive methods are described in Appendix B.
14. Male subjects must refrain from sperm donation from screening through [redacted] after the last dose of study drug.
15. Female subjects must refrain from egg donation from screening through [redacted] after the last dose of study drug.
16. Ability to complete all study-required procedures and assessments.
17. Provision of written informed consent signed and dated by the subject and the Investigator, before any study interventions are performed.

5.2. Exclusion Criteria

1. Locally advanced/metastatic solid tumor that is a candidate for curative treatment through radical surgery and/or radiotherapy, or chemotherapy.
2. Presence or history of any other active malignancy within 3 years other than a history of adequately treated basal or squamous cell carcinoma of the skin, or any adequately treated in situ carcinoma.
3. Presence of only one measurable tumor lesion that has already been resected or irradiated before enrollment in the study.
4. Known presence of RET gatekeeper mutation(s) (eg, RET V804X) based on most recent applicable molecular testing.
5. Exposure to more than 1 prior selective RET inhibitor (eg, pralsetinib [BLU-667], or selpercatinib [LOXO-292]) unless a subject has discontinued a RET inhibitor treatment due to intolerance in which case Sponsor approval for eligibility is required.
6. Major surgery within 4 weeks of the start of study.
7. Clinically significant cardiovascular disease (either active or within 6 months before enrollment): myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Classification

Class ≥ II), cerebrovascular accident or transient ischemic attack, symptomatic bradycardia, requirement for anti-arrhythmic medication. Ongoing cardiac dysrhythmias of CTCAE version 5.0 grade ≥ 2.

8. Any of the following cardiac criteria:
   - Mean resting corrected QT interval (ECG interval measured from the onset of the QRS complex to the end of the T wave) for heart rate (QTcF) > 470 msec obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value
     - For patients with QRS > 120 msec: QTcF > 500
   - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec)
   - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, congenital long QT syndrome, family history of long QT syndrome, or any concomitant medication known to prolong the QT interval
9. [redacted]
10. [redacted]
11. Known clinically significant active infections not controlled with systemic treatment (bacterial, fungal, viral including HIV positivity). Subjects with chronic HIV must have a CD4+ T cell count ≥ 350 cell/microliter for eligibility. Subjects with chronic hepatitis B virus infection must have an undetectable viral load (and start antiviral therapy if required according to local or regional guidelines) prior to start of TPX-0046. Subjects with a history of hepatitis C viral infection must have an undetectable viral load.
12. Gastrointestinal disease (eg, Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact drug absorption.
13. Concurrent participation in another therapeutic clinical study.
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or TPX-0046 administration, or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study, or could compromise protocol objectives in the opinion of the Investigator and/or Sponsor.
15. The concomitant use of known strong CYP3A4 inhibitors or inducers is prohibited including their administration within at least 2 weeks prior to the first TPX-0046 dose and throughout the study. Subjects should avoid grapefruit juice or grapefruit/grapefruit-related citrus fruits (Seville oranges, pomelos). See Appendix A for a list of known CYP3A4 inhibitors and inducers.
16. Current or anticipated use of drugs that are known to be sensitive substrates of CYP3A or CYP2B6 should be avoided, including their administration within at least 2 weeks prior

to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of sensitive CYP3A or CYP2B6 (eg, bupropion, efavirenz) substrates must be approved by the Sponsor. See Appendix A for a list of known sensitive substrates of CYP3A.

17. Current or anticipated need for drugs that are sensitive CYP2C9 substrates with narrow therapeutic indices, such as celecoxib, phenytoin, or warfarin is not permitted including their administration at least within 2 weeks prior to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of being a CYP2C9 substrate with narrow therapeutic index must be approved by the Sponsor.

18. Current or anticipated use of drugs that are known to be [redacted] is not permitted, including their administration within at least 2 weeks prior to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of [redacted] must be approved by the Sponsor.

19. Known oncogene drivers other than RET including, eg, anaplastic lymphoma kinase [ALK], ROS1 [receptor tyrosine kinase encoded by the ROS1 gene], or epidermal growth factor receptor [EGFR]) conferring sensitivity to targeted therapies.

6. STUDY TREATMENT

6.1. Allocation to Treatment

All subjects will be allocated to receive TPX-0046. For the Phase 1 dose-escalation portion of the study, subjects will be assigned according to the currently open dosing level at the time of enrollment.

Dose level allocation will be performed by the Sponsor after subjects have given their written informed consent and have completed the necessary baseline assessments. The site staff will complete a Registration Form for the designated Sponsor study team member or designee. The Sponsor will assign a subject identification number and supply this number to the site. The subject identification number will be used on all study related documentations at the site.

No subject shall receive TPX-0046 until the Investigator or designee has received the following information in writing from the Sponsor:

- Confirmation of the subject's enrollment;
- Specification of the dose level for that subject and;
- Permission to proceed with dosing the subject.

6.2. Investigational Product Supplies

6.2.1. Dosage Forms and Packaging

The investigational TPX-0046 drug product is supplied as [redacted] capsules (Table 10). TPX-0046 capsules are [redacted] capsules manufactured for use in the proposed clinical program. High-density polyethylene

(HDPE) bottles induction sealed with child resistance caps were selected as the container closure. TPX-0046 will be supplied in bottles containing 30 capsules of a single strength. TPX-0046 will be supplied by the Sponsor. See the Investigator's Brochure for details on the original and new formulations.

Table 10: TPX-0046 Investigational Product

Product Name:	TPX-0046
Dosage Form:	Capsules
Unit Dose:	[redacted]
Route of Administration:	Oral
Physical Description:	[redacted]

NOTE: Drug product will not be available past July 2023.

6.2.2. Investigational Product Storage and Accountability

TPX-0046 will be stored at 20 °C – 25 °C (68 °F – 77 °F) with excursions permitted between 15 °C and 30 °C (59 °F – 86 °F). Subjects should be instructed to keep their medication in its original container and stored at 15 °C to 30 °C (59 °F to 86 °F). Returned medication should be stored separately from medication that is yet to be dispensed. The TPX-0046 capsule bottle must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

6.2.3. Destruction of Investigational Product Supplies

At each cycle visit, and at the end of the treatment study, all unused or partially used bottles must be returned by subjects to the Investigator and the Sponsor will provide instructions as to disposition of any unused TPX-0046. If the Sponsor authorizes destruction at the study site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

6.3. Administration

TPX-0046 (capsules) will be administered orally according to the assigned dose regimen with approximately 8-oz water (240 mL) [redacted] in 28-day continuous cycles. If a subject misses a daily dose, they must be instructed not to “make it up” the next day. If a subject vomits at any time after taking a dose, they must be instructed not to “make it up,” but to resume subsequent doses as prescribed. If a subject inadvertently takes 1 extra dose during a day, the subject should not take the next dose of TPX-0046. Subjects should also be instructed to swallow the trial medication whole and not chew the capsule prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact.

6.3.1. Dose Escalation

TPX-0046 (capsules) will be administered orally as a [redacted] On Cycle 1 Day 1, TPX-0046 will be administered either QD or BID per the dosing regimen with approximately 8-oz water (240 mL) [redacted] in 28-day continuous cycles. [redacted]

For the QD regimen, TPX-0046 will be administered orally approximately twenty-four hours apart. Subjects should take their medication at approximately the same time each day and not take more than the prescribed dose at any time. However, a variance of up to 12 hours is allowed for any given dose, rather than miss a day's dose for subjects on QD regimen.

For the BID regimen, TPX-0046 will be administered orally approximately twelve hours apart. Subjects should take their medication at approximately the same time each day and not take more than the prescribed dose at any time. However, a variance of up to 6 hours is allowed for any given dose, rather than miss a day's dose for subjects on BID regimen.

For the [redacted], a [redacted] dose of TPX-0046 (eg, [redacted]) will be administered as [redacted]. On Cycle 1 Day 1, the [redacted] dose will be administered [redacted]. If tolerated ([redacted] treatment related adverse events), patients will have their doses [redacted] to a [redacted] If not tolerated, patient [redacted] should be discussed with the Sponsor Medical Monitor.

6.3.2. Food Requirements (except for the Food Effect Sub-study)

TPX-0046 capsules will be administered orally every day with approximately 8-oz (240 mL) of water [redacted]. The subject should refrain from [redacted] for at least [redacted]. [redacted] will be allowed ad libitum except for 1 hour before and 1 hours after drug administration. This requirement may be removed pending receipt of data from the food effect sub-study.

6.4. Subject Compliance

All doses of TPX-0046 will be dispensed by the appropriately designated study staff at the investigational site.

Subjects will be required to bring the dosing diary and all empty and partially used TPX-0046 bottles and any leftover TPX-0046 to every visit. The number of capsules returned by the subject will be counted, documented, and recorded. Treatment compliance will be evaluated by noting the discrepancy among the assigned dose, the dose administered, and the reason for the discrepancy will be recorded in the source documents.

6.5. Concomitant Treatments

The CRF must capture all concomitant medications, blood products, as well as non-drug interventions (eg, paracentesis) received by subjects from the date of signed informed consent until the EOT visit. The Investigator should be alerted if the subject is taking any agent known to affect or with the potential for drug interactions.

6.5.1. Prohibited Concomitant Medications

The concomitant use of known strong CYP3A4 inhibitors is prohibited including their administration at least within 2 weeks prior to the first TPX-0046 dose and throughout the study. Subjects should avoid grapefruit juice or grapefruit/grapefruit-related citrus fruits (Seville oranges, pomelos). Coadministration of TPX-0046 in combination with strong CYP3A4 inducers is prohibited including their administration at least within 2 weeks prior to the first TPX-0046 dose and throughout the study. See Appendix A for a list of known CYP3A4 inhibitors and inducers.

Current or anticipated use of drugs that are known to be sensitive substrates of CYP3A or CYP2B6 should be avoided, including their administration within at least 2 weeks prior to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of sensitive CYP3A or CYP2B6 (eg, bupropion, efavirenz) substrates must be approved by the Sponsor. See Appendix A for a list of known sensitive substrates of CYP3A.

Current or anticipated use for drugs that are sensitive CYP2C9 substrates with narrow therapeutic indices, such as celecoxib, phenytoin, or warfarin is not permitted including their administration at least within 2 weeks prior to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of being a CYP2C9 substrate with narrow therapeutic index must be approved by the Sponsor.

Concomitant use of drugs that are known to be [redacted] is prohibited including their administration at least within 2 weeks prior to the first TPX-0046 dose and throughout the study. Concomitant medication suspected of [redacted] must be approved by the Sponsor.

If there is a question about a particular concomitant medication, discuss with the Medical Monitor.

6.5.2. Other Anti-tumor or Investigational Drugs

Additional systemic anti-tumor therapy is not permitted while subjects are receiving study therapy.

6.5.3. Supportive Care

Palliative and supportive care for disease-related symptoms may be administered at the Investigator's discretion and according to the specific supportive care product Prescribing Information or the current American Society of Clinical Oncology (ASCO) guidelines.

6.5.4. Anti-diarrheal, Anti-emetic Therapy

Primary prophylaxis of diarrhea, nausea, and vomiting is [redacted] in the first cycle in the Phase 1 dose escalation portion of the study. Primary prophylaxis in subsequent cycles is at the Investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the Investigator with Sponsor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatments section.

6.5.5. Anti-inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatments section.

6.5.6. Corticosteroids

Chronic systemic corticosteroid use (prednisone ≥ 12.5 mg/day or dexamethasone ≥ 2 mg/day) for palliative or supportive purpose is not permitted (unless administered for adrenal insufficiency). Acute emergency administration, topical application, inhaled sprays, eyedrops or local injections are permitted.

6.5.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and TPX-0046 required to minimize the risk of [redacted] has not been determined. Stopping TPX-0046 is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate TPX-0046 treatment should be based on a clinical assessment of satisfactory [redacted] recovery from surgery.

7. STUDY ASSESSMENTS

As no new subjects will be enrolled in this study, Investigators will follow assessments for subjects currently enrolled as described in the schedule of activities for Phase 1 dose escalation (Table 1). Additional testing considered necessary for safety related to study drug may be performed at the discretion of the Investigator.

7.1. Informed Consent

Prior to conducting protocol-specific assessments for Phase 1 (dose escalation, dose expansion, and food effect) and Phase 2, written informed consent and any other authorizations must be signed and dated by the subject or subject's legal representative.

Remaining subjects will be notified of the close of enrollment and termination of development of the protocol via informed consent.

7.2. Physical Examination

A complete physical examination, including a targeted neurological examination, will be performed by either the Investigator or a sub-Investigator according to the Schedules of Activities.

Height and weight will be collected as part of the physical exam. Height will be collected at Screening only.

Clinically significant abnormal findings must be recorded in the applicable electronic CRF and followed by the Investigator, sub-Investigator, or other qualified site staff at the next scheduled visit or earlier as clinically indicated.

7.3. Performance Status

The ECOG performance scale will be assessed at Screening and according to the Schedules of Activities.

7.4. Subject Diary and Compliance

All doses of TPX-0046 will be dispensed by the appropriately designated study staff at the investigational site.

Subjects will be required to bring the dosing diary and all empty and partially used TPX-0046 bottles and any leftover TPX-0046 to every visit. The number of tablets returned by the subject will be counted, documented, and recorded. Treatment compliance will be evaluated by noting the discrepancy between the assigned dose and the dose administered, and the reason for the discrepancy will be recorded in the source documents.

7.5. Laboratory Assessments

Laboratory assessments as described in Table 11 will be performed per Schedule of Activities (Table 1). Assessments beyond Cycle 3 will be done based on symptomatology and per Investigator discretion.

Table 11: Safety Laboratory Tests

Hematology	Complete Blood Count with Differential: Hemoglobin, platelets, WBC, Absolute Neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute Basophils or % reticulocytes
Chemistry	ALT, AST, ALP, Sodium, Potassium, Magnesium, Chloride, Total calcium, Total bilirubin, BUN or Urea, Creatinine, Uric Acid, Glucose (nonfasted), Lipid panel (total cholesterol, LDL, HDL, triglycerides), Albumin, Phosphorus or Phosphate, Bicarbonate, Total protein, Lactate dehydrogenase, [redacted]
Coagulation	PT or INR, PTT
Urinalysis	Urine dipstick for urine protein: If positive and clinically significant, microscopic (Reflex Testing) Urinalysis includes the analysis of protein, glucose, ketones, blood, and specific gravity. A microscopic (white blood cells/high-power field [HPF], red blood cells/HPF, and any additional findings) exam will be performed only if the urinalysis result is abnormal.
Pregnancy Test	Serum pregnancy test for female subjects of childbearing potential

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high-density lipoprotein; INR = International normalized ratio; LDL = low-density lipoprotein; PT = prothrombin; PTT = prothrombin time; WBC = white blood cell.
*For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

7.6. Cardiac Safety Monitoring

7.7. Cardiac safety monitoring should be done based on symptomatology and at Investigator's discretion. Tumor Response Assessments

Tumor response assessments will be performed per standard of care.

Imaging studies will include a computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the brain, chest, abdomen, pelvis. For subjects diagnosed with primary brain tumors, only the MRI of the brain will be required at Screening and during the study.

Tumor assessments will include all known or suspected disease sites and will be performed per specified timepoints according to the Schedules of Activities. For all tumor assessments, the method of assessment that was used at Screening should be the same method used throughout the study.

For all subjects, radiographic confirmation of objective tumor response or disease progression will be based on RECIST v1.1 and assessed locally.

Subjects discontinuing study treatment before documented radiographic progression will complete an EOT visit and safety follow-up visit per Section 8.4.

For subjects discontinuing the study treatment due to documented radiographic progression survival status will be obtained via a phone call or medical chart review, including information about subsequent anticancer therapies (including best response) every three months until death, loss of follow-up, or withdrawal of consent, whichever comes first.

8. STUDY CONDUCT

Scheduled protocol-related activities will be performed at specified timepoints and within windows as outlined in the Schedule of Activities for Dose Escalation (Table 1). If a visit is missed for any reason, the next scheduled visit should occur as originally planned.

8.1. Screening And Eligibility

All patients being considered for the study and are eligible for screening must provide informed consent for the study prior to completing any study-specific procedures (up to 28 days prior to initial dose). A patient number will be assigned. Subjects will be screened within 28 days prior to the administration of TPX-0046 to confirm that they meet the eligibility criteria. Subjects participating in the Phase 1 Dose Escalation, Dose Expansion (QD, BID, and [redacted]) and Food effect Sub-study must have eligibility confirmed [redacted].

The following items must be completed as part of the screening procedures:

- Eligibility checklist (see complete list in Sections Section 5.1 and Section 5.2) must be completed for each subject and sent to the Sponsor for eligibility confirmation before enrollment
- Source documents for molecular pathology report, detailing the specific test that confirms *RET* gene fusion, should be submitted for the Sponsor's approval of eligibility

- Imaging studies (CT or MRI of the chest, abdomen, and pelvis and MRI of the brain) should be submitted and confirmed by BICR (Phase 2 only)

8.2. Timing of Clinical Procedures

On visits that require in-clinic dosing, clinical assessments should be conducted as described in Table 1.

8.3. Study Duration

Subjects will remain on study treatment until disease progression, development of unacceptable toxicity, the ability to move to alternative care is identified, or withdrawal of consent.

8.4. Subject Treatment Discontinuation

Subjects discontinuing the study treatment prior to documented radiographic progression will complete an EOT visit (Section 8.5) and safety follow-up visit (Section 8.6).

8.5. End of Treatment Visit

For subjects who discontinue study drug, the EOT visit should occur as soon as possible (within 7 days) after the last dose of investigational product.

8.6. Safety Follow-up Visit

The safety follow-up visit should occur approximately 28 days after the last dose or before any new anticancer treatment is started.

8.7. Subject Discontinuation and Withdrawal from Study

A subject may be discontinued from study treatment at any time if the subject, the Investigator, or the Sponsor Medical Monitor determine that it is not in the subject's best interest to continue on study. The following is a list of possible reasons for early discontinuation of study treatment:

- Disease progression (treatment beyond radiographic or clinical progression will not be allowed)
- Any adverse event that cannot be adequately managed with dose modifications, including dose interruption > 28 days (unless there is reasonable evidence of clinical benefit to justify continuation on the protocol - which must be previously discussed with Turning Point Therapeutics)
- Protocol violation requiring discontinuation of study treatment
- Subject is not compliant with study procedures
- Lost to follow-up
- Subject withdrawal of consent for further treatment
- Investigator identifies alternative treatment option for the patient
- Turning Point Therapeutics' early termination of study. Reasons for terminating the study may include, but are not limited to, the following:

- All enrolled subjects have discontinued study treatment
- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

Data to be collected for the EOT visit are described in the Schedules of Assessments.

Subjects will be followed for at least 28 calendar days after the last dose of TPX-0046. If a subject is discontinued from treatment due to an AE, the subject will be followed until the AE has resolved or stabilized as per Section 9.3.4.

8.7.1. Withdrawal of Consent

A subject may withdraw consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the Investigator in writing of the decision to withdraw consent from future follow up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is only from further receipt of the investigational product or also from study procedures and/or posttreatment study follow up and entered on the appropriate CRF page. If vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

8.7.2. Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow up with persons authorized by the subject as noted above. Lost to follow up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the Investigator's use of a third-party representative to assist in the follow-up part of the study has been included in the subject's informed consent, then the Investigator may use a Sponsor retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up part of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information. If, after all attempts, the subject remains lost to follow up, then the last known alive date as determined by the Investigator should be reported and documented in the subject's medical records.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject refuses further visits, no further study-specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

9. ADVERSE EVENT REPORTING

Adverse event assessments will be performed at times specified at each clinic visit as specified in the Schedules of Activities:

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be reported as an AE or serious adverse event (SAE). Radiographic progression according to RECIST v1.1 criteria should be documented to support disease progression. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

Adverse events will be graded according to CTCAE version 5.0. The type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory abnormalities will be reported.

9.1. Adverse Events, Serious Adverse Events, and Anticipated Serious Adverse Events

9.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a subject or 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 considered related to the medicinal product. For this study, AEs will be recorded starting at the time of first administration of the investigational product through the last follow-up visit for all dose levels/cohorts.

AEs include, but are not limited to, (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For recording purposes, pregnancy in the partner of a healthy male subject is a medical condition and is not considered an AE.

Subjects should be questioned in a general way, without leading the subject or asking about the occurrence of any specific symptom.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a gastric ulcer, it would not be appropriate to record the AE by describing the symptoms “stomach pain,” “indigestion,” or “appetite loss”. The AE medical term of “gastric ulcer” should be recorded as the AE.

9.1.2. Definition of Serious Adverse Events

A serious AE (SAE) (an experience or a reaction) is an AE that leads to one or more of the following:

- Death – An AE that causes or contributes to a fatal outcome
- Is life-threatening – Refers to an event/reaction, in the view of the Investigator, places the subject at immediate risk of death. It does not refer to an event/reaction that hypothetically might cause death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization, except for the following:
  - Hospitalization for respite care or social admissions (eg, lack of housing, economic inadequacy, family circumstances)
  - Hospitalization solely for coordination of care, including hospice arrangements
  - Hospitalization due solely to progression of the underlying cancer
  - Hospitalization that was necessary solely because of subject requirement for outpatient care outside of normal outpatient clinic operating hours
  - Hospitalization for same day surgeries (as outpatient/same day/ambulatory procedures)
  - Planned hospitalization required by the protocol (eg, for study drug administration or insertion of access device for study drug administration)
  - Hospitalization for a preexisting condition, provided that the hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease and the subject has not experienced an adverse event
- Results in persistent or significant disability/incapacity (ie, the adverse event results in substantial disruption of the subject's ability to conduct normal life functions)
- Congenital anomaly/birth defect
- Important medical events, when based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

9.1.3. Definition of Anticipated Serious Adverse Events

Anticipated SAEs are SAEs that could be anticipated due to the underlying metastatic disease in the population being studied in this clinical trial. This list of possible anticipated SAEs by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms was adapted from Hyde, 1974; Chute, 1985; and Silvestri, 1995.

- Cough
- Abnormal loss of weight
- Weight decreased
- Dyspnoea
- Chest pain

- Neck pain
- Hemoptysis
- Cancer pain
- Bone pain
- Dysphonia
- Musculoskeletal pain
- Headache
- Muscular weakness
- Lymphadenopathy
- Malignant neoplasm

9.2. Relationship to the Investigational Product

The Investigator will document his or her opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 12. A "reasonable possibility" that the investigational product caused the AE means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable," the event will be considered related to the investigational product.

Table 12: Relationship of Adverse Events to Investigational Product

Relationship	Description
Related	1. A clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the investigational product, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge) 2. An event that could also be explained by concurrent disease or other drugs or chemicals where information on investigational product withdrawal may be lacking or unclear 3. Re-challenge or de-challenge information is not required to fulfill this definition
Not Related	4. A clinical event, including a laboratory test abnormality, with sufficient evidence to accept that there is no causal relationship to investigational product administration (eg, no temporal relationship to investigational product administration, because the investigational product was administered after the onset of the event; investigation shows that the drug was not administered; proof of other cause) 5. An event with a temporal relationship to investigational product administration, which makes a causal relationship improbable, and other drugs, chemicals, or underlying disease provide plausible explanations

Adverse events will be assessed using CTCAE version 5.0. AEs must be assessed for severity (mild, moderate, severe, life-threatening, or fatal), and must be entered on the AE page of the eCRF. The CTCAE version 5.0 grade refers to the severity of the AE. The CTCAE version 5.0 grading system and severity assessments are described in Table 13. It should be noted that the

term “severe” is used to grade intensity and is not synonymous with the term “serious.” The assessment of severity is made regardless of the investigational product relationship or the seriousness of the AE.

Table 13: Severity of Adverse Events

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[bc]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by subjects who are not bedridden.
[c] If an event is assessed as a "significant medical event," it must be reported as a SAE per the definition of SAE.
[d] Grade 4 and 5 events must be reported as SAEs per the definition of SAE.

9.3. Reporting of Adverse Events and Serious Adverse Events

9.3.1. Reporting of Adverse Events

Adverse event data will be collected from the time of first dose until 28 days after last dose.

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the subject’s medical records, in accordance with the Investigator’s normal clinical practice and on the AE CRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product. Redacted medical record source documents will be requested for all SAEs and emergency room visits.

9.3.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all responsibilities for immediately reporting SAEs to the Sponsor. Immediate reporting implies within 24 hours of becoming aware of the occurrence of an SAE.

After informed consent for the clinical trial has been obtained but prior to initiation of study drug, only SAEs related to protocol-mandated assessments should be reported.

SAE data will be collected from the time of the first dose until 28 day after the last dose.

The Investigator will assess whether the event is causally related to the investigational product. The Sponsor will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after

the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by completing and sending a Serious Adverse Event Report Form.

The Investigator must report SAEs by completing and sending a Serious Adverse Event Report Form and completing the AE/SAE CRF section.

Investigators should record all case details that can be gathered immediately (ie, within 24 hours after learning of the event) on the SAE report form and submit the report via fax or email (please refer to the Study Manual).

The Sponsor or designee will notify the appropriate regulatory authorities in accordance with local government regulations.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the Sponsor in the same manner as described above for the initial SAE report. Redacted medical record source documents will be requested for all SAEs and emergency room visits.

9.3.3. Deaths

Death due to disease progression will not be reportable as an SAE. All deaths, regardless of relationship to study drug, must be recorded on the Death CRF and on the Adverse Event CRF if considered an adverse event.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event CRF. Generally, only one such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event CRF. If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.

9.3.4. Follow-up of Adverse Events and Serious Adverse Events

All AEs must be followed until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the subject is lost to follow-up.

AEs ongoing at the final follow-up assessment that are deemed to be “related” to the investigational product or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the subject or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented in the CRF. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

9.4. Pregnancy

9.4.1. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, because of treatment or environmental exposure) the investigational product; or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to the investigational product. An example of environmental exposure would be a case involving direct contact with the TPX-0046 product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male subject has been exposed (eg, because of treatment or environmental exposure) to the investigational product before or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the subject's treatment or within [redacted] after the last dose of the investigational product, for female subjects and male subjects respectively, the Investigator must submit this information to [redacted] on a Pregnancy Report Form In addition, the Investigator must submit information regarding environmental exposure to a Sponsor product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage). This must be done regardless of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

The Investigator will follow the pregnancy until completion or until pregnancy termination and notify the Sponsor's Medical Monitor/or designee of the outcome as a follow-up to the initial pregnancy report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion to include miscarriage and missed abortion.
- Neonatal deaths that occur within one month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after one month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg,

follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will request consent from the study subject and partner for additional information. The Investigator must document in the source documents that consent was requested.

9.4.2. Pregnancy Reporting

Female subjects or partners of male subjects of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within [redacted] after the last dose of the investigational product, for female subjects and male subjects respectively.

The Investigator should discontinue the investigational product and counsel the subject or partner of a male subject, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (eg, an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported and submitted within 24 hours.

9.4.3. Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female subject or partner of a male subject exposed to the investigational product should be classified as an SAE and reported as such. Any spontaneous abortion or miscarriage should be reported in the same fashion (therapeutic abortions are excluded from expedited reporting and would be captured as pregnancy outcome information).

For additional guidance regarding use of contraceptives see Appendix B.

10. STATISTICAL METHOD ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor or their designee. The SAP may modify the initial analysis plan outlined in the protocol; however, any major modifications of the primary endpoint and/or analysis methods will also be reflected in a protocol amendment.

10.1. Analysis Sets

10.1.1. Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects who receive at least one full or partial dose of TPX-0046. This will be the same as the Safety Analysis Set. The FAS set will be used for the summary of subject dispositions, demographics, and baseline characteristics, and safety analysis.

10.1.2. Efficacy Evaluable Analysis Set

Efficacy Evaluable (EE) Analysis Set will include all enrolled subjects who (1) have received at least one dose of study treatment; (2) *RET* fusion+ or mutation+ from local testing (LTD) can be confirmed by central lab; (3) have a baseline tumor assessment with measurable disease and have

at least 1 on-study tumor assessment per RECIST v1.1; and (4) have no major protocol violations that could affect efficacy.

The EE analysis set will be used for efficacy analyses for Phase 1.

10.1.3. Safety Analysis Set

The Safety Analysis Set includes all enrolled subjects who receive at least one dose of TPX-0046. Each subject will be classified into and analyzed consistently within one treatment group.

10.2. Sample Size Determinations

10.2.1. Phase 1 Dose Escalation

For Phase 1 dose escalation, 41 subjects have enrolled across 9 dose levels. Enrollment is closed.

10.3. Statistical Analysis

10.3.1. General Considerations

10.3.1.1. Software

All data listings, summaries and statistical analyses will be generated using SAS® Version 9 or above, or equivalent statistical software.

10.3.1.2. Missing Data

All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified missing data will not be imputed. Partial dates for AEs and concomitant medications will be imputed using the most conservative rules.

10.3.1.3. Baseline Measurements

The last measurement on or prior to the date of the first dose will serve as the baseline measurement and should be within 28 days of first dose.

10.3.1.4. Data Presentation

Categorical variables will be summarized in frequency tables, with the counts and percentage of subjects in each category. Percentages given in the summary tables will be rounded and thus may not always add up to exactly 100 percent. For continuous variables, summary statistics will include N, mean, standard deviation, median, and minimum and maximum values (range).

10.3.1.5. Duration

Duration, except for duration of treatment, is calculated as:

Duration (days): (End Date – Start Date + 1)

Duration (weeks): (End Date – Start Date + 1)/7

Duration (months): (End Date – Start Date + 1)/30.4375*

Duration (years): (End Date – Start Date + 1)/365.25**

*Average number of days in a month = 30.4375, which is based on 365.25/12 where 365.25 represents the average number of days in a year and 12 represents the number of months in a year
**Average number of days in a year = 365.25, reflecting the Julian Year of three years with 365 days each and one leap year of 366 days.

10.3.2. Subject Disposition

A disposition table will summarize the number of subjects enrolled, treated, discontinued from study treatment and the reasons for treatment discontinuation, and end-of-study and reasons. The reason for discontinuation and end-of-study will be summarized using the categories specified in the Study Discontinuation, and End-of-Study CRF page, by cohort.

10.3.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics including disease staging, histology, smoking history, ECOG performance status, CNS metastasis at baseline, prior treatment history, and molecular diagnostic test results on oncogenic *RET* fusions or mutations will be summarized from the CRF data for all subjects in the FAS by cohort.

10.3.4. Efficacy Analyses

Radiologic assessments evaluated by the Investigator will be explored for Phase I in efficacy analysis set. Number of subjects with ORR will be summarized.

10.3.4.1. Objective Response Rate

The ORR will be defined as the proportion of subjects with a confirmed complete response (CR) or partial response (PR). A confirmed response is a response that persists on a repeat imaging performed at least 4 weeks after initial documentation of response. Subjects with a confirmed objective response (CR or PR) will be referred to as responders. Non-responders will include subjects without a confirmed objective response, stable disease (SD), progressive disease (PD), not evaluable (NE), or non-CR/non-PD (NN).

10.3.5. Safety Analyses

Safety analyses will be performed using the Safety Population for each cohort, as well as for all cohorts combined.

10.3.5.1. Extent of Exposure

Exposure analysis will be based on the actual dose administered for the investigational product. Duration of treatment will be calculated as the last dose date minus the first dose date plus one day. Duration of treatment and total daily dose amount will be summarized using descriptive statistics. The number of subjects treated by cycles will be summarized.

10.3.5.2. Adverse Events

AEs will be graded according to the CTCAE version 5.0 and coded to preferred term and system organ class using the MedDRA version 21.1 or higher.

All AEs reported during the AE reporting period (inclusive AEs after the [redacted] post last dose of the investigational product) will be considered as treatment-emergent adverse events (TEAEs).

For the dose escalation phase, the number of subjects with DLTs by dose level will be listed.

Incidence rates will be summarized with frequency and percentage by MedDRA SOC and preferred term. In addition, AE incidence rates will also be summarized by severity and relationship to investigational product. Treatment-related AEs are those judged by the Investigator to be at least possibly related to the investigational product. Subjects with multiple occurrences of events will be counted only once at the maximum severity to investigational product for each preferred team, SOC, and overall. Deaths that occur within 28 days after the last dose of the investigational product are defined as on-study deaths and reported as SAEs within the required reporting period.

11. QUALITY CONTROL AND QUALITY ASSURANCE

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported for each subject. Source documentation supporting the data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

12. DATA HANDLING AND RECORD KEEPING

12.1. Case Report Forms/Electronic Data Record

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries will be entered, tracked, and resolved directly through the electronic data capture (EDC) system. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

12.2. Study Monitoring, Audits, and Inspections

Site visits will be conducted by an authorized Sponsor representative, who will inspect study data, subjects' medical records, and CRFs according to GCP, the FDA, and the International Conference on Harmonisation (ICH) guidelines. In addition to monitoring by the Sponsor or its designees, the study may be audited by representatives of the FDA or other regulatory authorities, who will also be permitted access to study documents. The Investigator should immediately notify the Sponsors' Clinical Operations department or designee of any proposed or scheduled audits by regulatory authorities.

The Investigator will permit authorized representatives of the Sponsor or designee and national or local health authorities to inspect facilities and records relevant to this study.

The Investigator must obtain Institutional Review Board (IRB)/IEC approval for the investigation. Initial IRB/IEC approval and all materials approved by the IRB/IEC for this study,

including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

12.3. Inspection of Records

The Sponsor and designees of the Sponsor will be allowed to conduct site visits to the investigational facilities for monitoring any aspect of the study. The Investigator agrees to allow Sponsor representatives to inspect the drug storage area, investigational product inventory, drug accountability records, subject charts and study source documents, and other records relative to the study conduct.

12.4. Record Retention

The Investigator will coordinate with the study site to ensure all documentations relating to the study for a period of 2 years after marketing application approval or, if not approved, 2 years after the notification to the FDA of the discontinuance of the investigational product for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer; but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of TPX-0046.

13. ETHICS

13.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC, as appropriate. The Investigator must submit written approval to the Sponsor before he or she can present informed consent and begin screening activities for any subject in the study.

The Investigator is responsible for informing the IRB/IEC of any amendment(s) to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study, if applicable. The protocol must be re approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

13.2. Protocol Compliance

The Investigator will conduct the trial in compliance with the protocol provided by the Sponsor. Modifications to the protocol may not be made without agreement of both the Investigator and

the Sponsor. Changes to the protocol will require a written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable, regulatory authority(ies) permit, and expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor/Designee and/or the Study Monitor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented on the appropriate CRF and in the source documentation and reported to the IRB/IEC per institutional and/or local requirements.

13.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Sponsors' (or its designee's) applicable policies and standard operating procedures (SOPs).

13.4. Written Informed Consent

The Investigator at the study center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk(s), and benefit(s) of the study. Subjects must also be notified that they are free to withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures.

The Investigator must maintain the original signed ICF. A copy of the signed ICF must be given to the subject.

13.5. Subject Confidentiality

To maintain subject privacy, data capture tools, investigational product accountability records, study reports, and communications will identify the subject only by initials and the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records, including medical history, laboratory studies, and medication administrations, for verification of data gathered and to audit the data collection process. This information will be accessed for the duration of the research study for data reconciliation purposes. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.6. Post-Trial Access

A subject will not be eligible to receive study drug after the end of the study since the Sponsor has decided to discontinue development of TPX-0046.

14. PUBLICATION OF STUDY RESULTS

All information regarding the investigational product supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for any other purposes without written consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of the Sponsors' investigational product program and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, shareholders, or consultants as required.

Additionally, the Investigator should obtain authorization from the clinical trial subjects in writing and ensure that all 18 identifiers (outlined in the Health Insurance Portability and Accountability Act ([HIPAA]) Privacy Rule (November 26, 2012) have been removed from the data.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. Investigator publication rights will be provided in the clinical trial agreement. Additionally, the Investigator should obtain authorization from the clinical trial subjects in writing and ensure that all 18 identifiers (outlined in the HIPAA Privacy Rule [November 26, 2012]) have been removed from the data.

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Appendix A. Strong CYP3A4/5 Inhibitors or Inducers, SENSITIVE CYP3A SUBSTRATES, and Medications that Cause QTc Prolongation

Strong CYP3A4/5 Inhibitors or Inducers of CYP3A4/5

Strong CYP3A4/5 Inhibitors	Strong CYP3A4/5 Inducers
Macrolide antibiotics: clarithromycin and telithromycin	Carbamazepine
	Efavirenz
Anti-fungal: itraconazole, ketoconazole, voriconazole, posaconazole	Phenobarbital
	Phenytoin
Anti-virals: lopinavir, indinavir, nelfinavir, ritonavir, saquinavir, amprenavir	Rifampin
	Rifabutin
Conivaptan	Rifapentin
Mibefradil	St John's wort
Nefazodone	
Troleandomycin	
Miscellaneous: Grapefruit juice	

Sensitive CYP3A Substrates

alfentanil	avanafil	buspirone	conivaptan
darifenacin	darunavir	ebastine	everolimus
ibrutinib	lomitapide	lovastatin	midazolam
nisoldipine	saquinavir	simvastatin	sirolimus
tacrolimus	tipranavir	triazolam	vardenafil
budesonide	dasatinib	dronedarone	eletriptan
eplerenone	felodipine	indinavir	lurasidone
maraviroc	quetiapine	sildenafil	ticagrelor
tolvaptan	naloxegol		

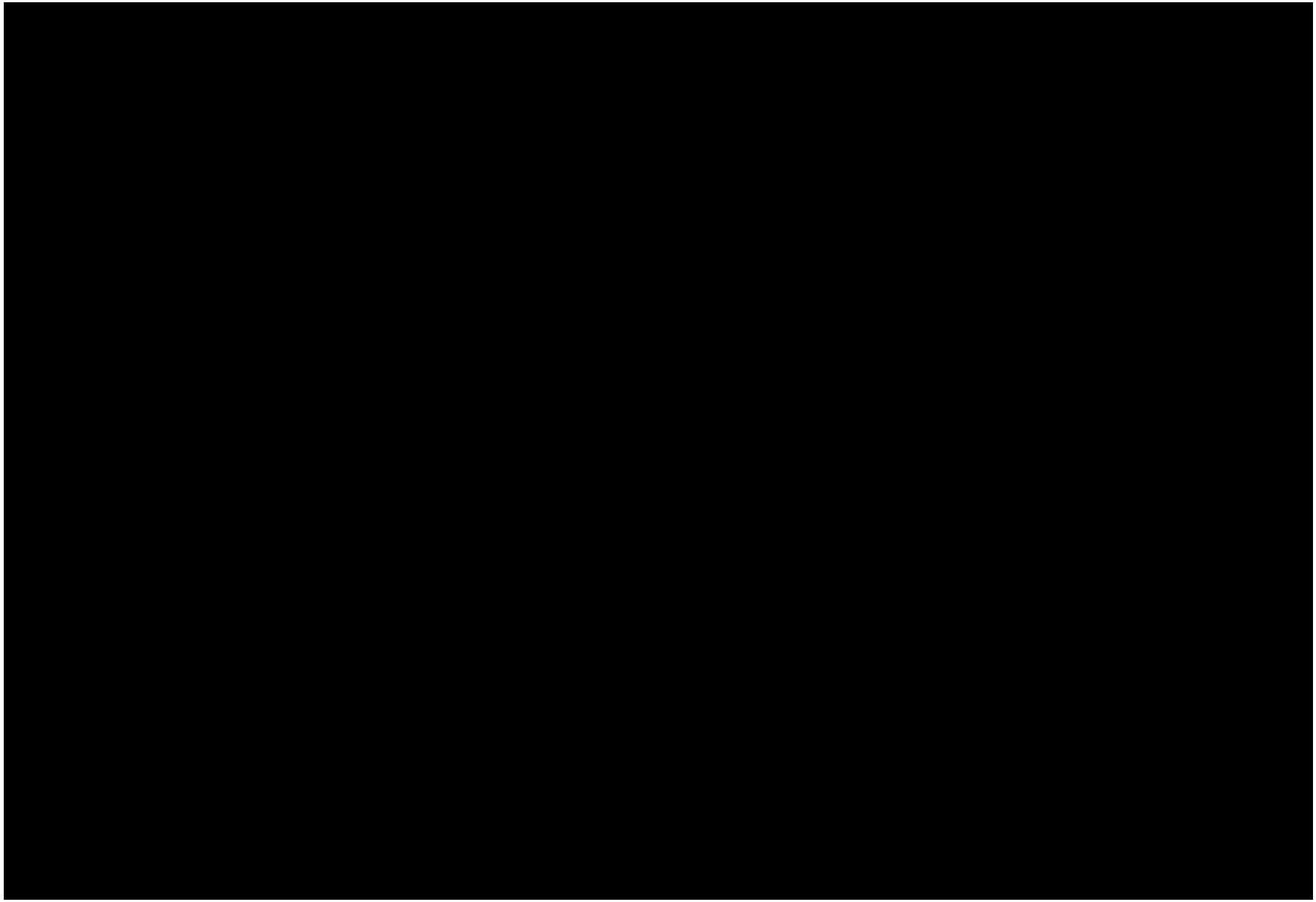
Medications That Cause QTc Prolongation

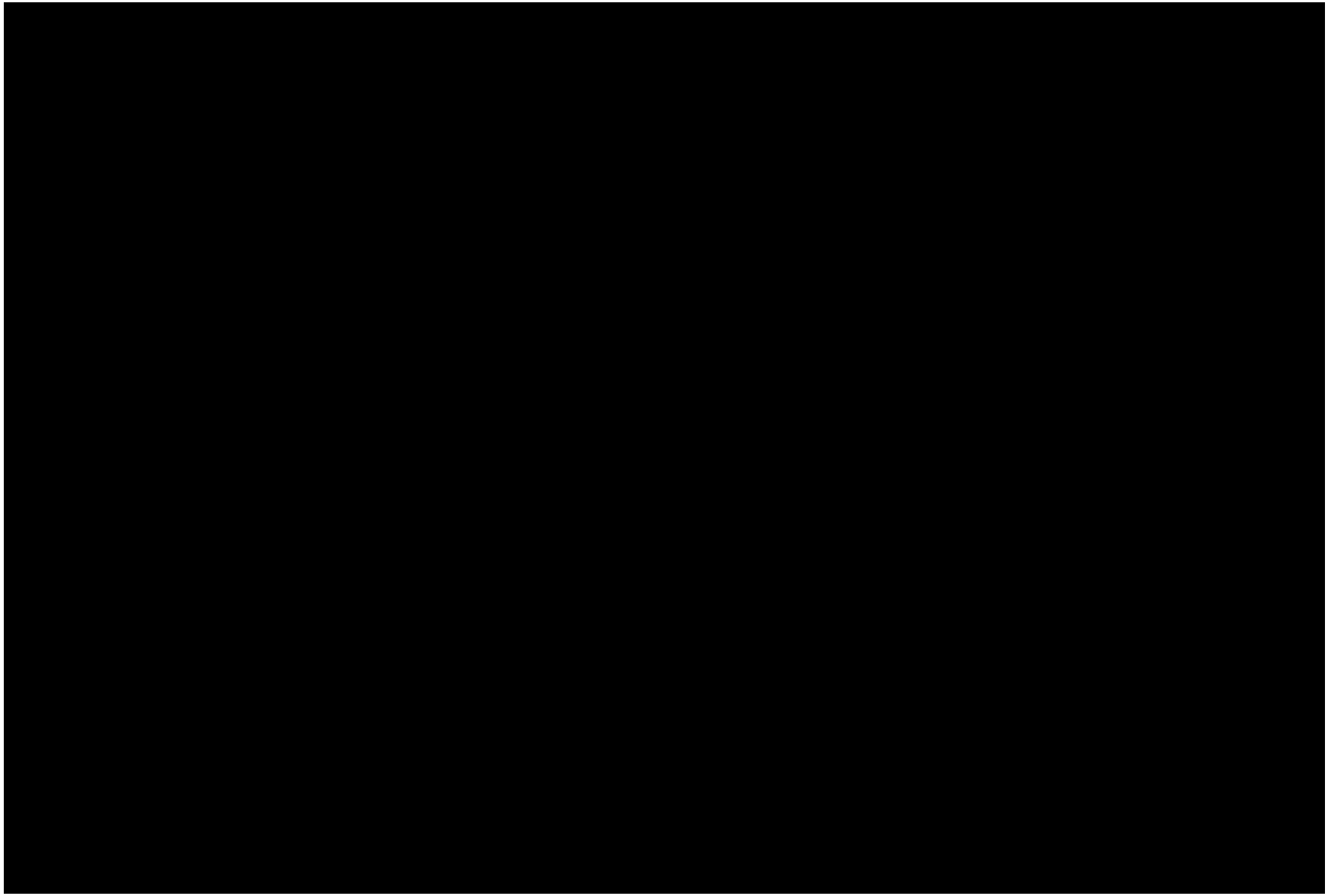
Amiodarone	Astemizole	Azithromycin	Chlorpromazine
Disopyramide	Terfenadine	Clarithromycin	Haloperidol
Dofetilide	Chloroquine	Erythromycin	Mesoridazine
Flecainide	Halofantrine	Moxifloxacin	Pimozide
Ibutilide	Probucol	Sparfloxacin	Thioridazine
Procainamide	Pentamidine	Domperidone	Levomethadyl
Quinidine	Bepridil	Droperidol	Methadone
Sotalol	Arsenic trioxide	Vavdetanib	Citalopram
Cisapride			

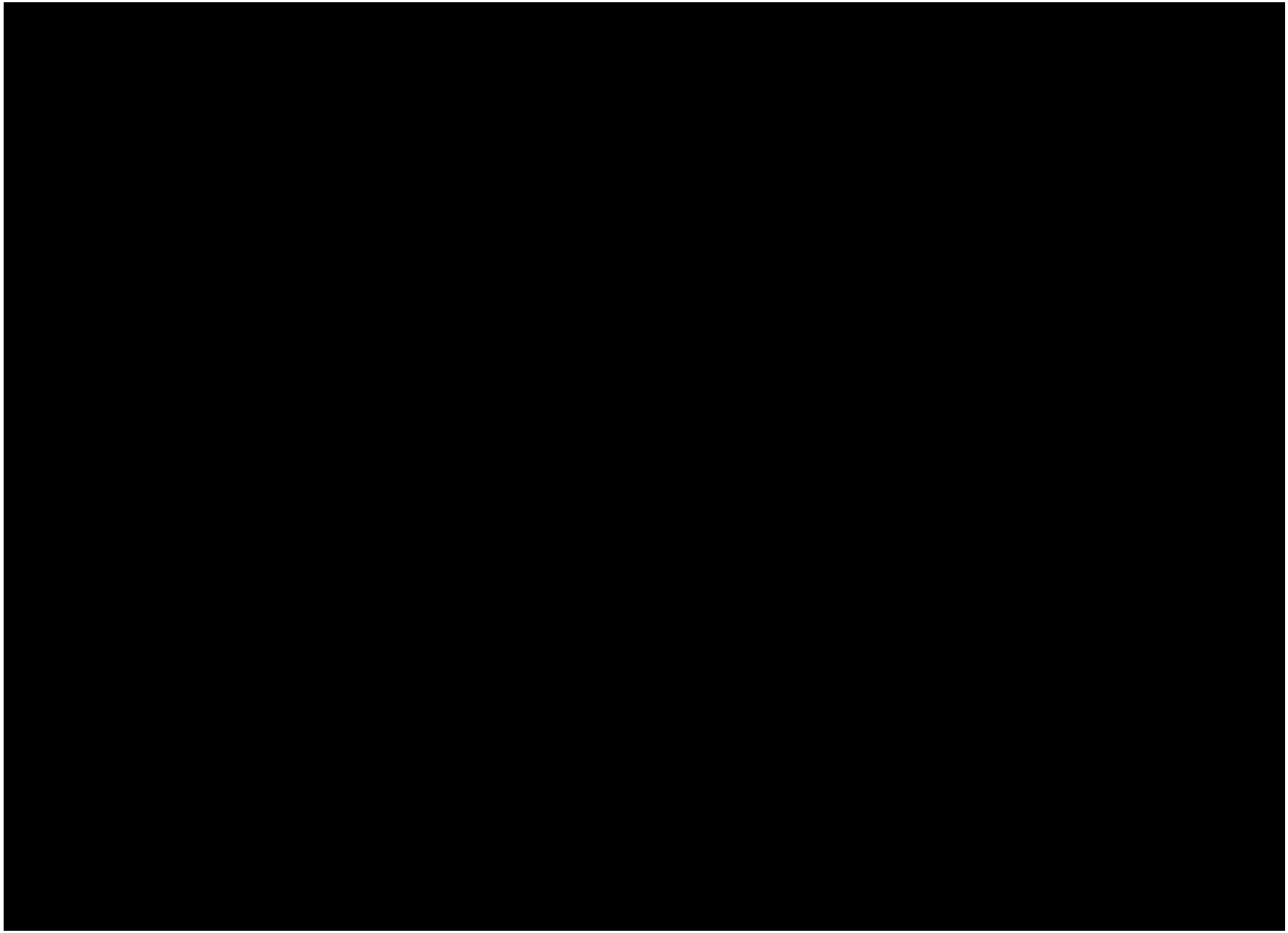
Appendix B. Contraceptive Requirements

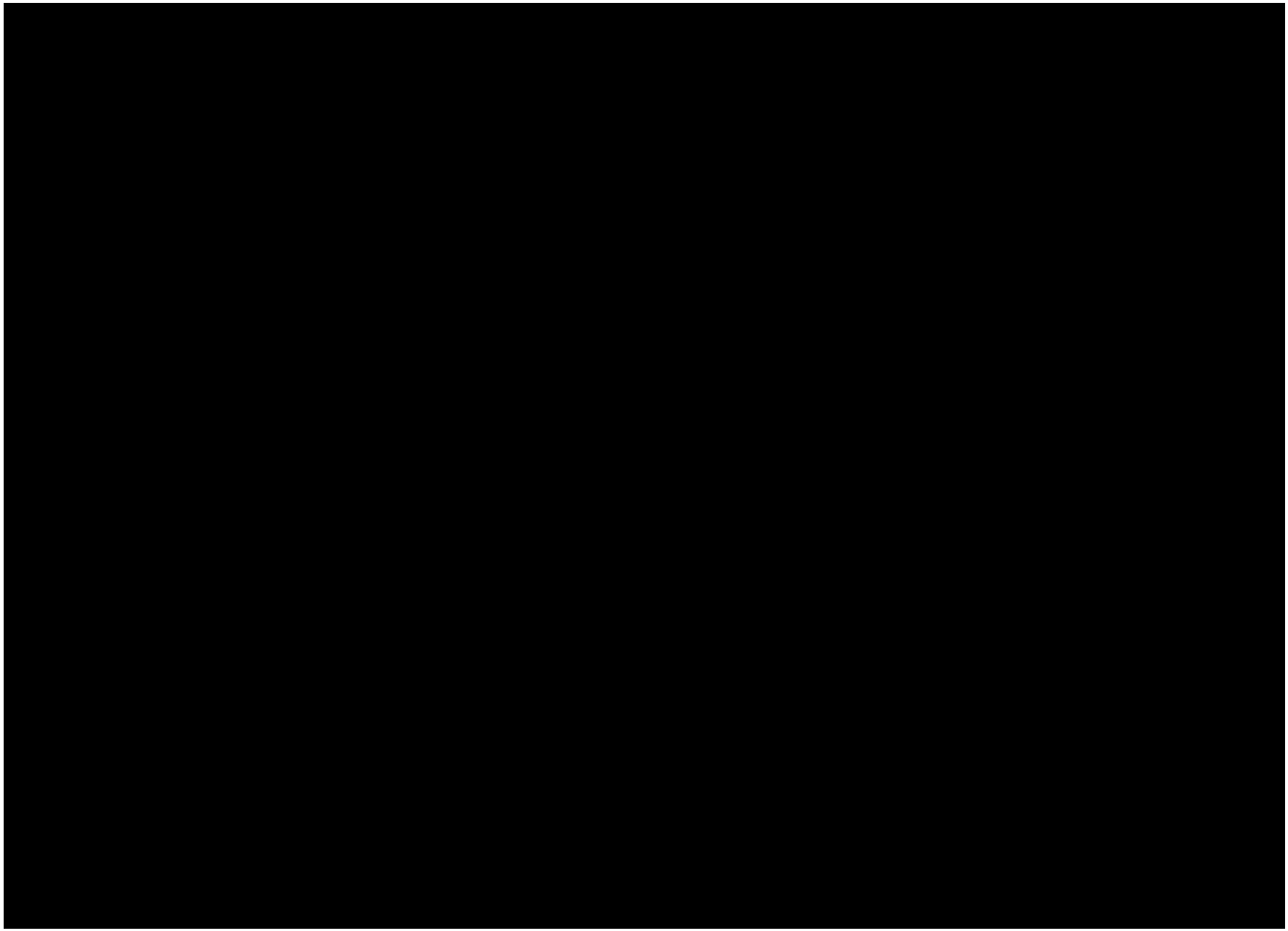
In this study, women of childbearing potential (WOCBP) will receive TPX-0046, a compound for which the teratogenic risk is currently unknown. Effective methods of contraception ***(combination of any of these options; hormonal, barrier method, or intrauterine device), or abstinence, or be surgically sterile*** prior to study entry, for the duration of study participation, for participating WOCBP and for men should be used during the study treatment and [redacted] following the last dose of any study medication, and include the following:

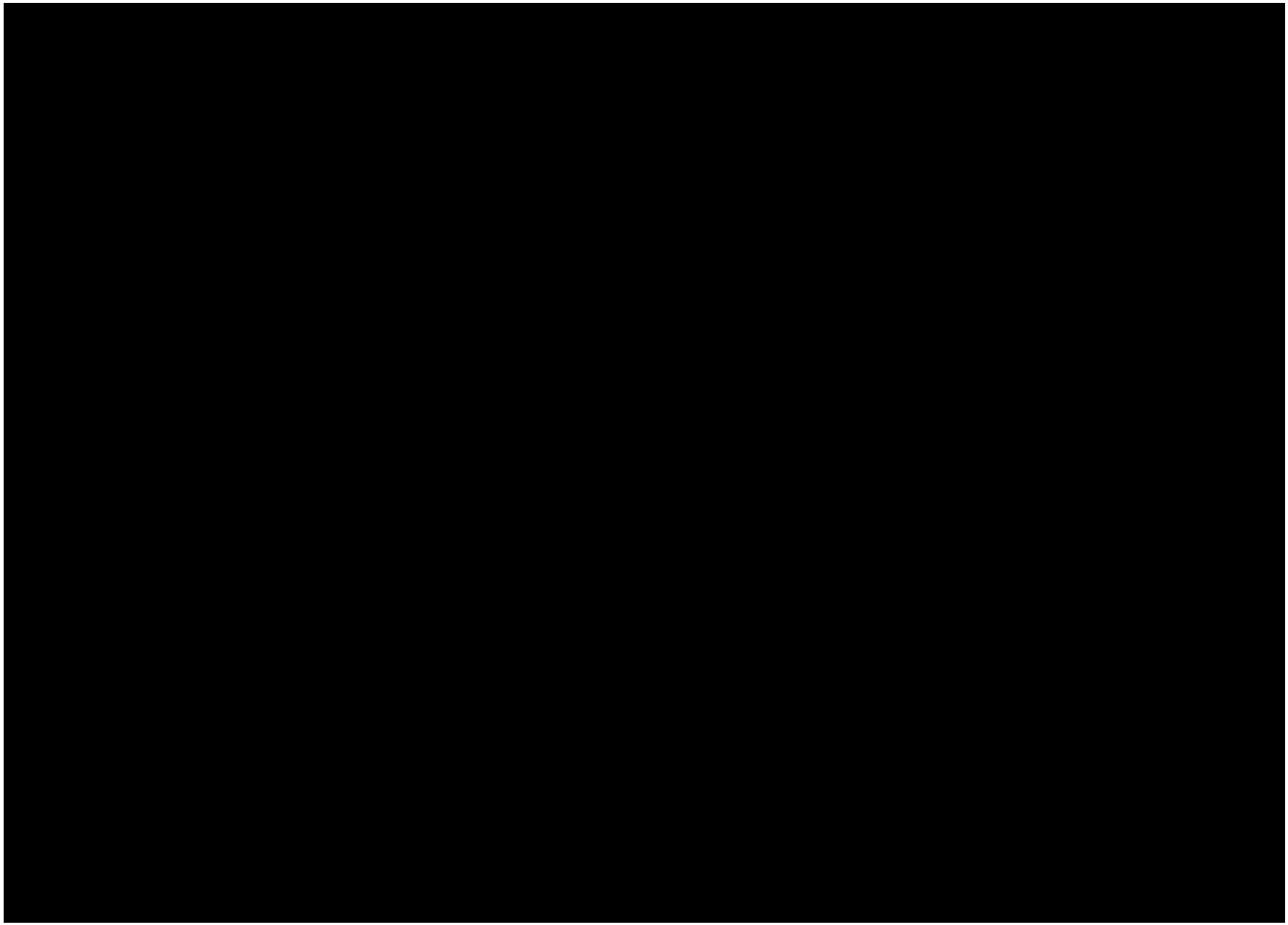
1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable). The hormonal contraception method must be supplemented with a barrier method by the male partner (preferably male condom).
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable). The hormonal contraception method must be supplemented with a barrier method by the male partner (preferably male condom).
3. Correctly placed copper-containing intrauterine device or intrauterine hormone-releasing system.
4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Participating men can be fertile or vasectomized. Fertile men are advised to use effective methods of barrier contraception during the study and [redacted] after administration of the last dose of any study medication. The Investigator, at each study visit, will discuss with the subject the need to use highly effective contraception consistently and correctly and document such conversation in the subject chart. In addition, the Investigator will instruct the subject to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected.
6. Female patients will be considered of childbearing potential unless they have undergone permanent contraception or are postmenopausal. Post menopause is defined as at least 12 months without menses with no other medical reasons (eg, chemical menopause due to anticancer treatment).
7. True abstinence: acceptable if evaluated as consistent with the preferred and the usual lifestyle of the subject. Periodic abstinence is not an acceptable method of contraception.

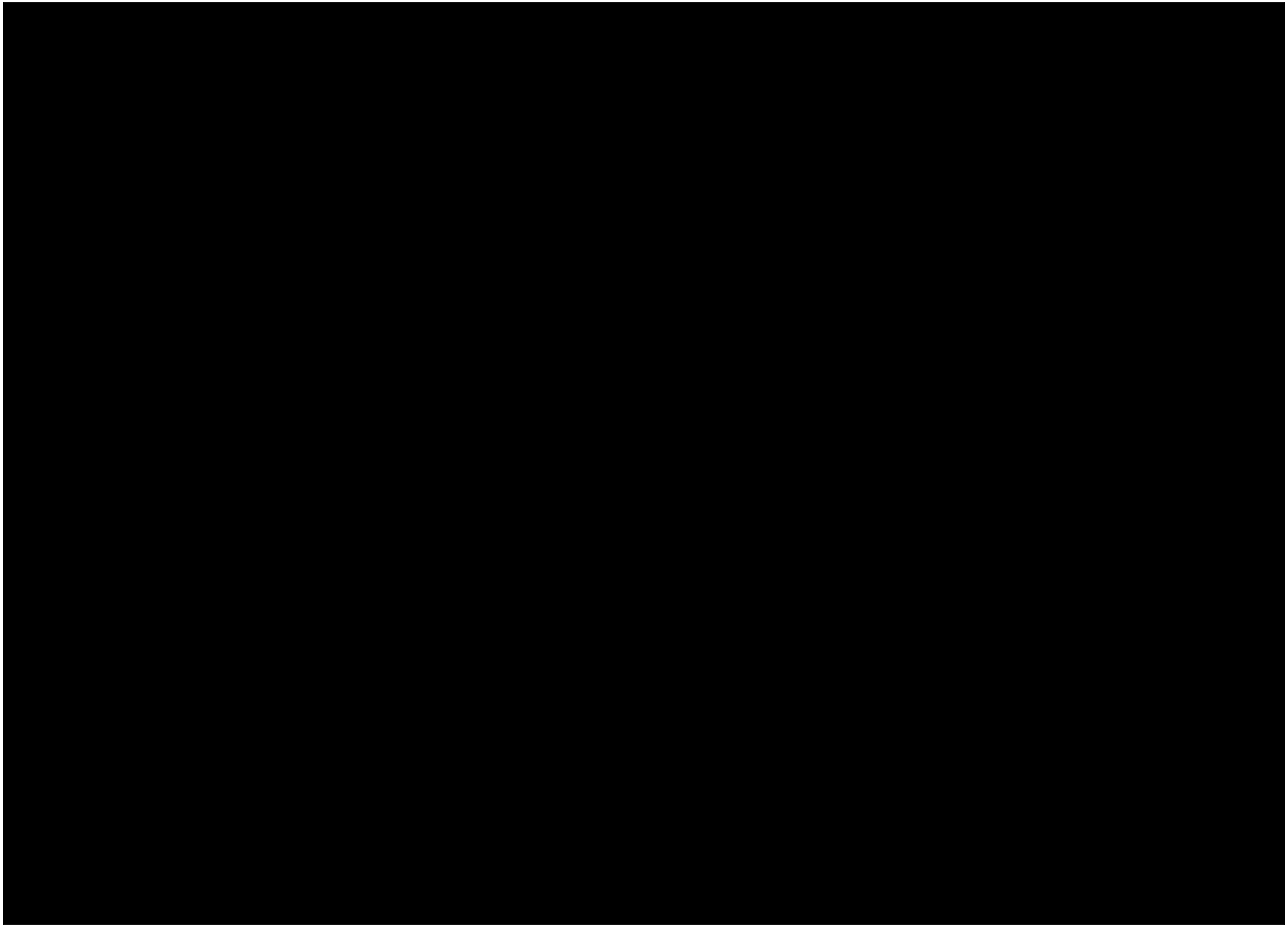


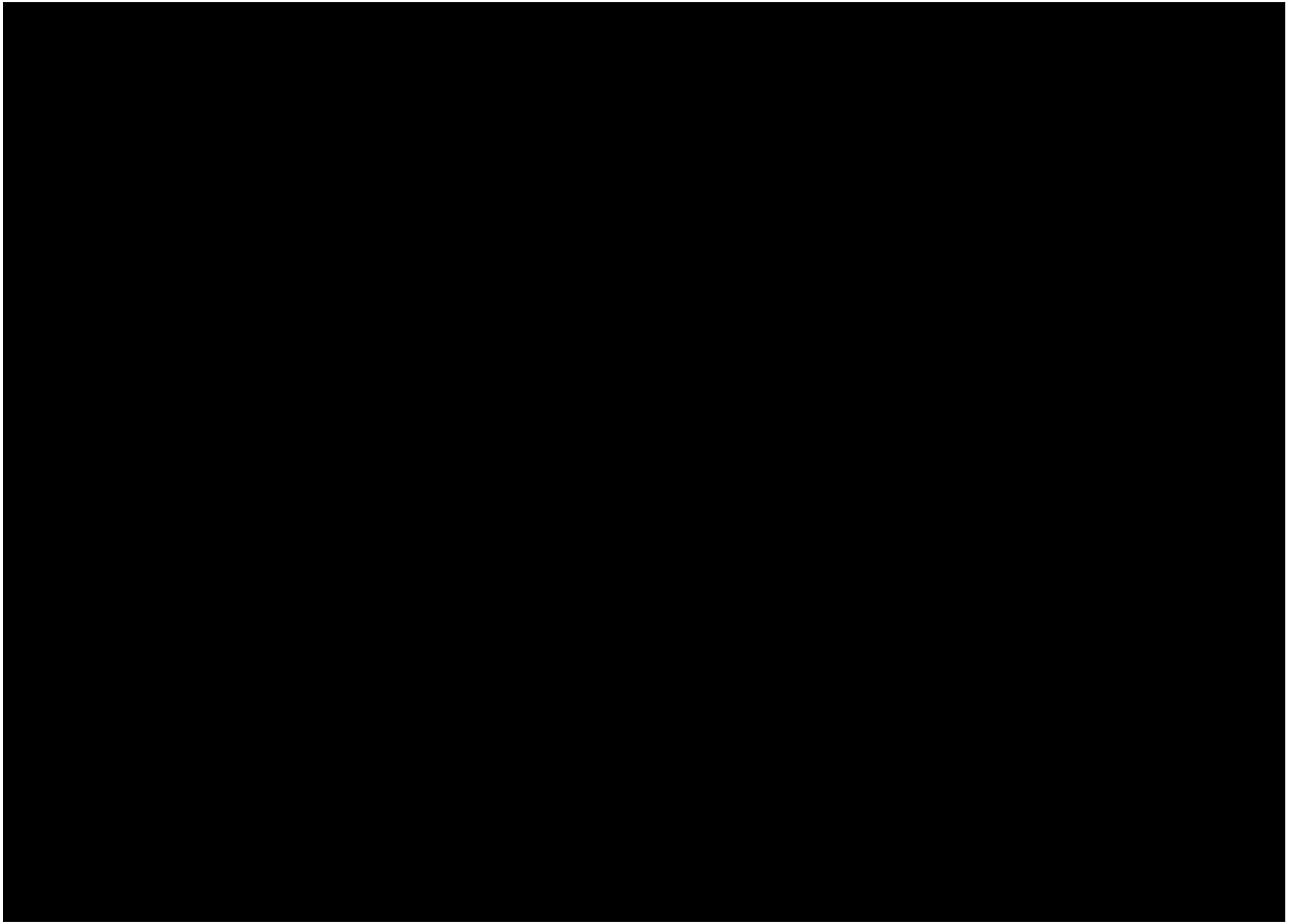


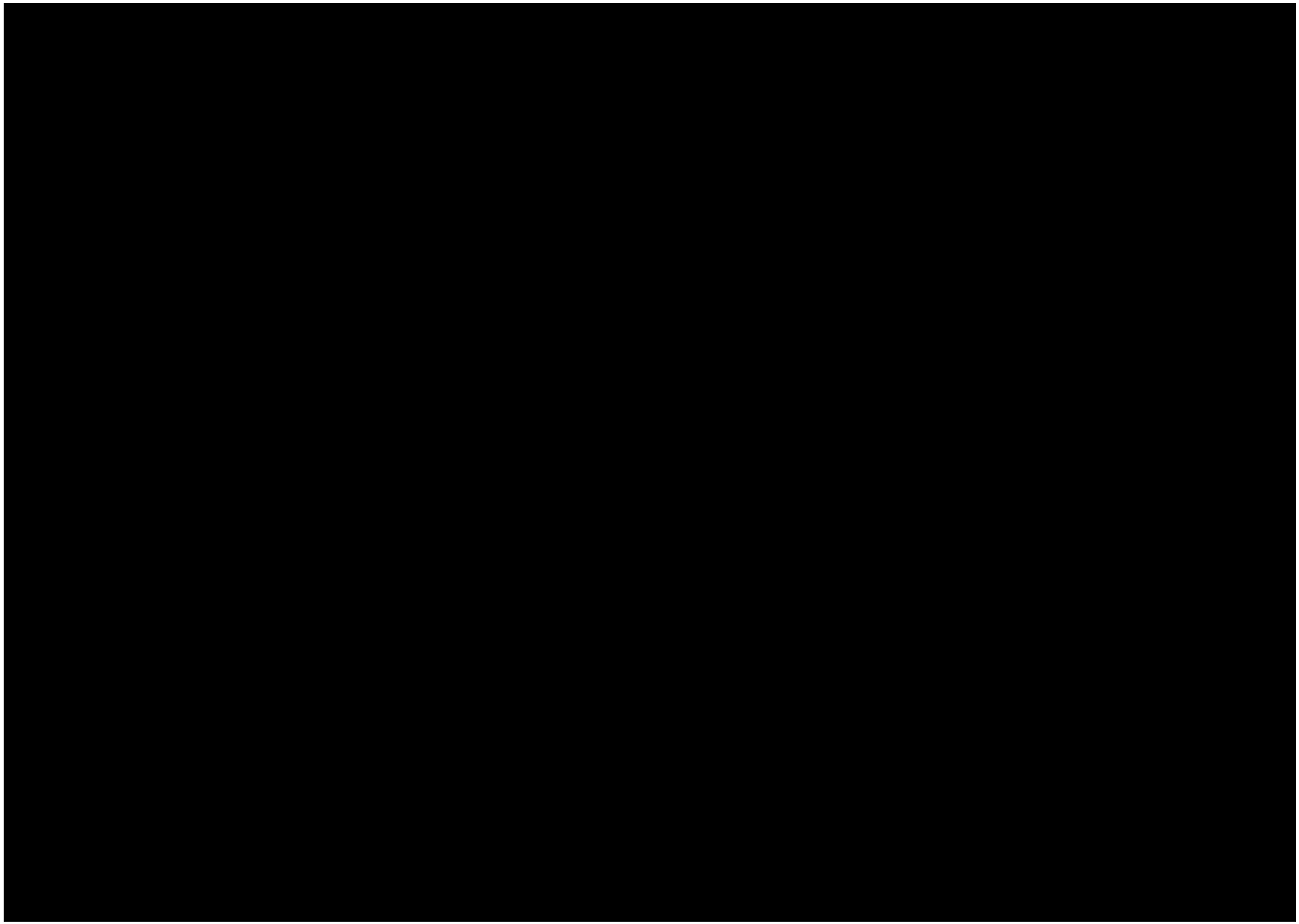


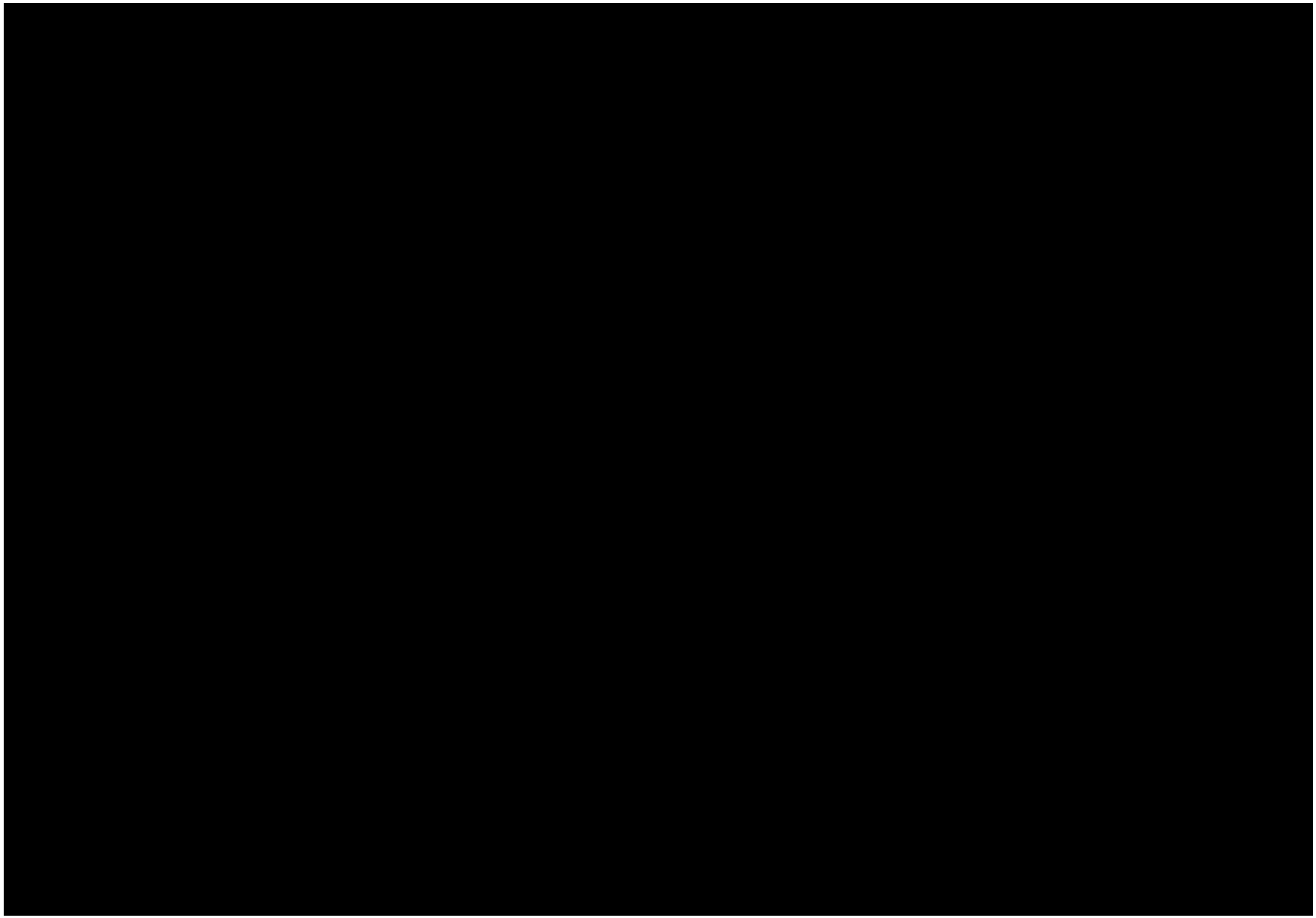


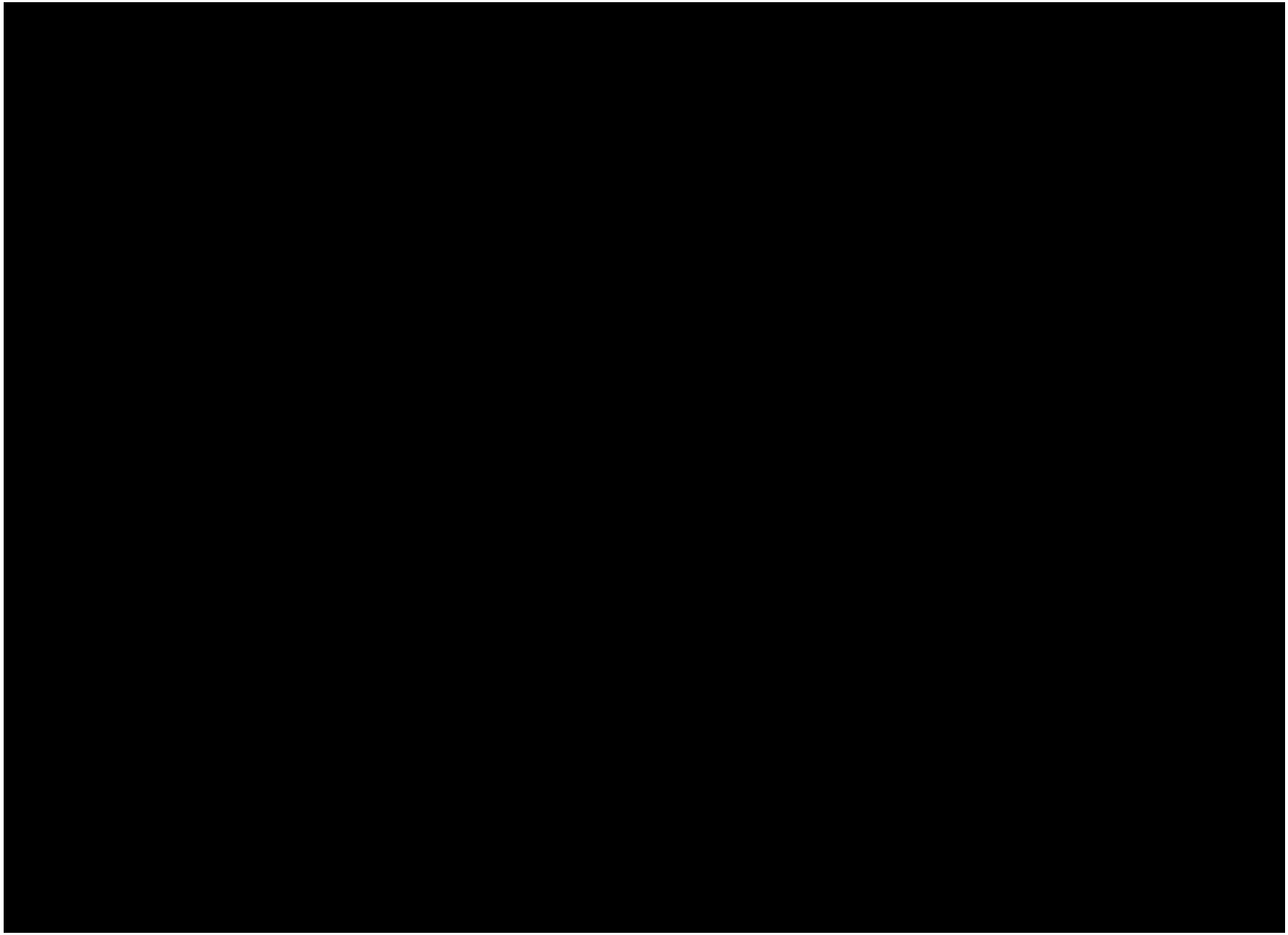


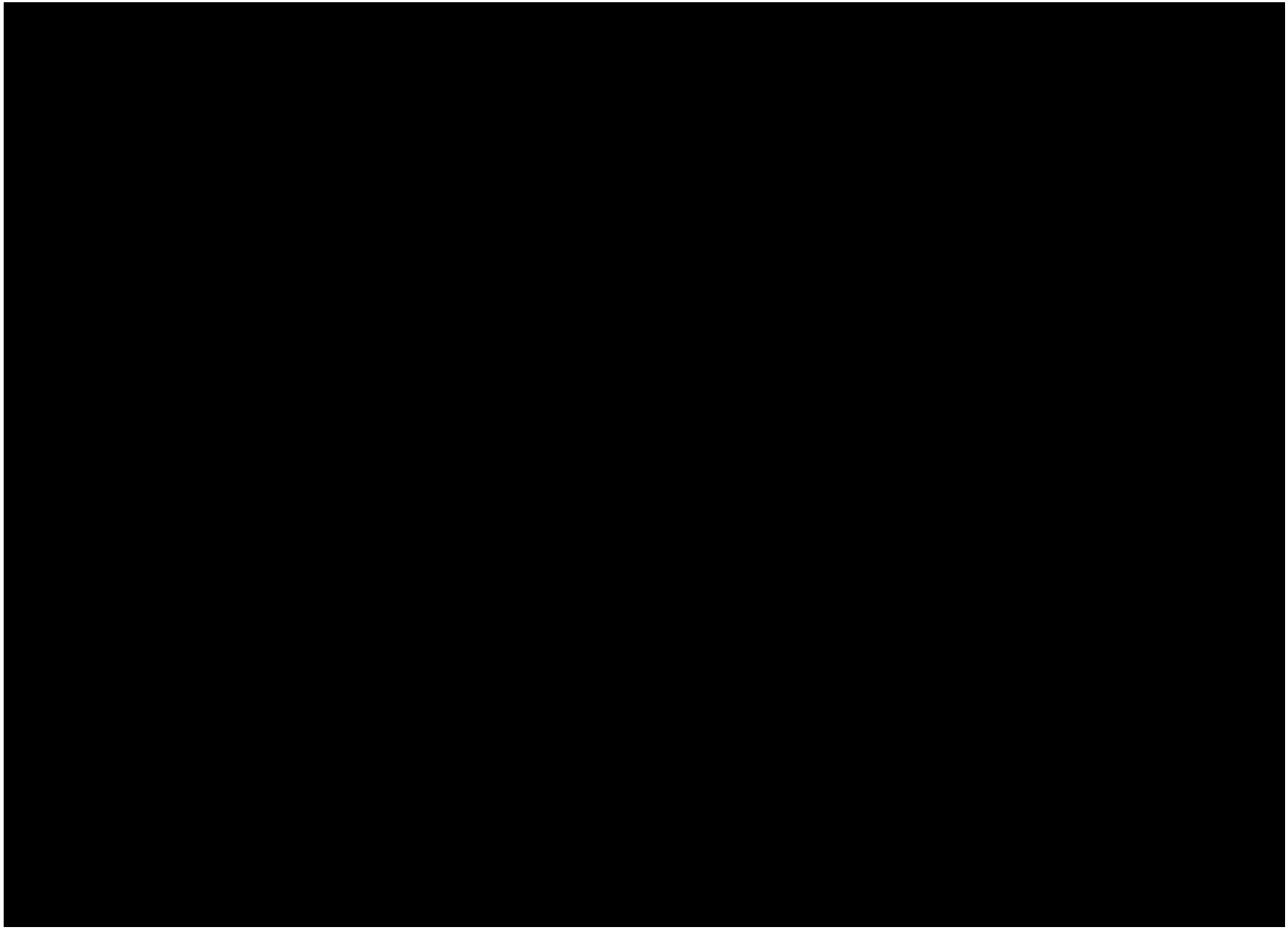


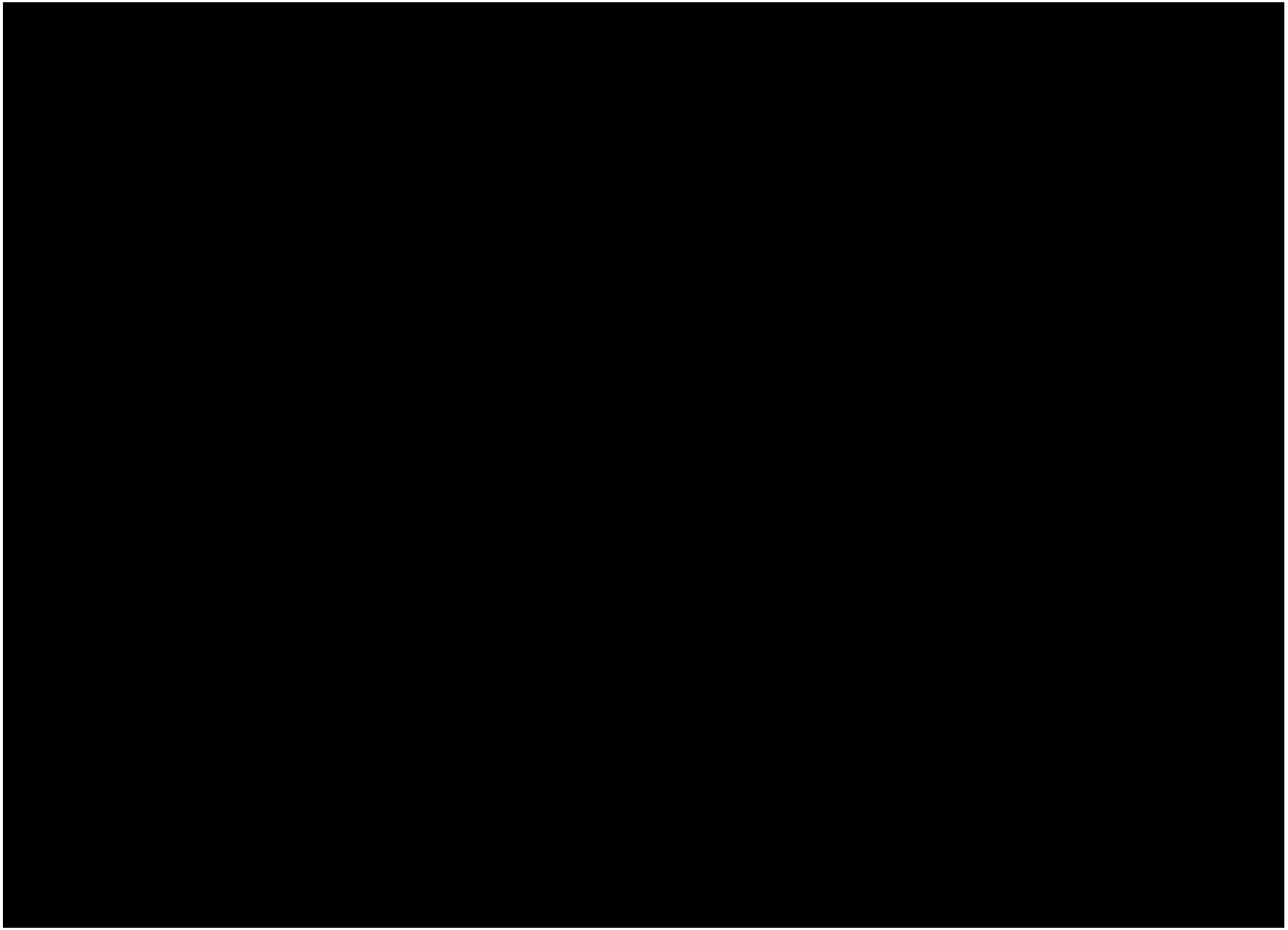


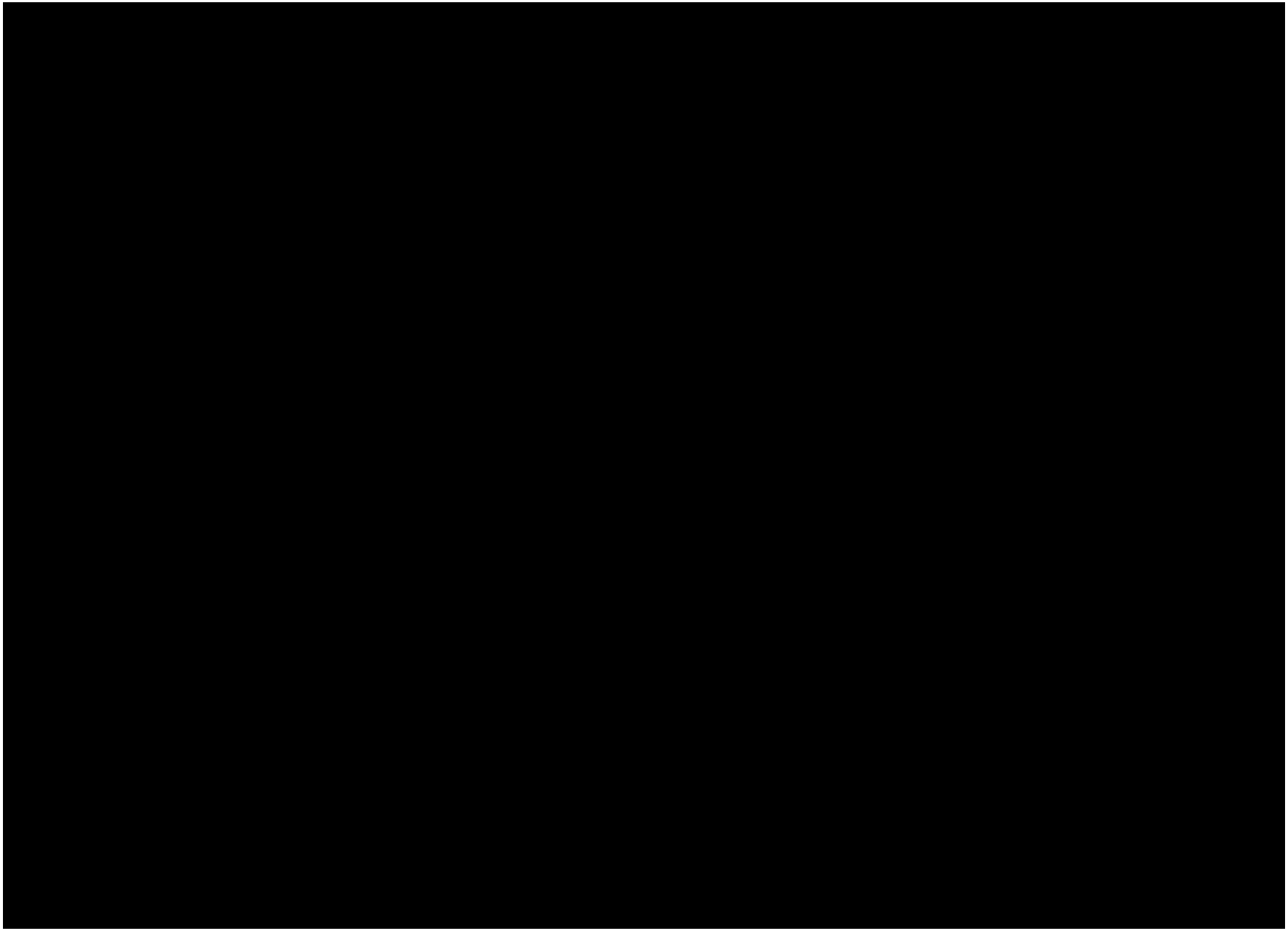


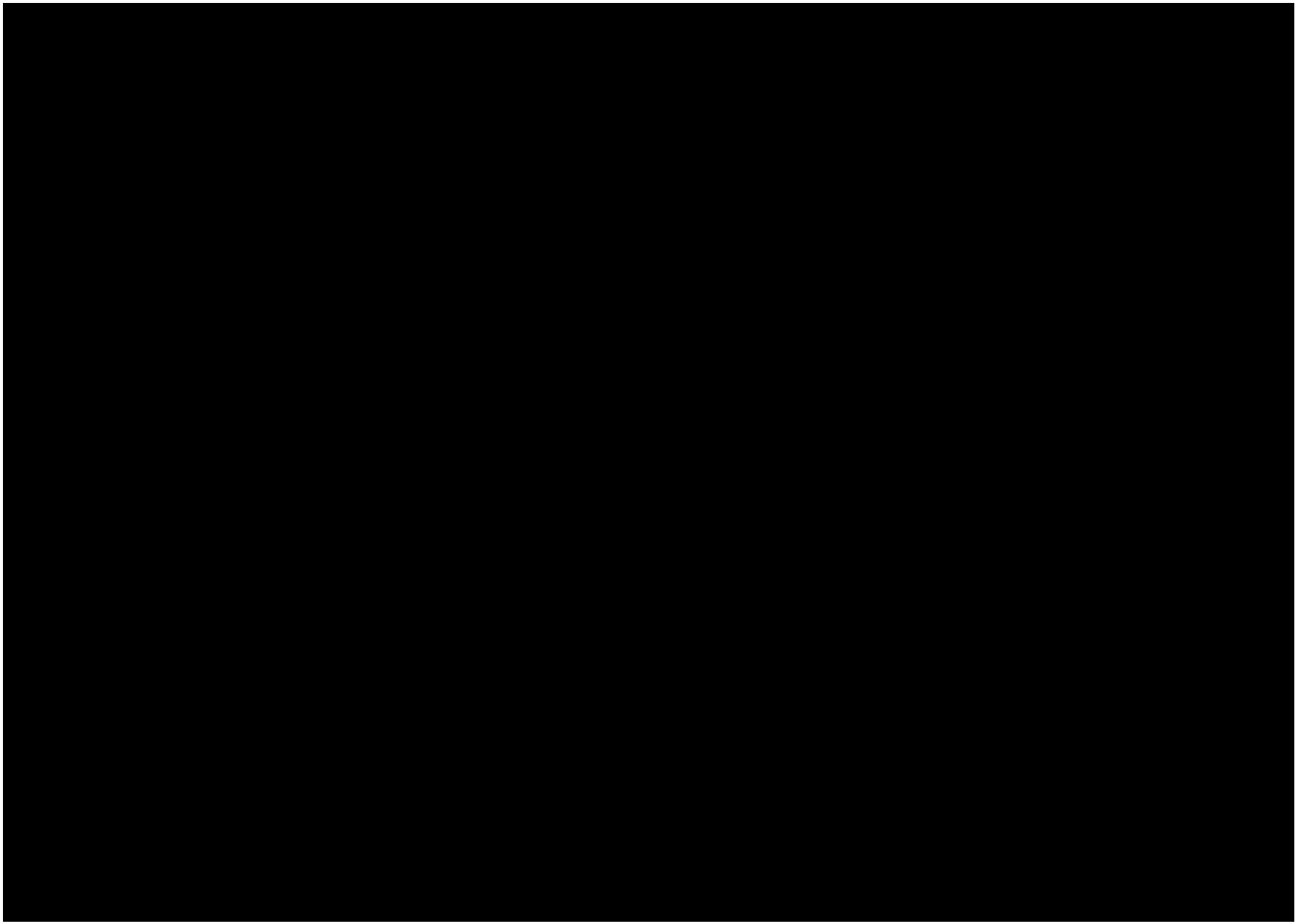


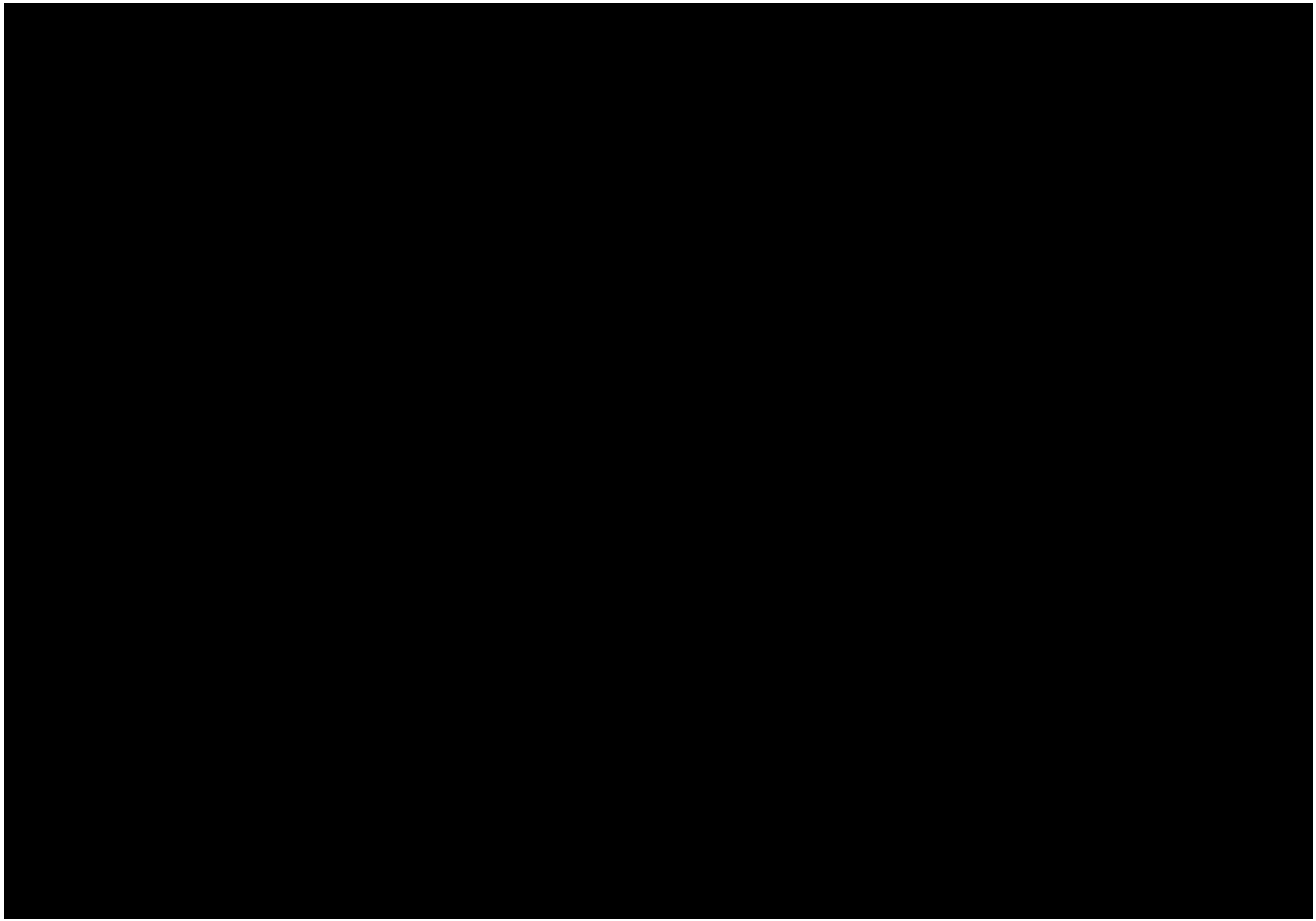


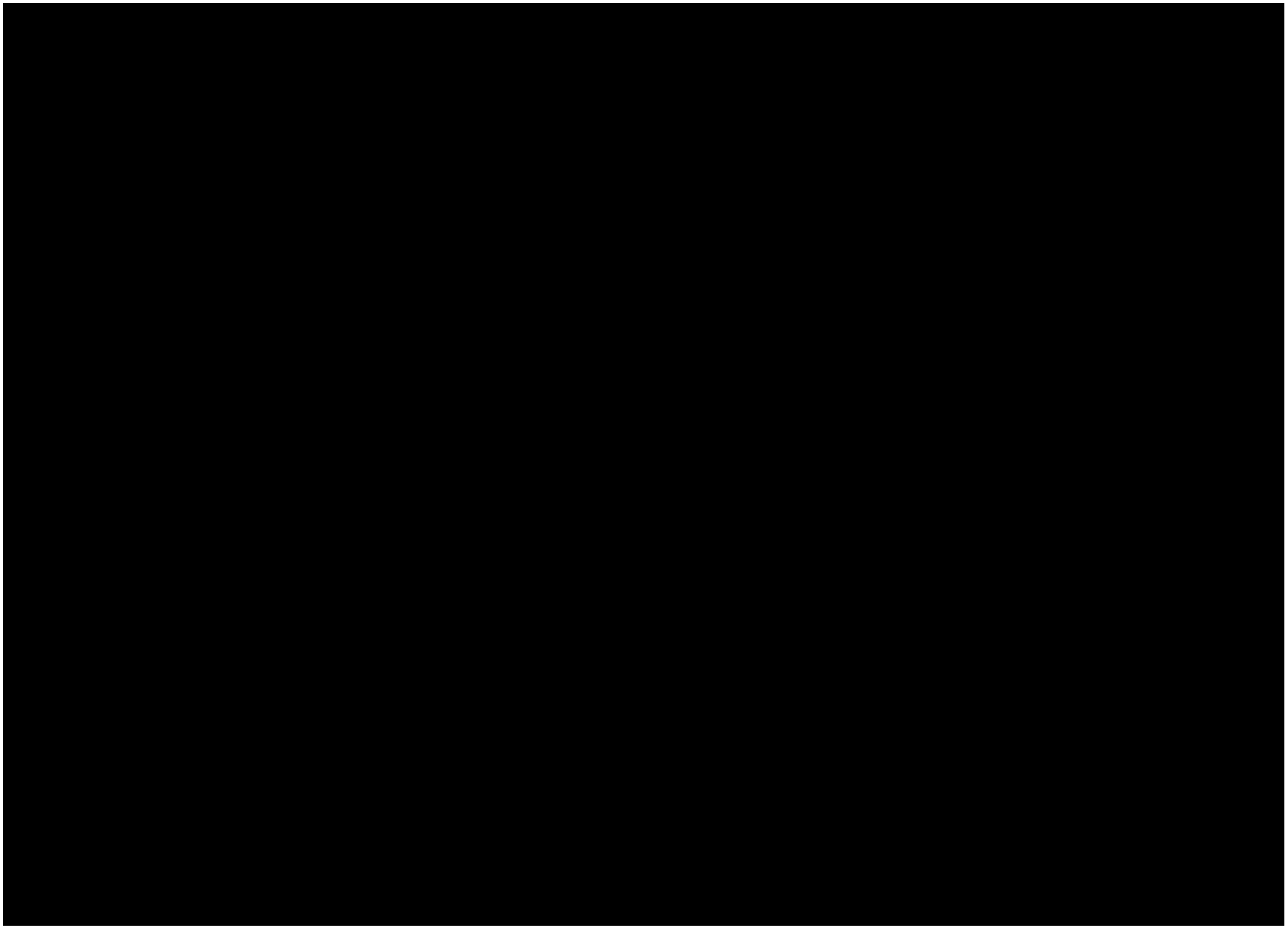


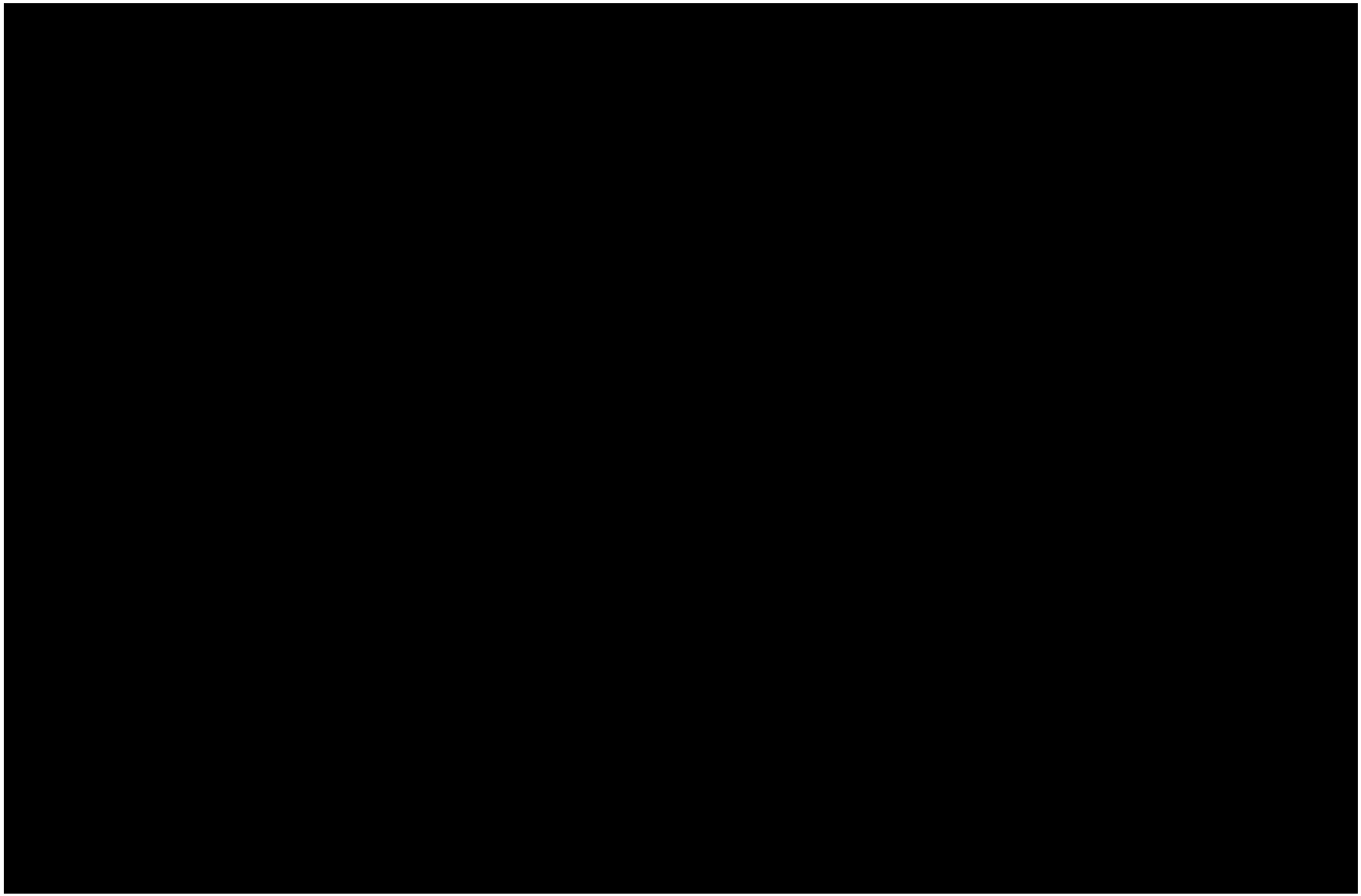


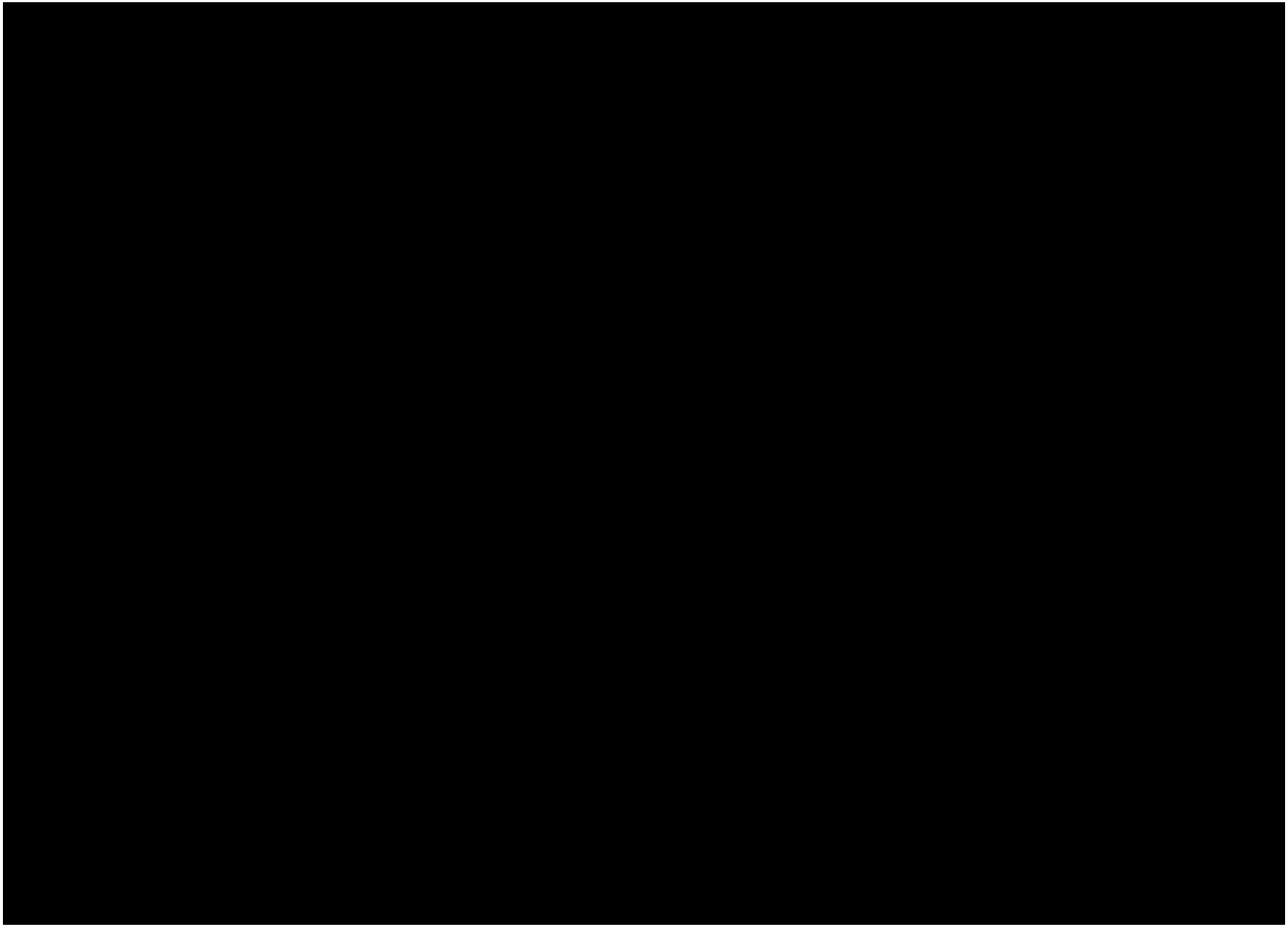


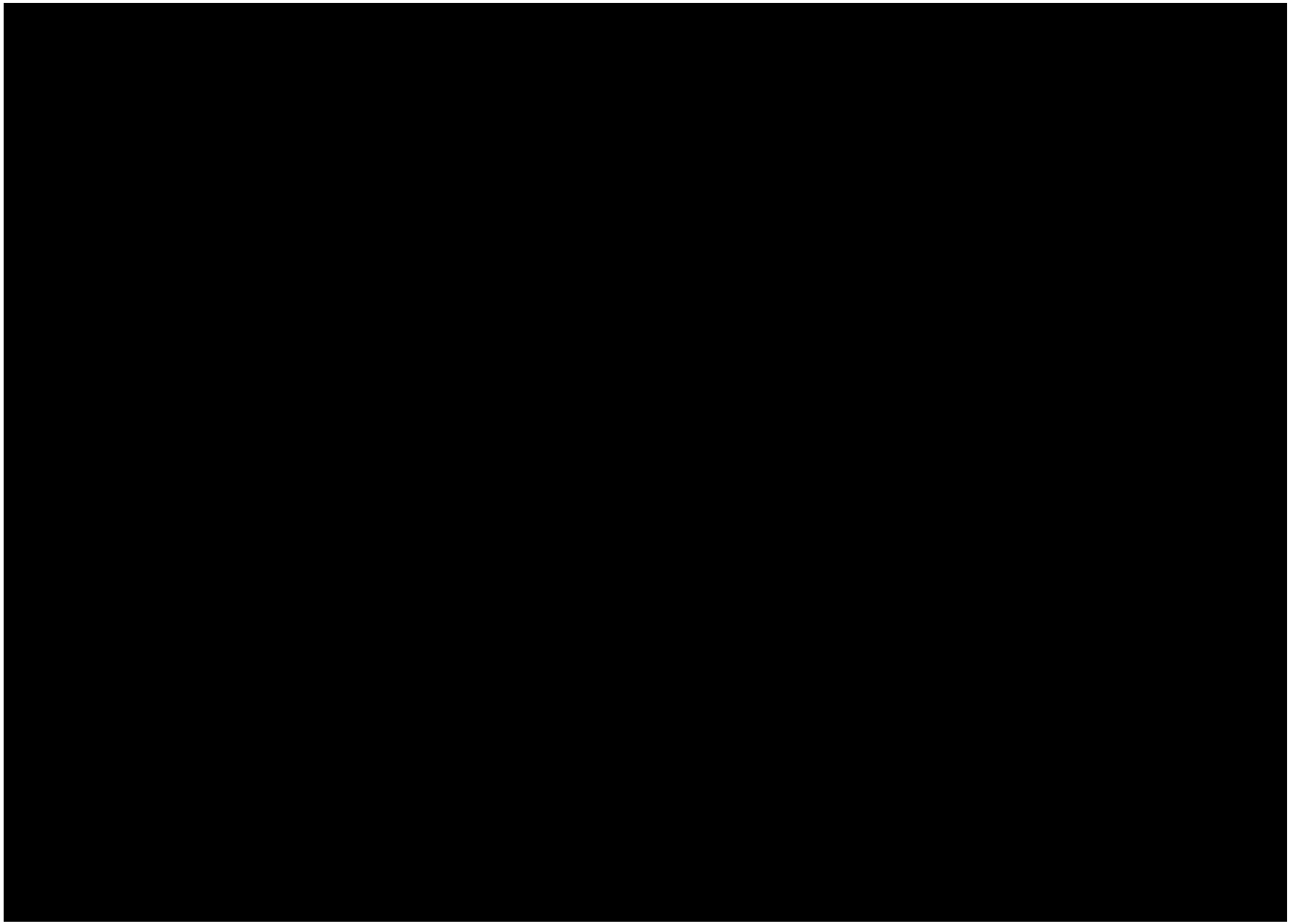


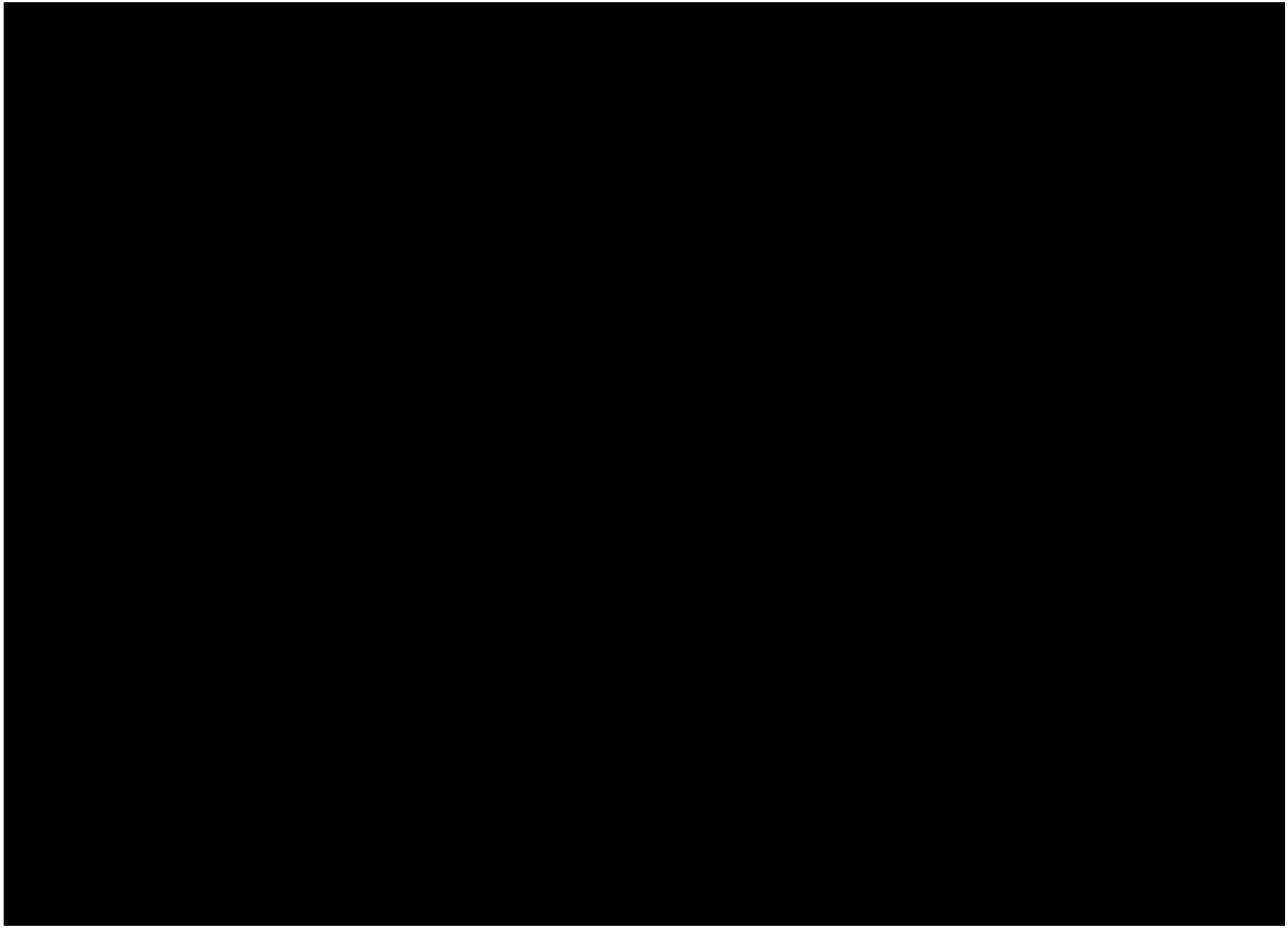


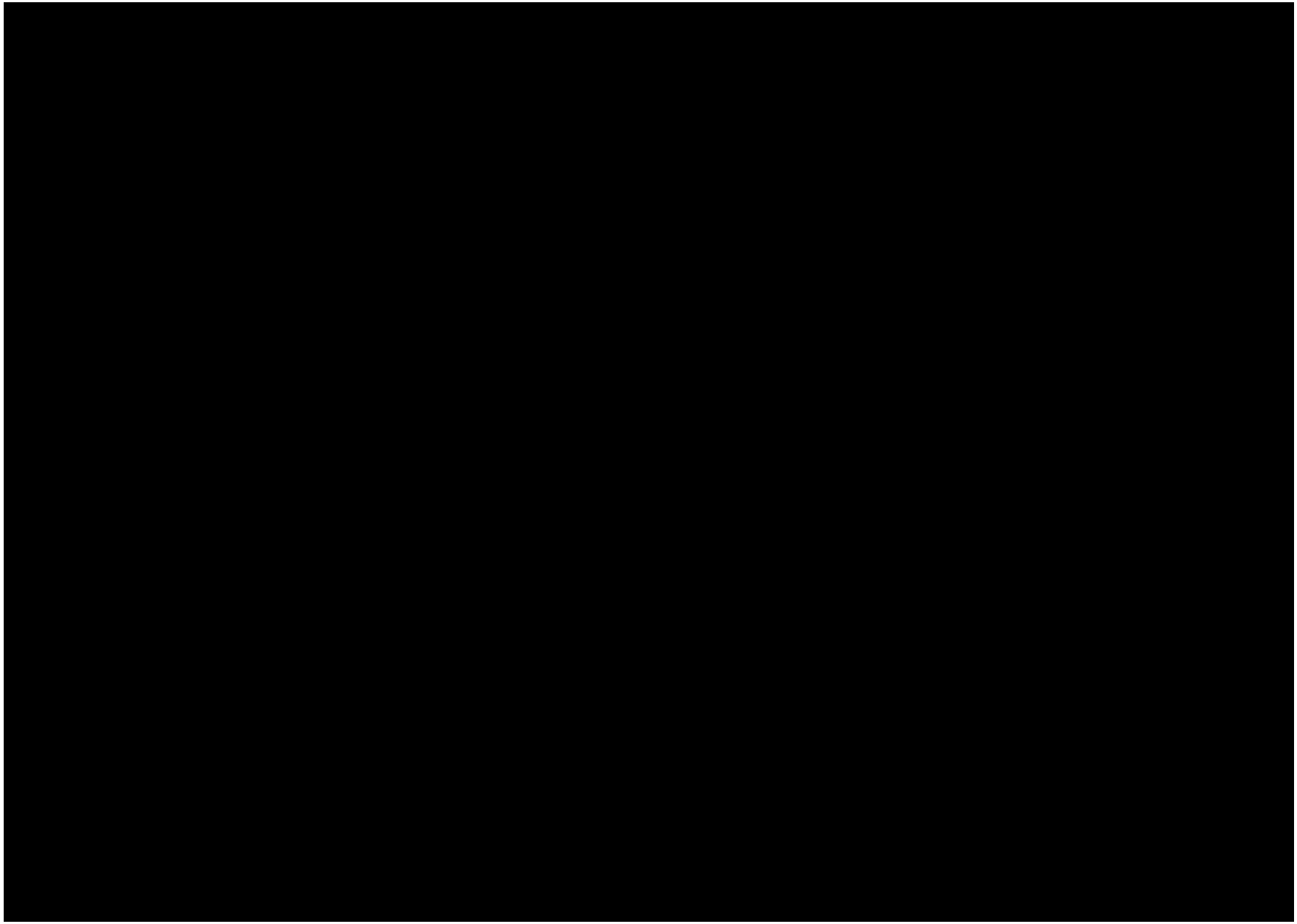


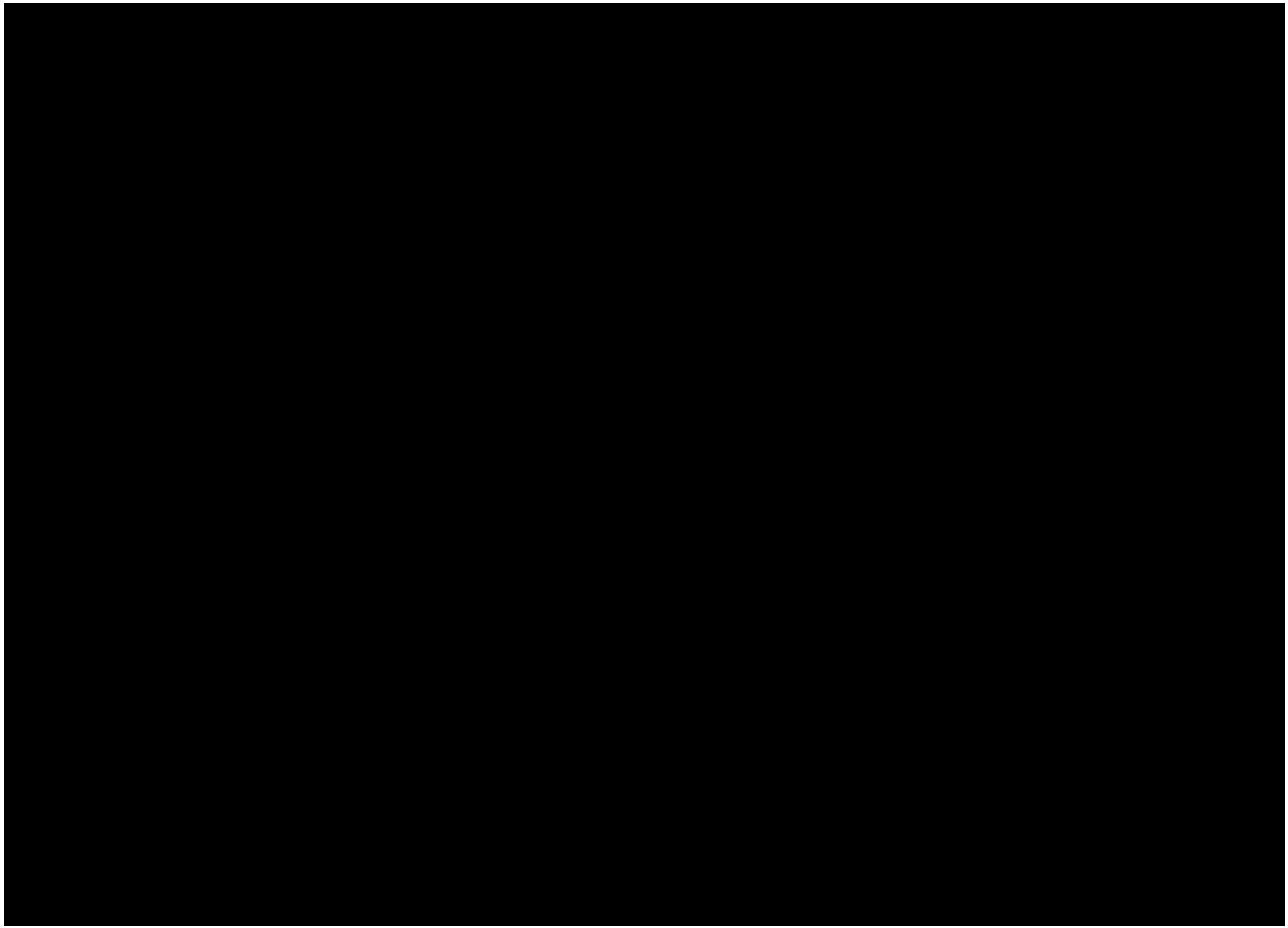


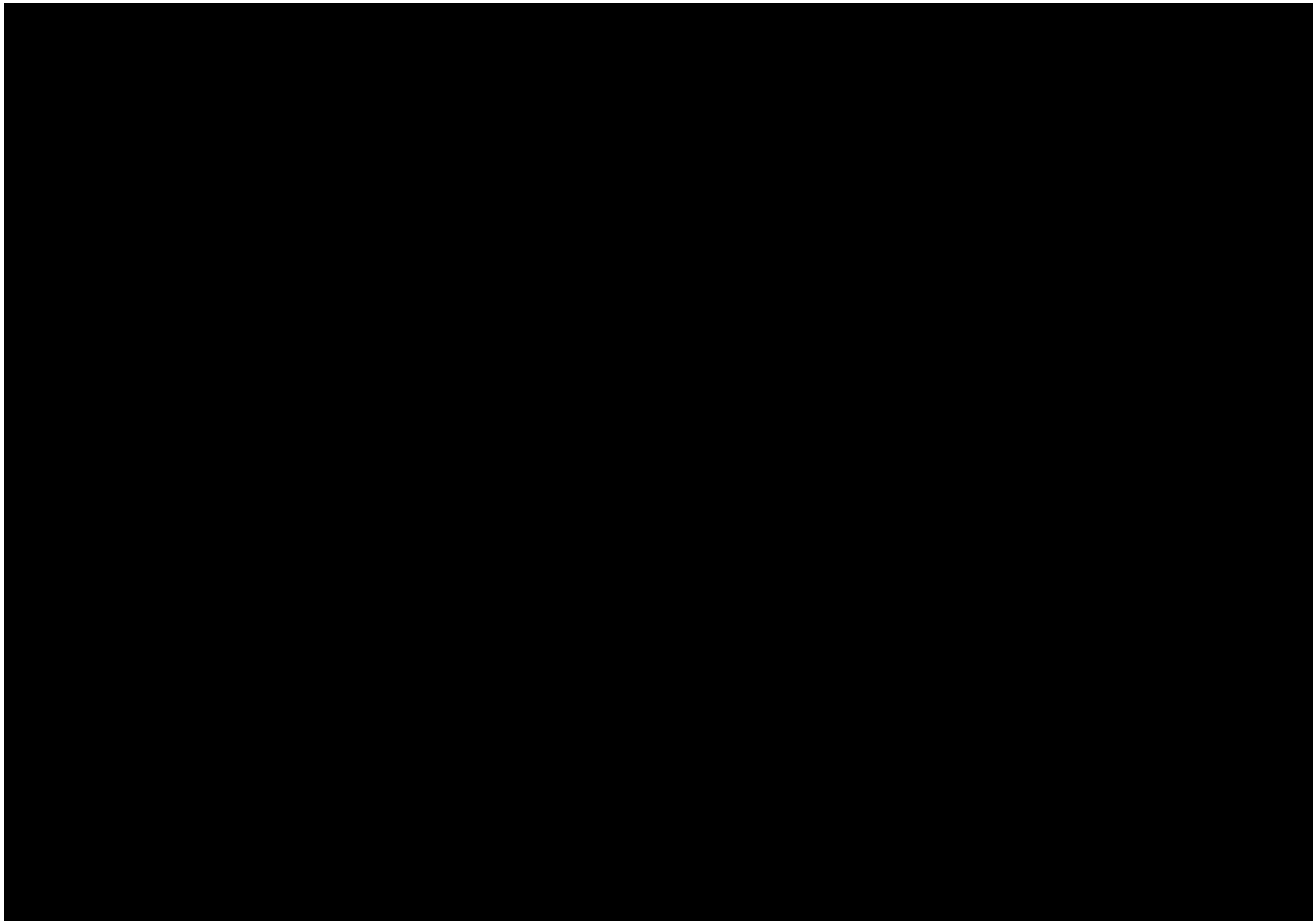


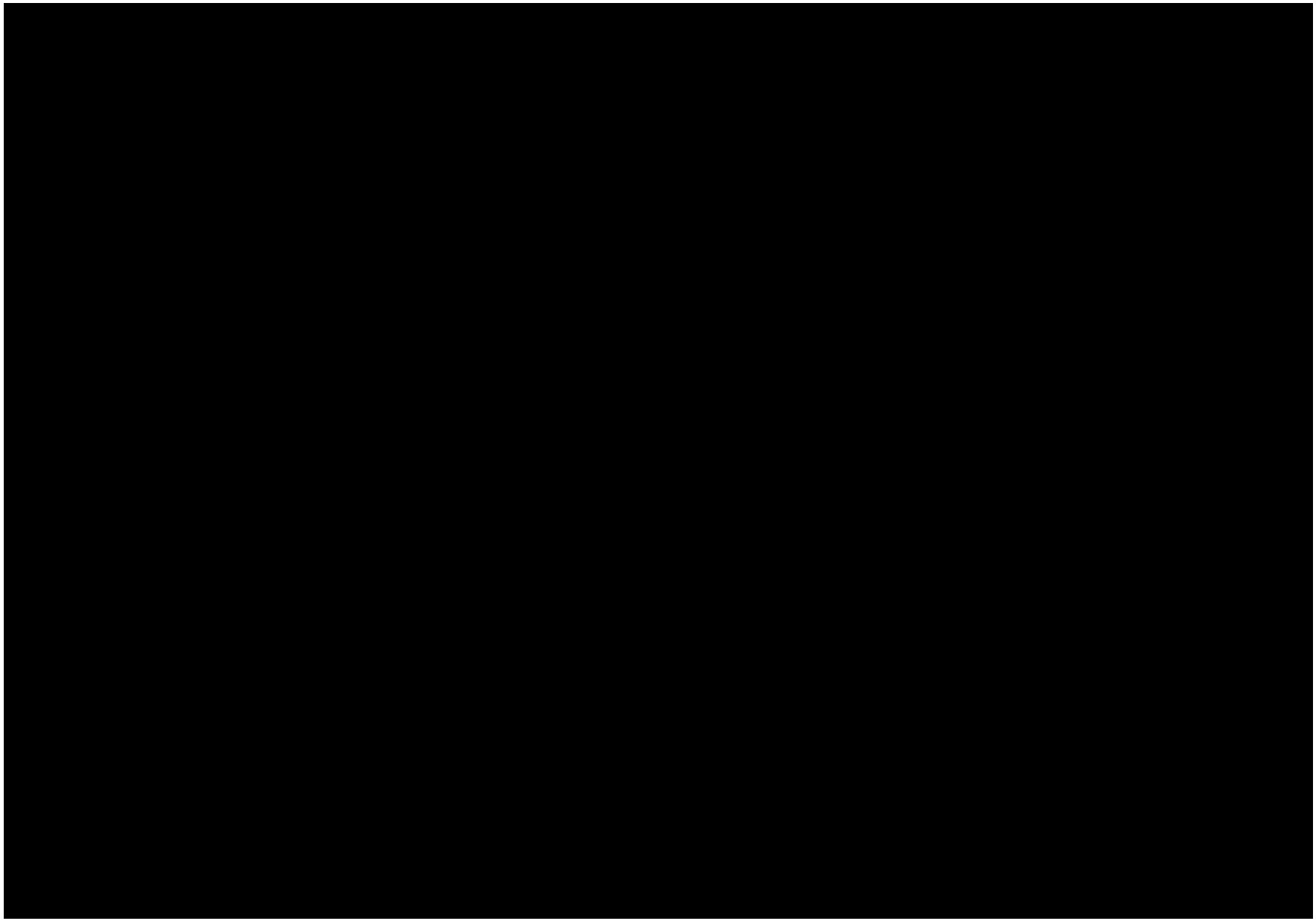


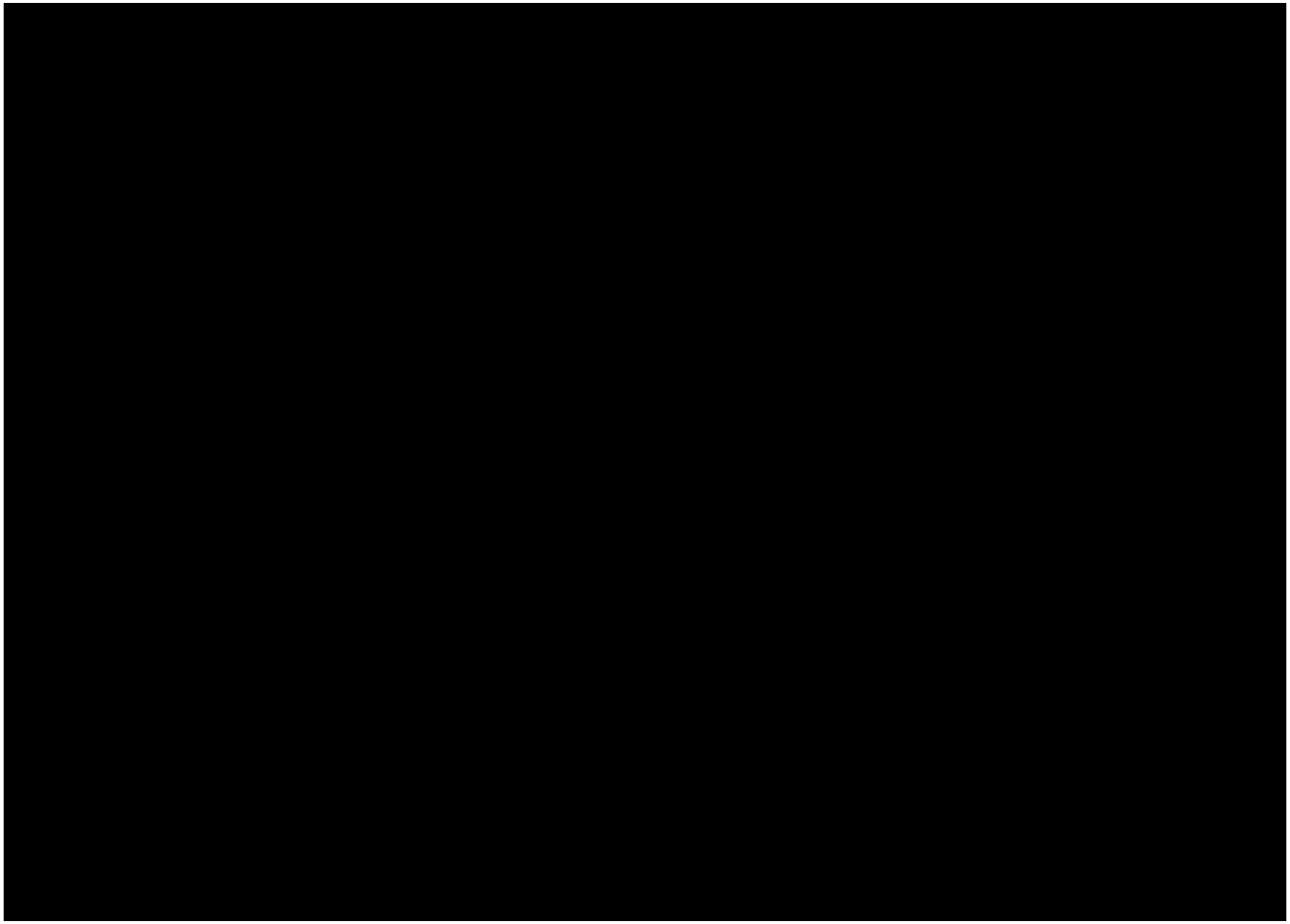


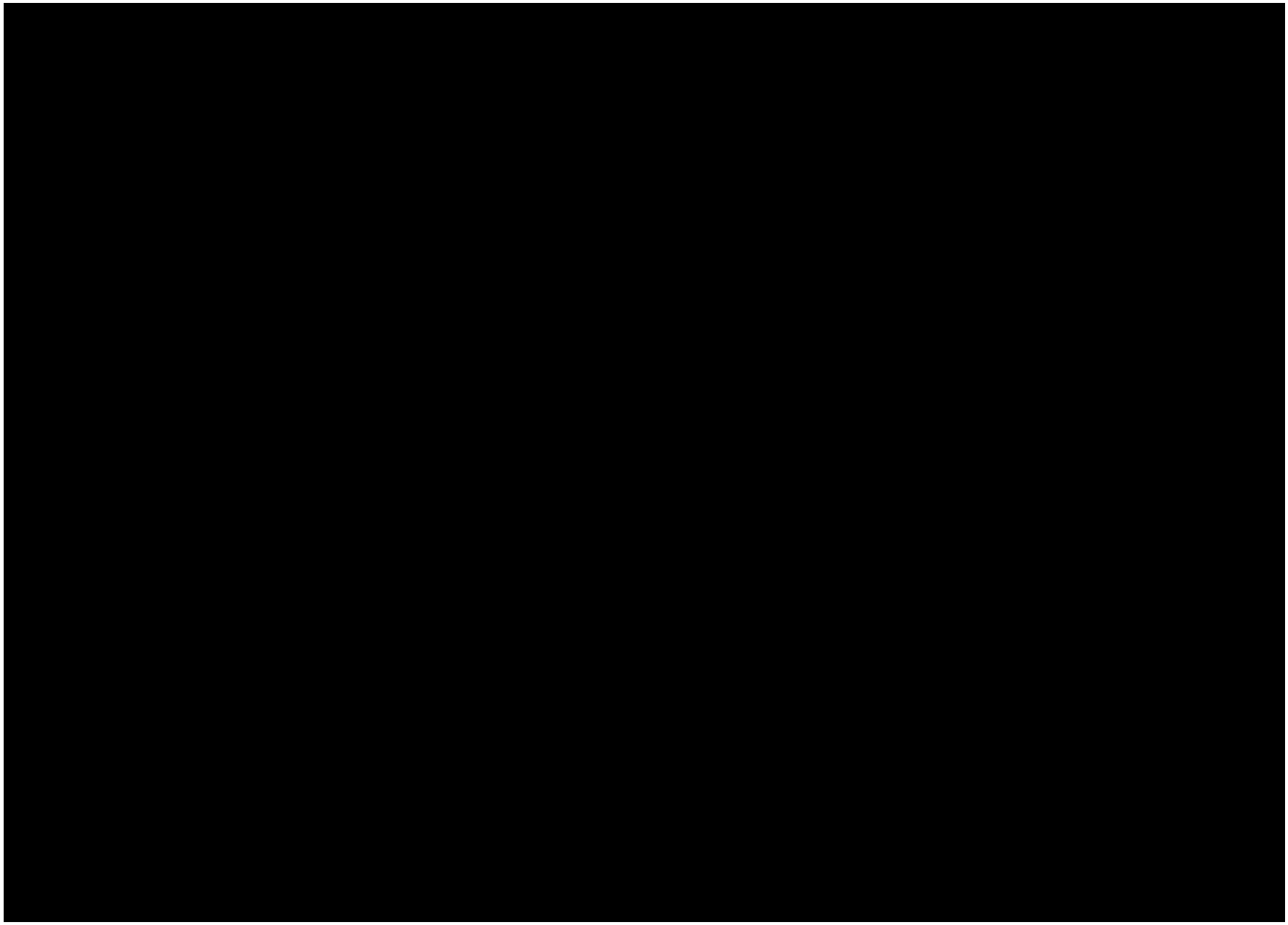


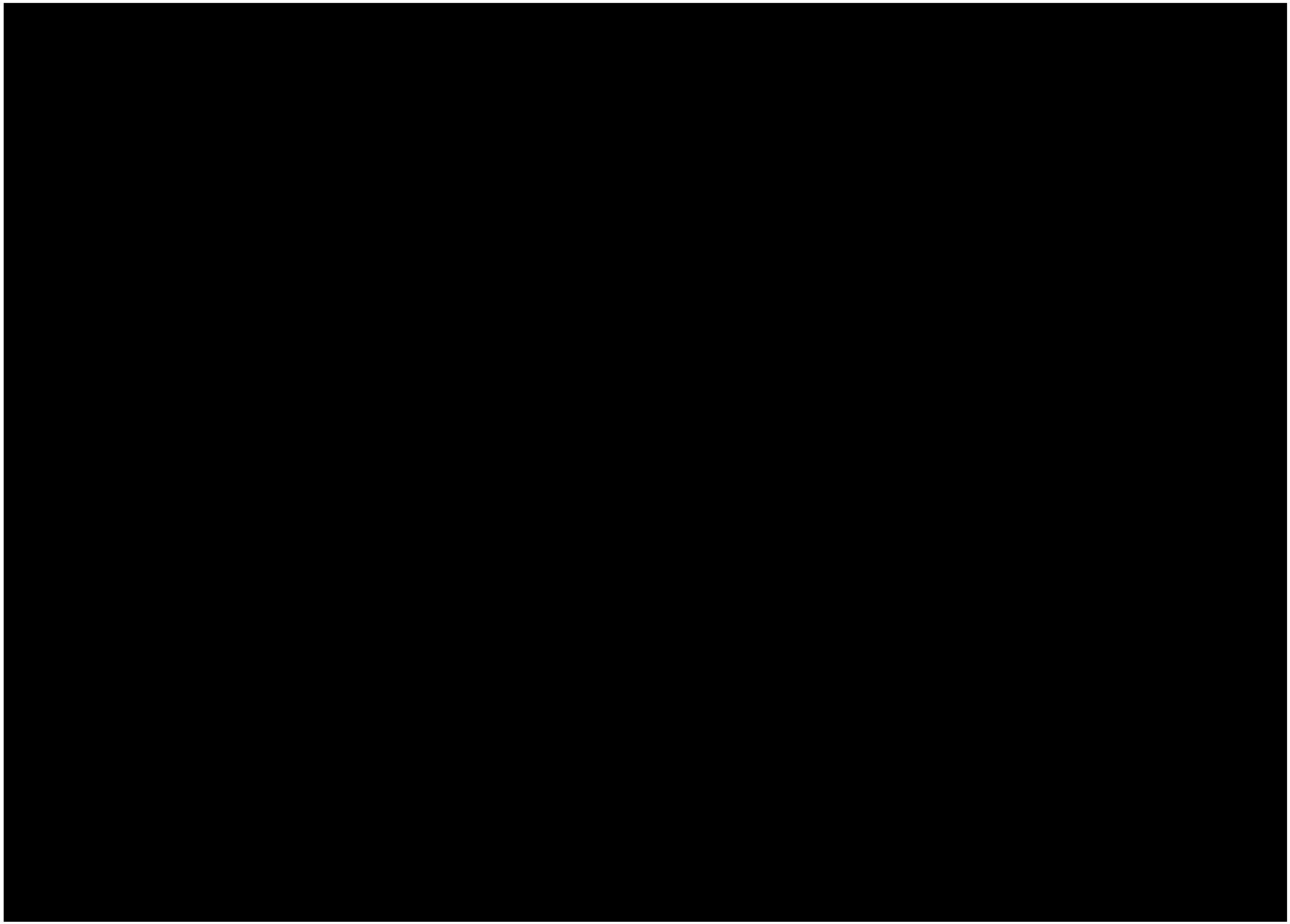


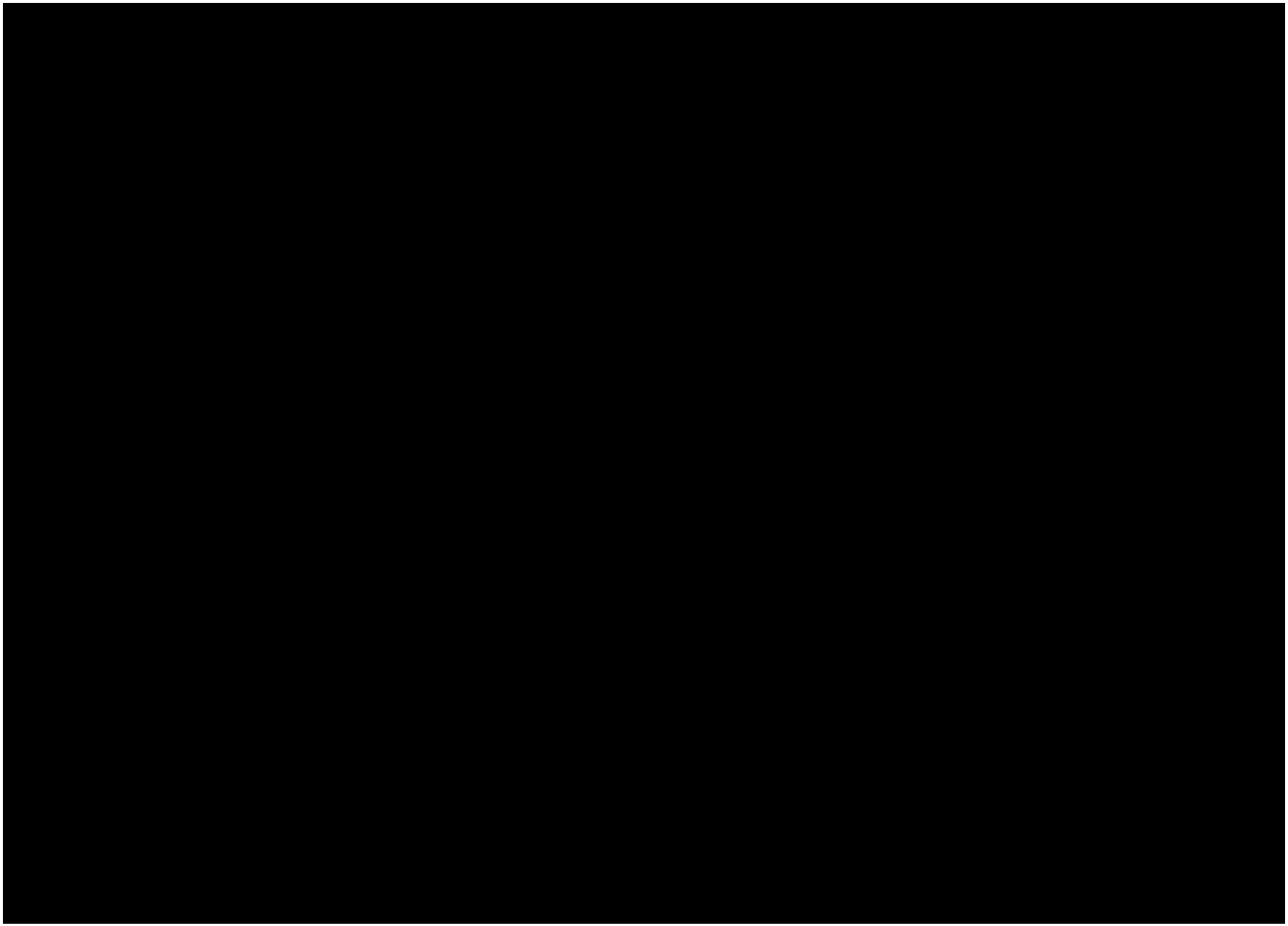


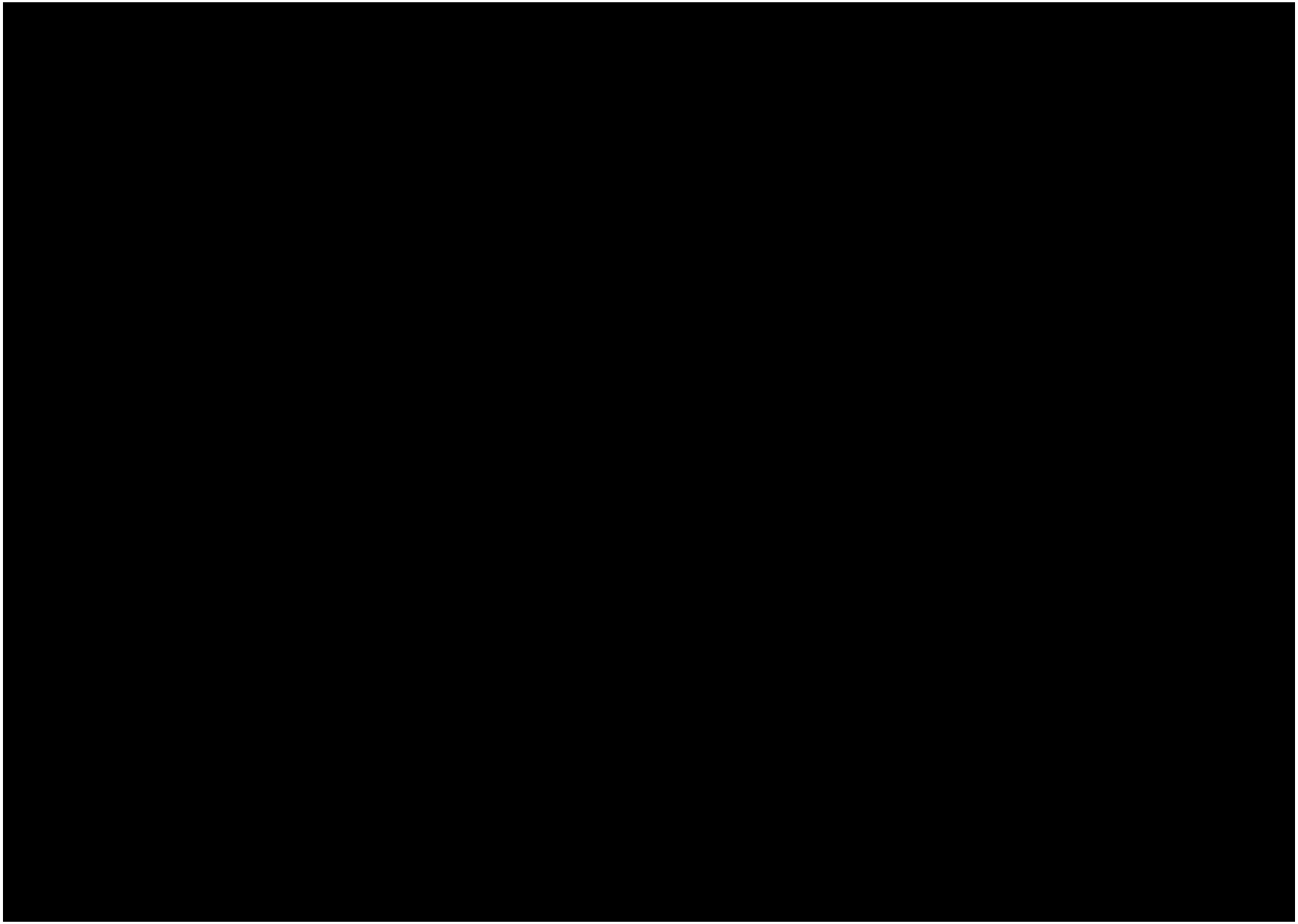


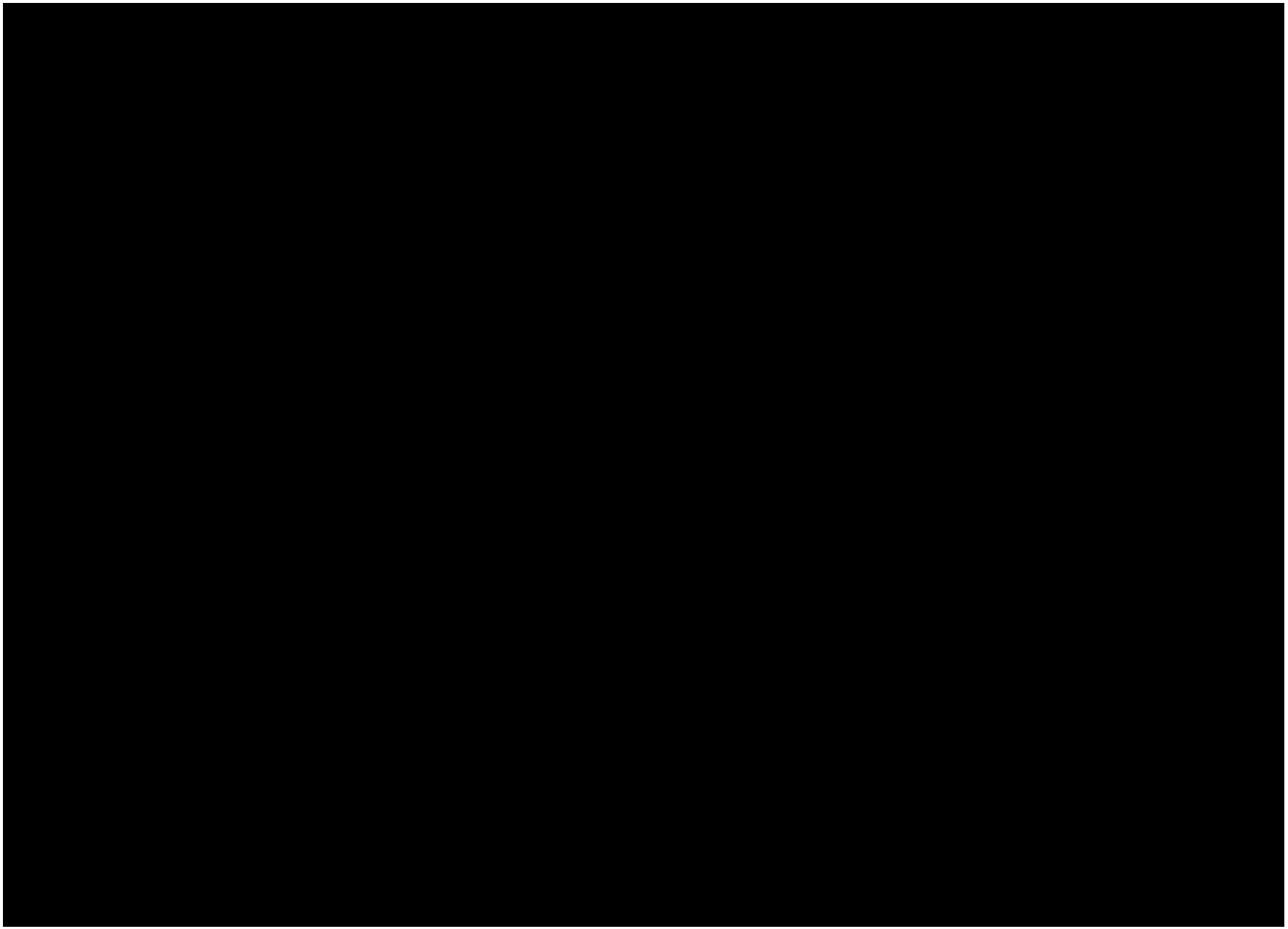


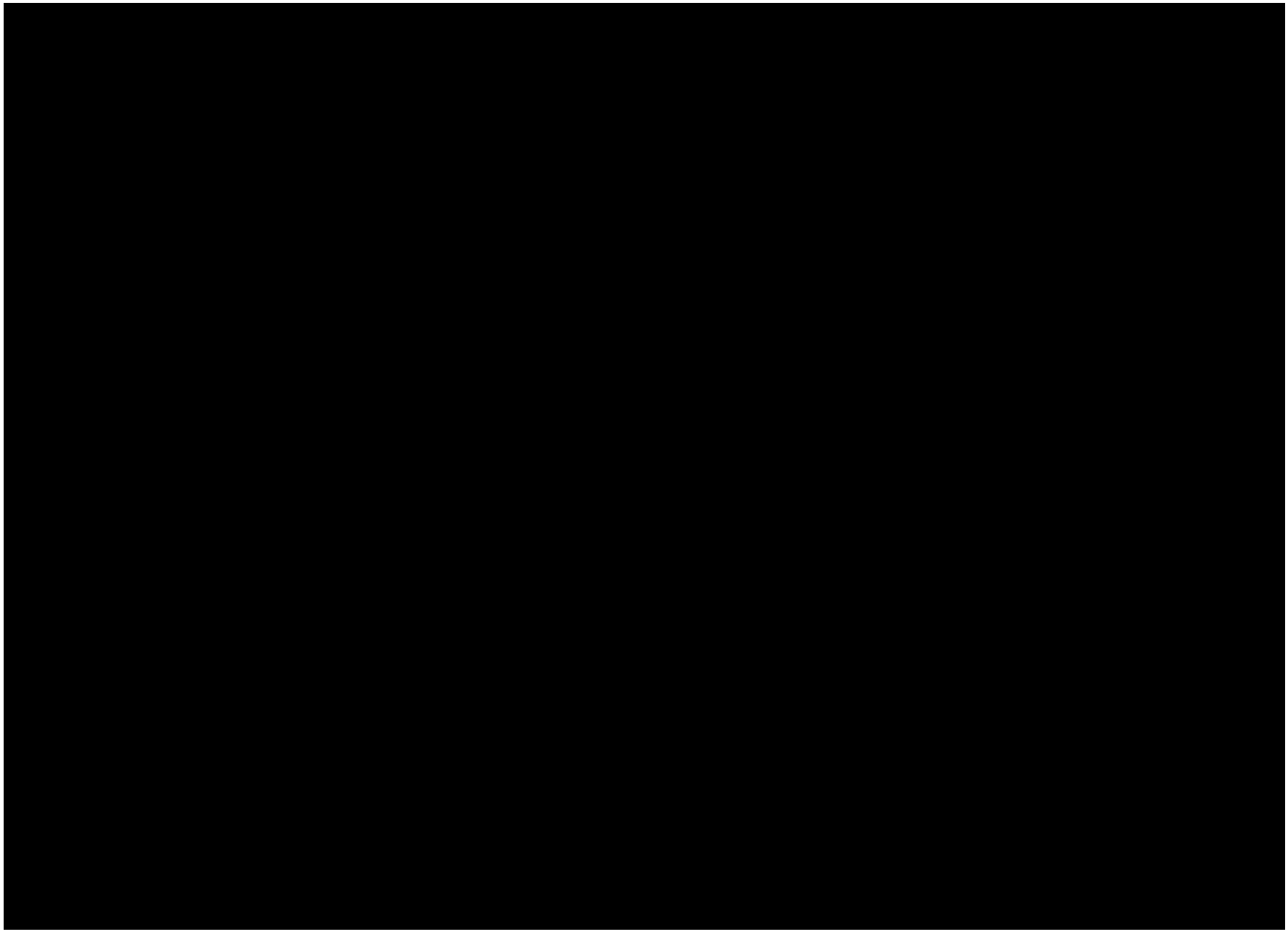


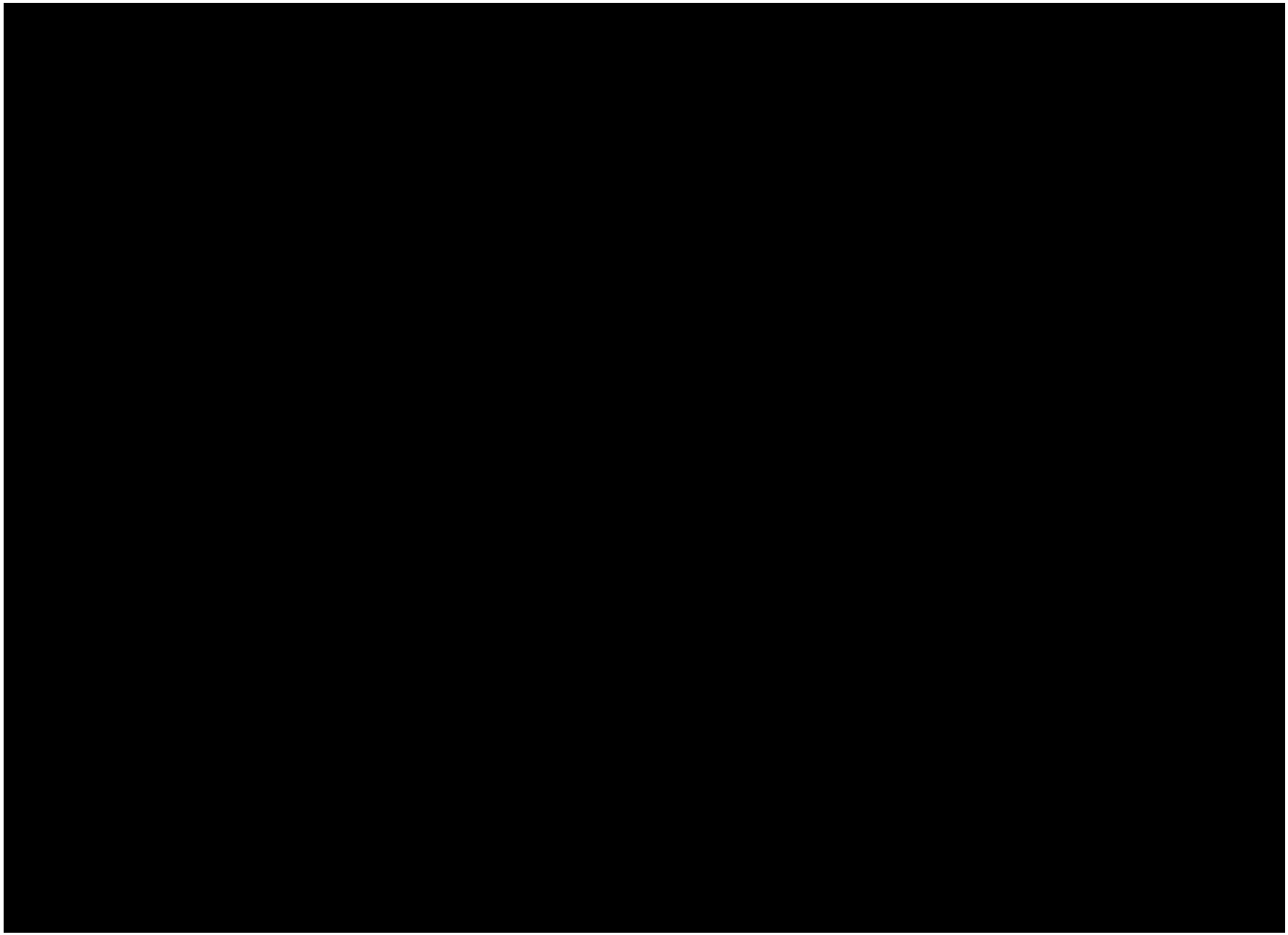


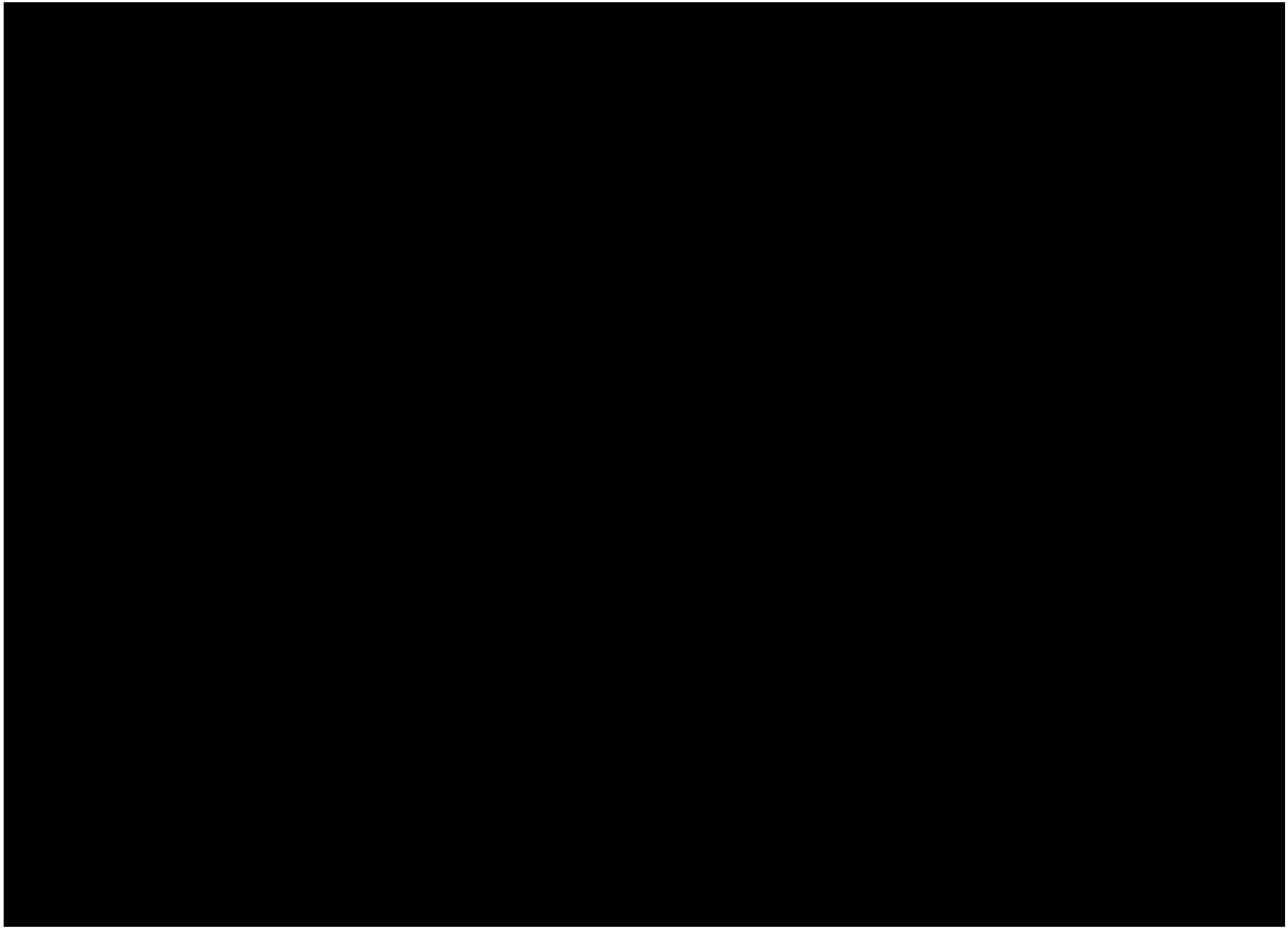


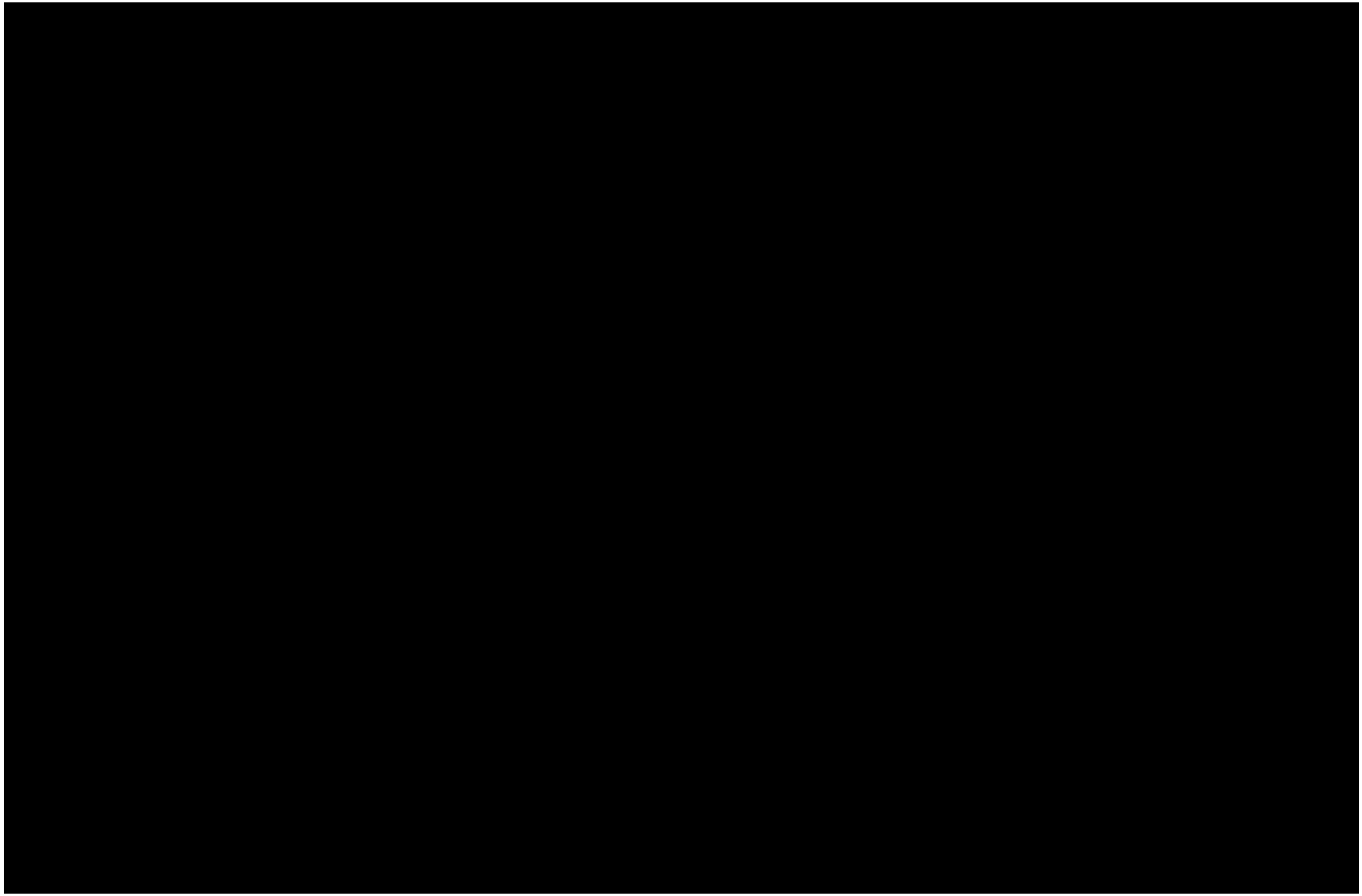












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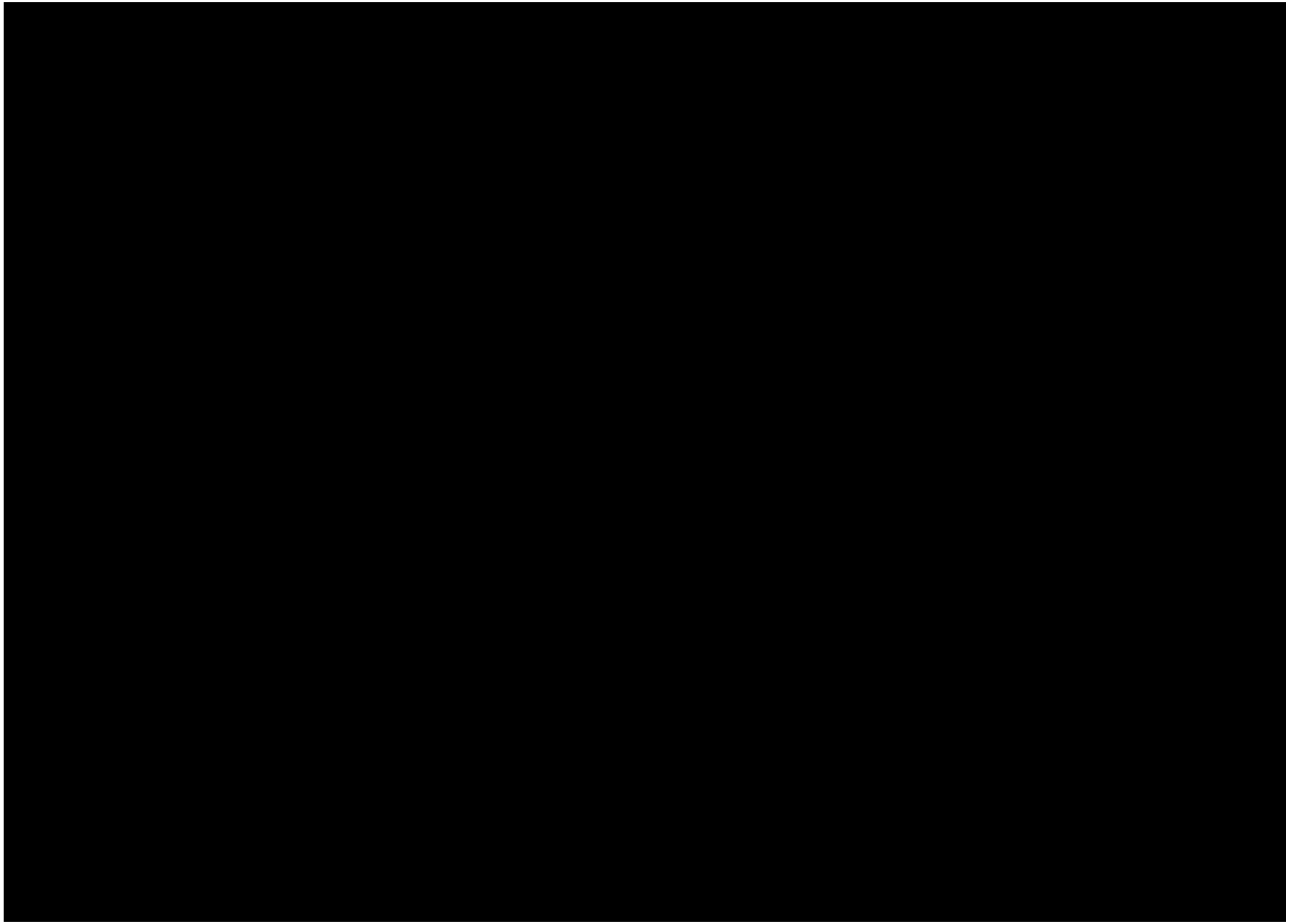

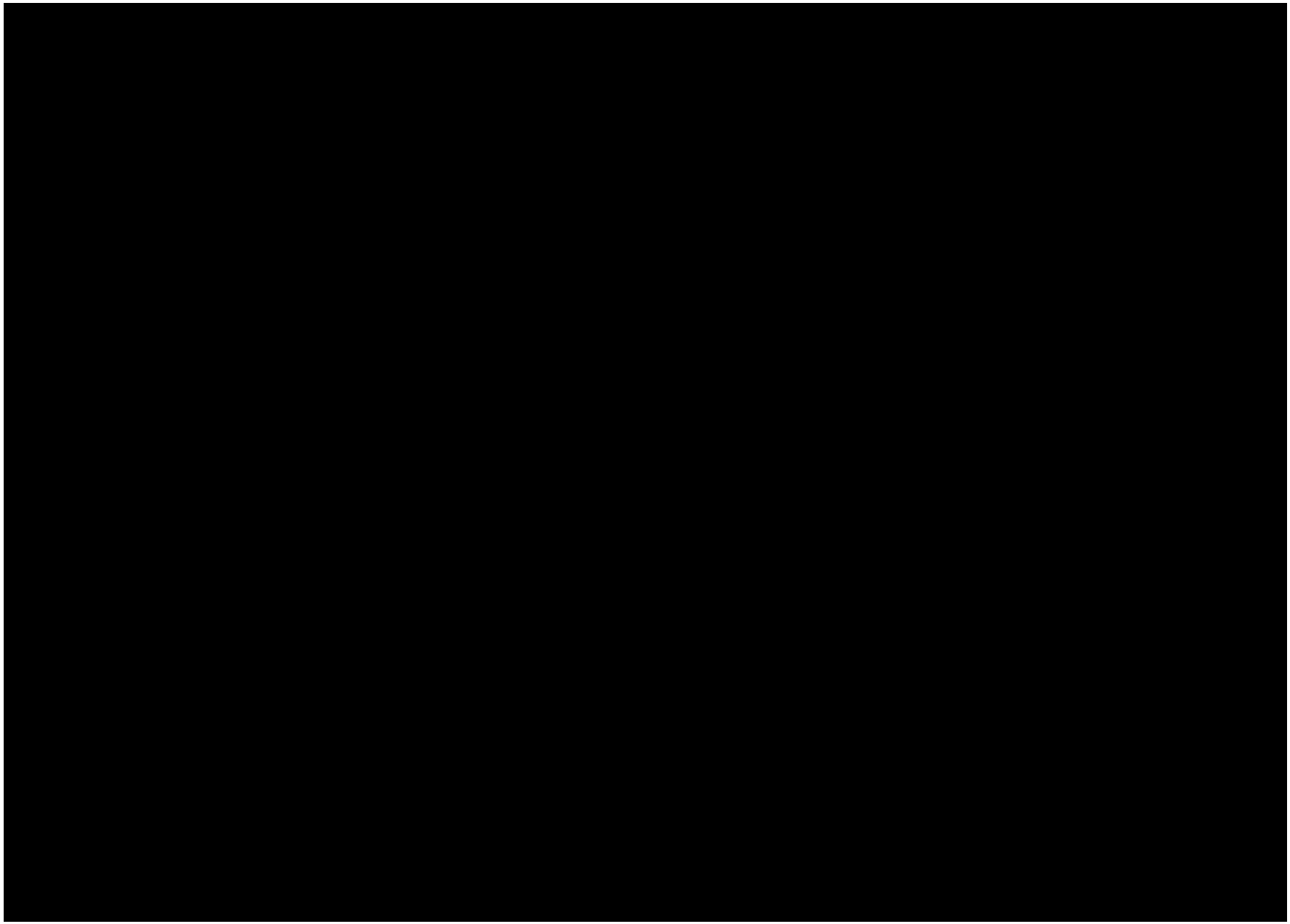

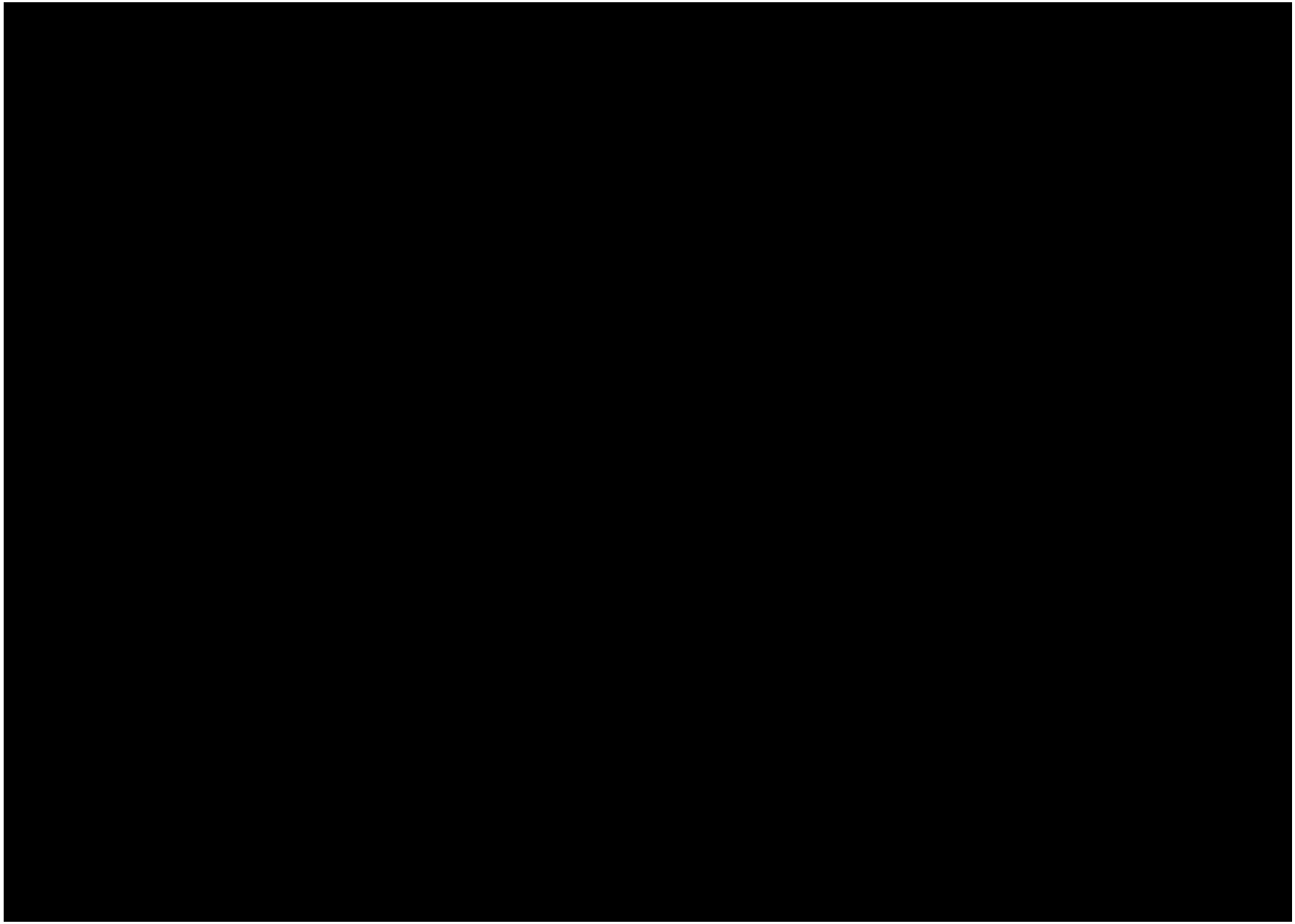

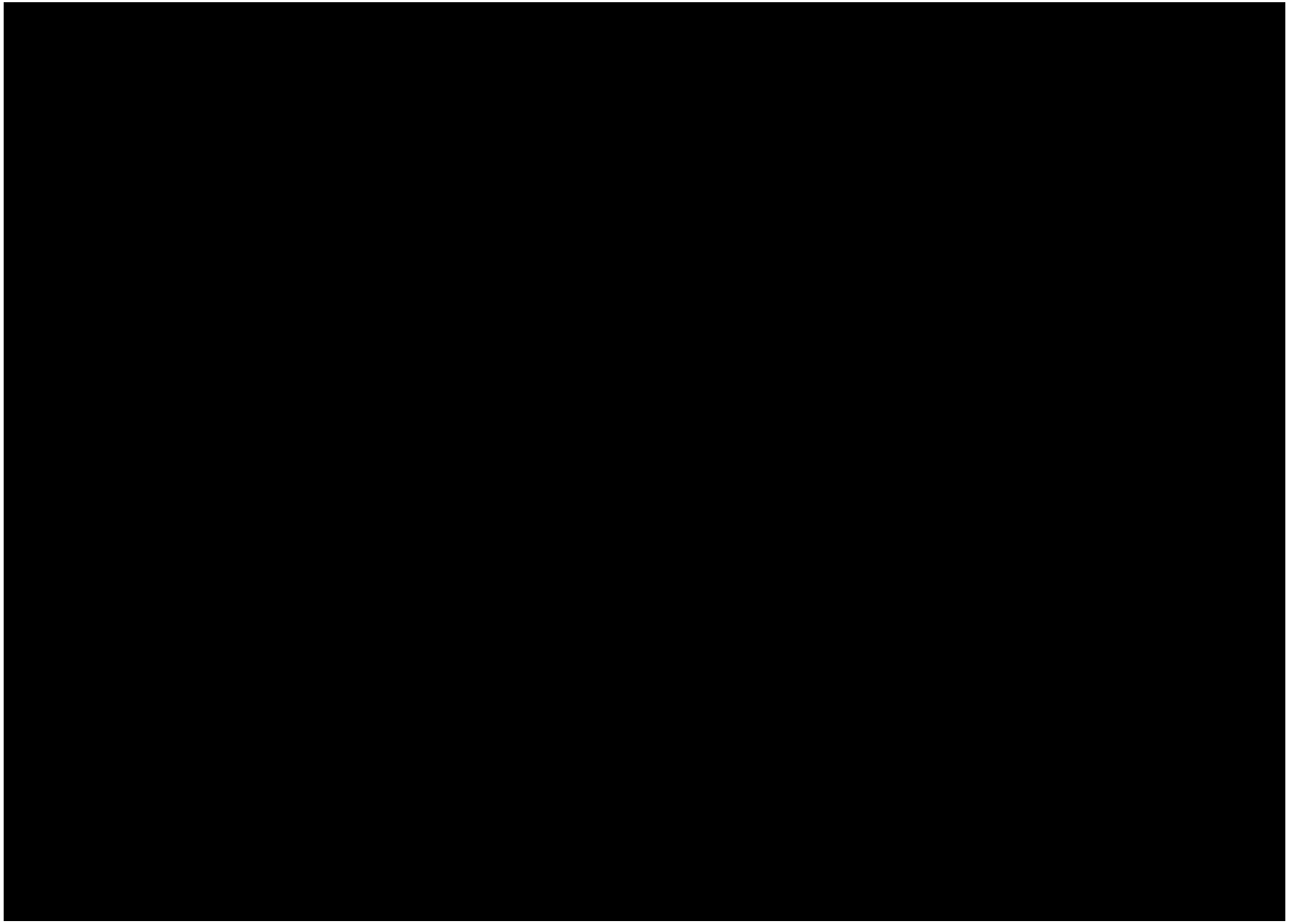

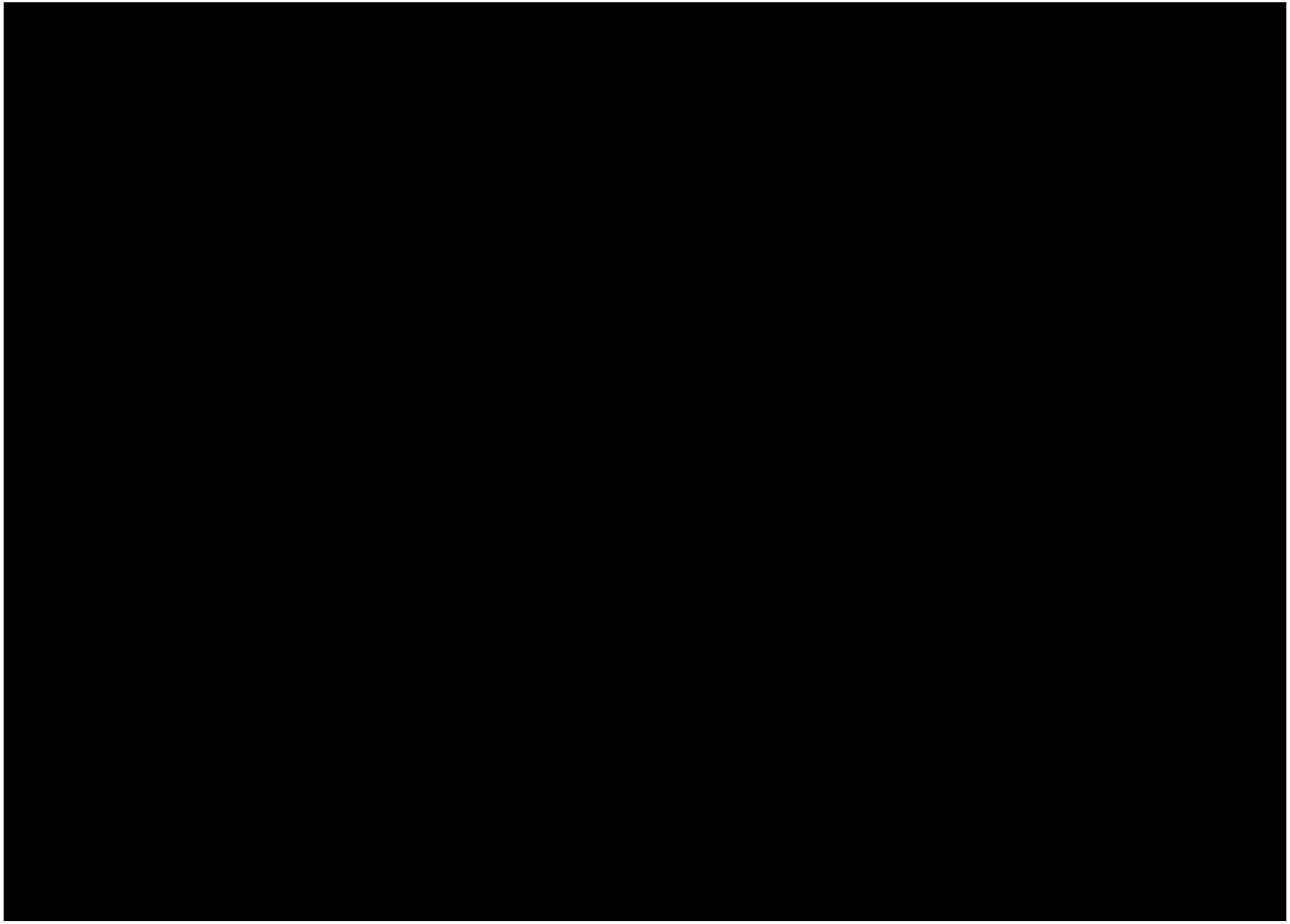

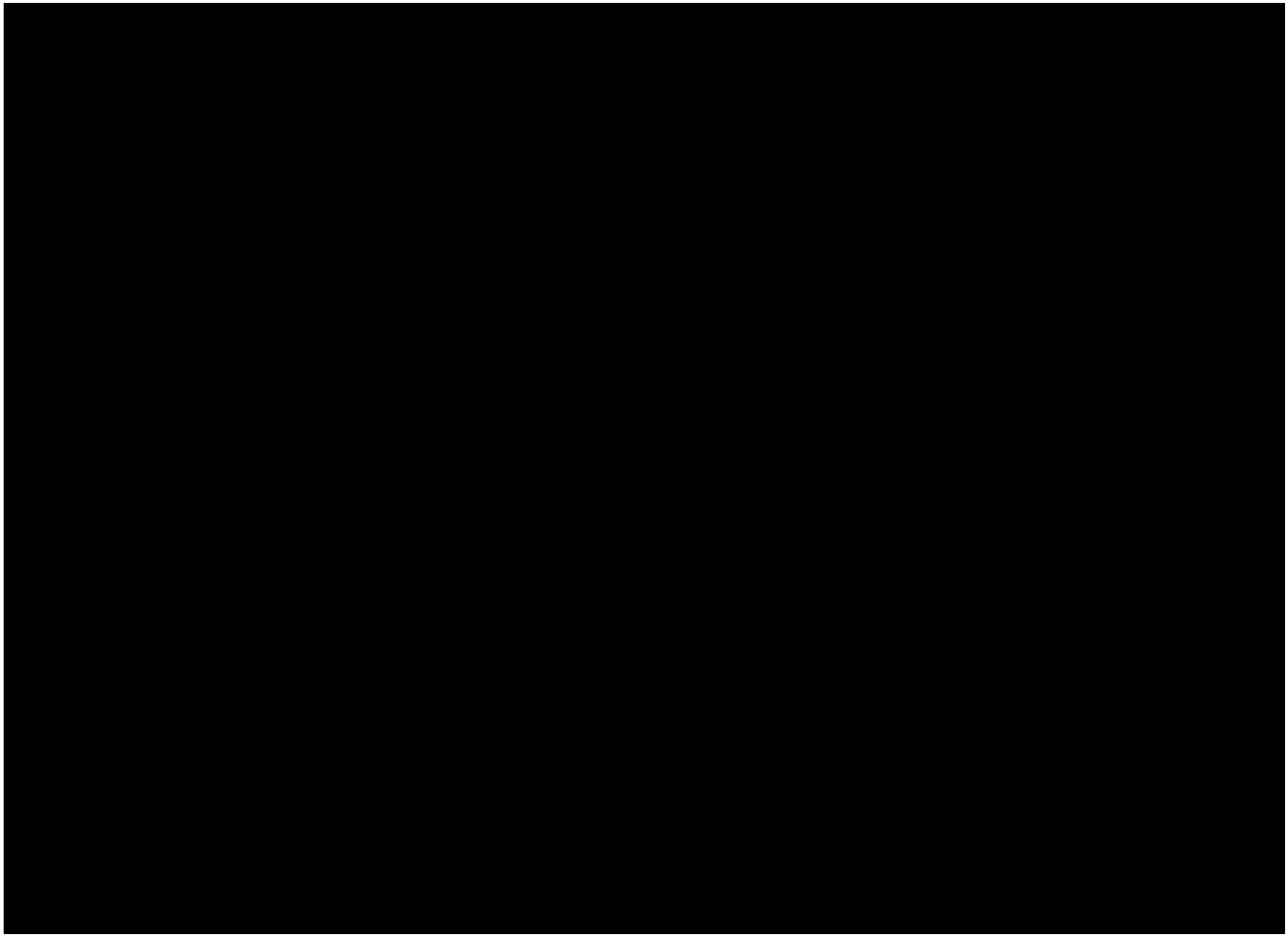

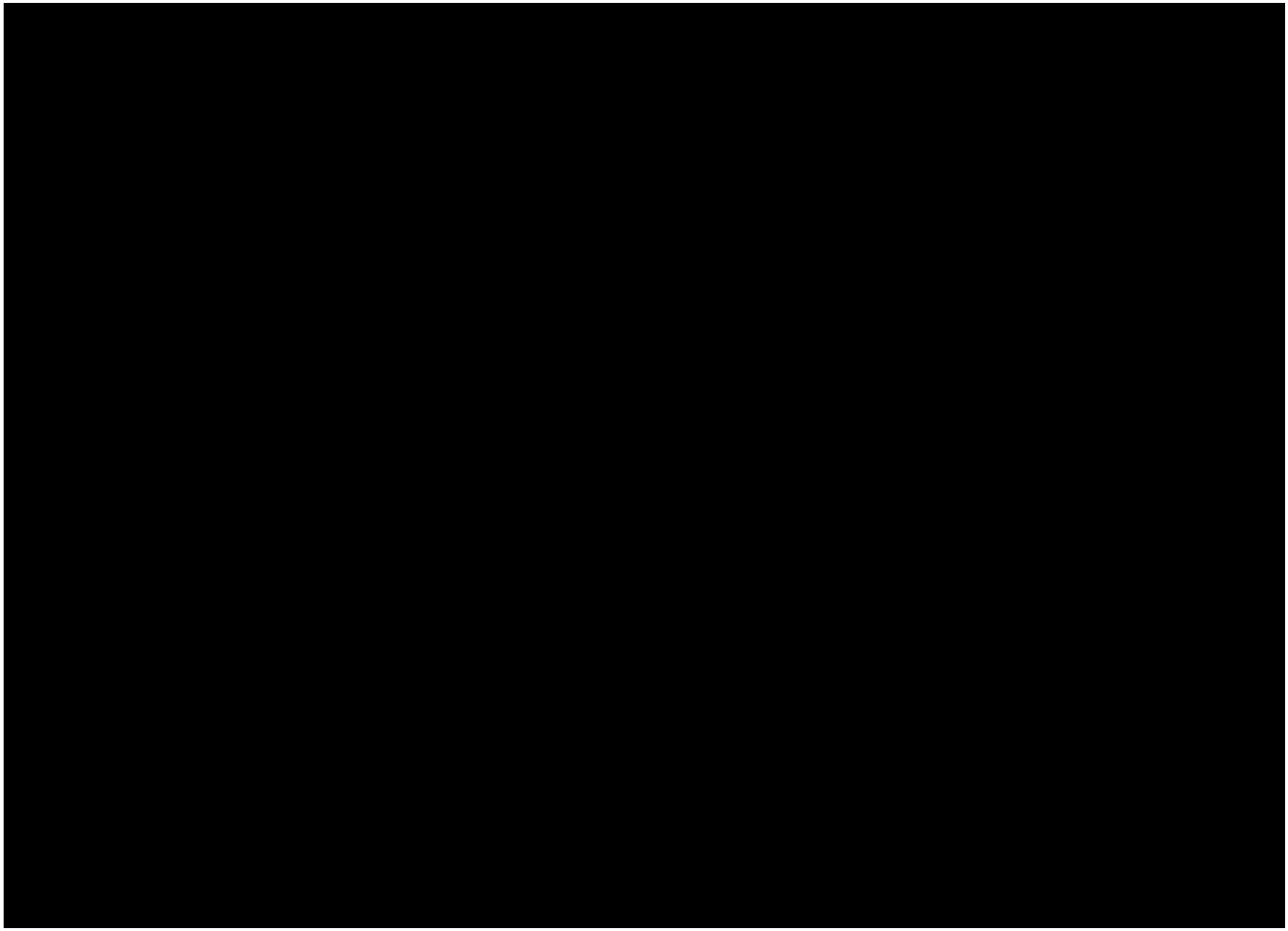

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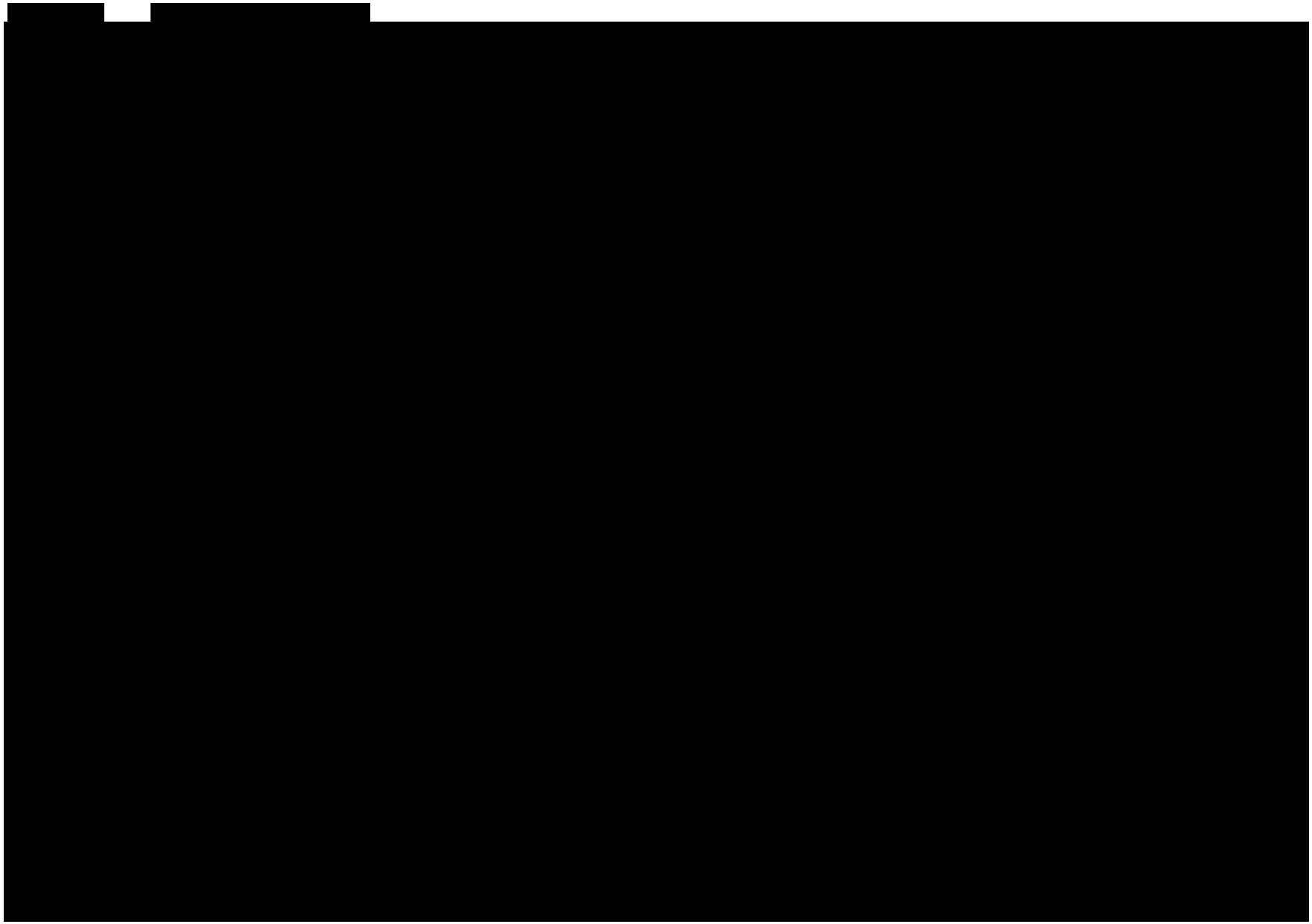

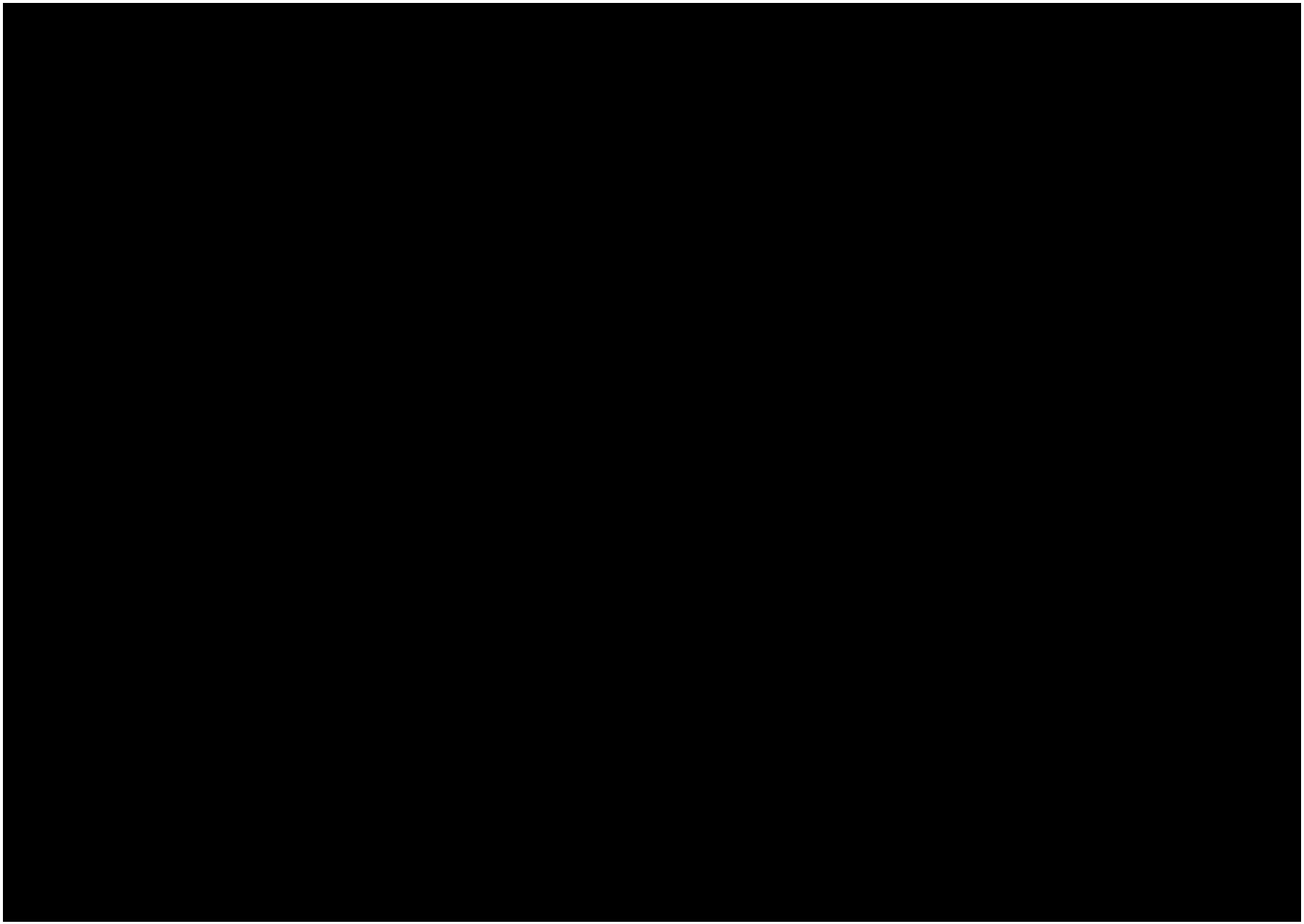

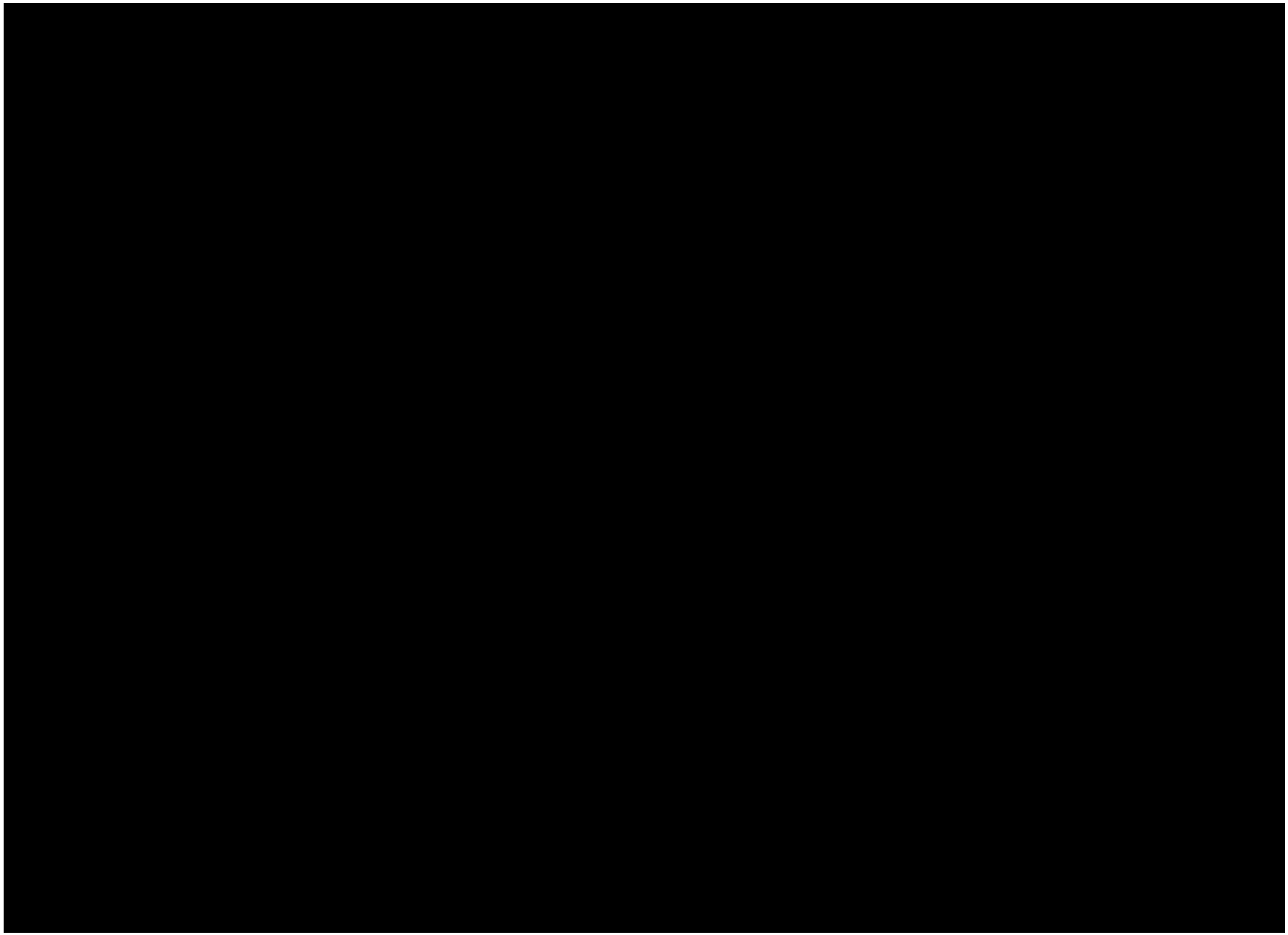

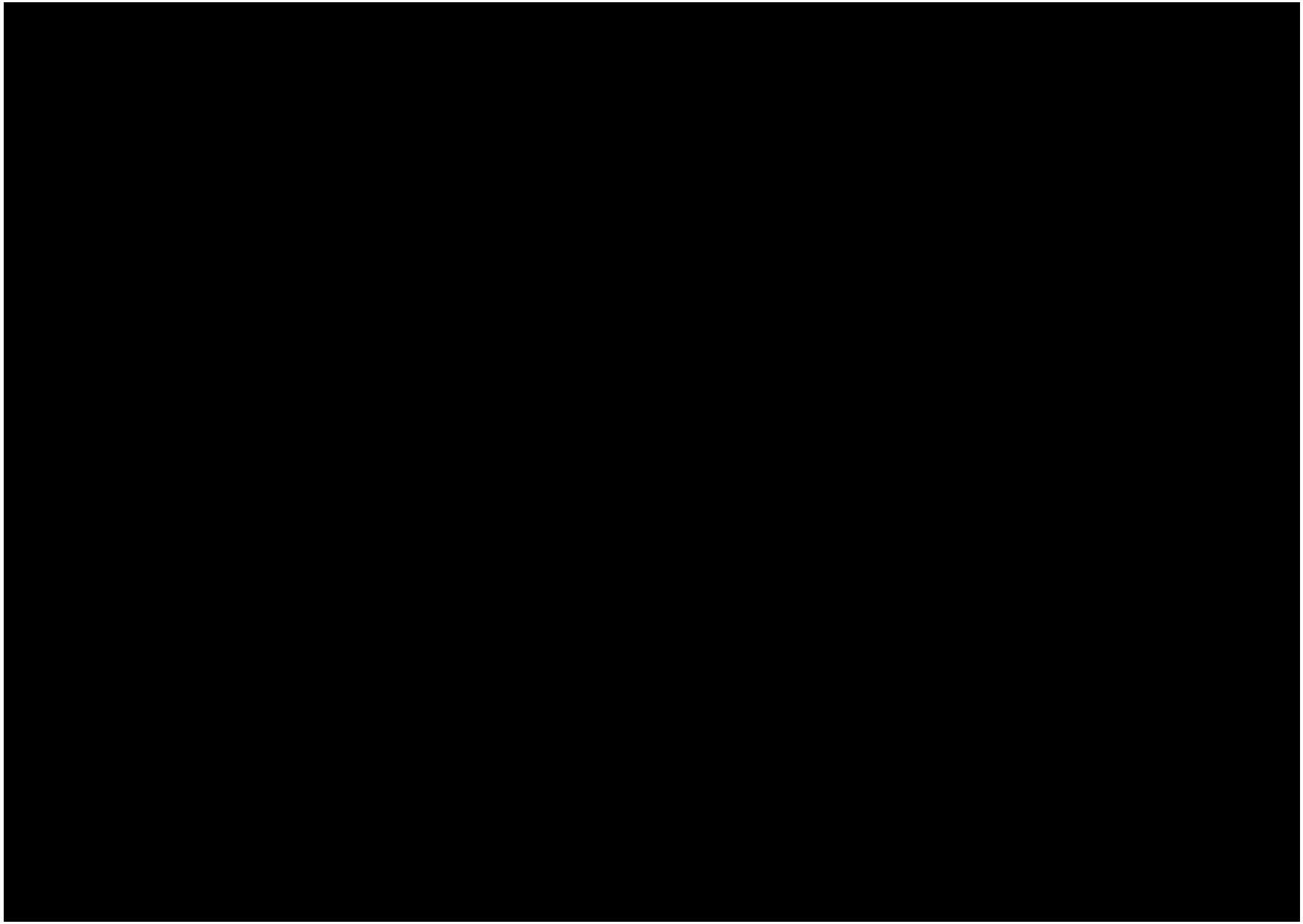

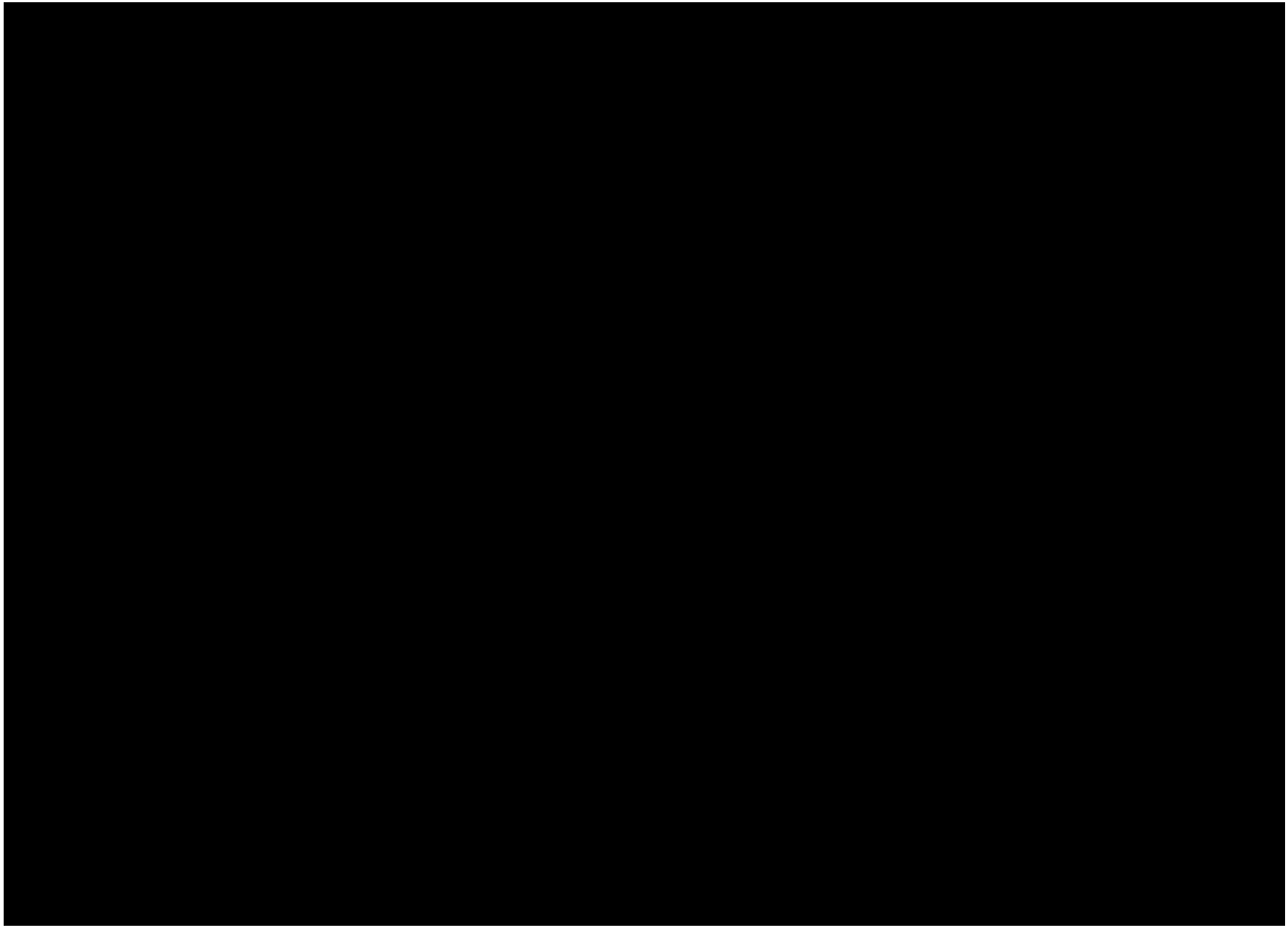

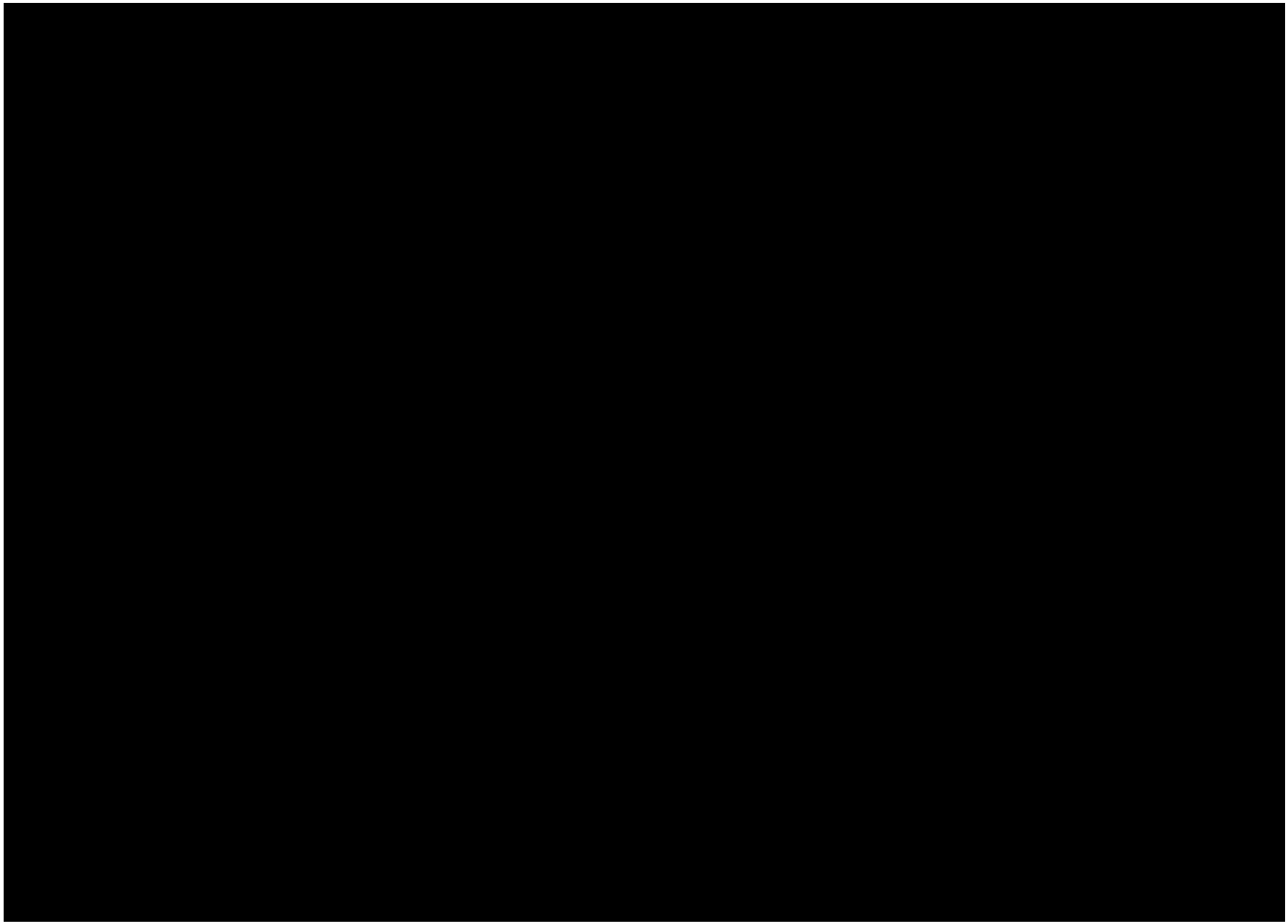

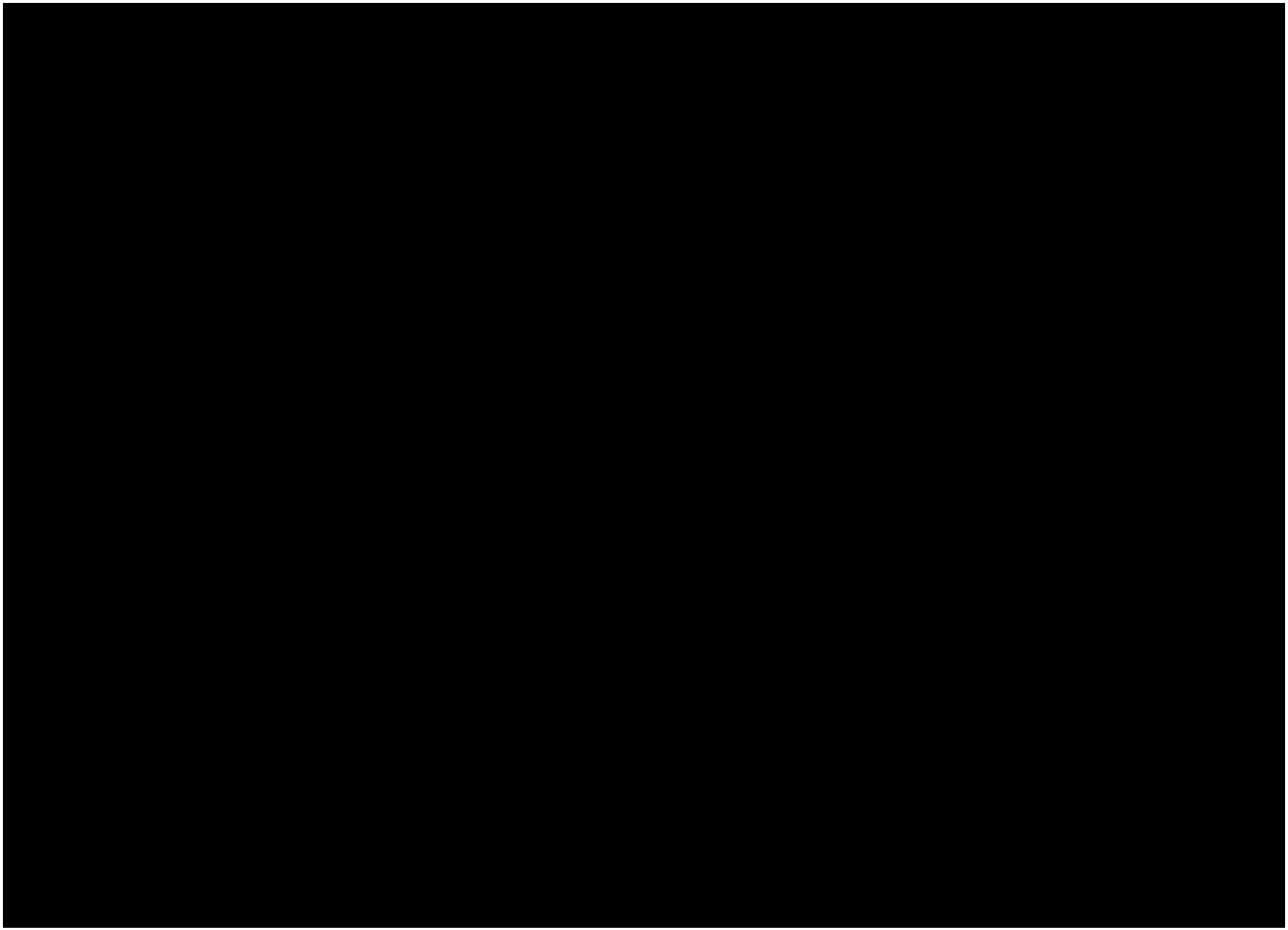

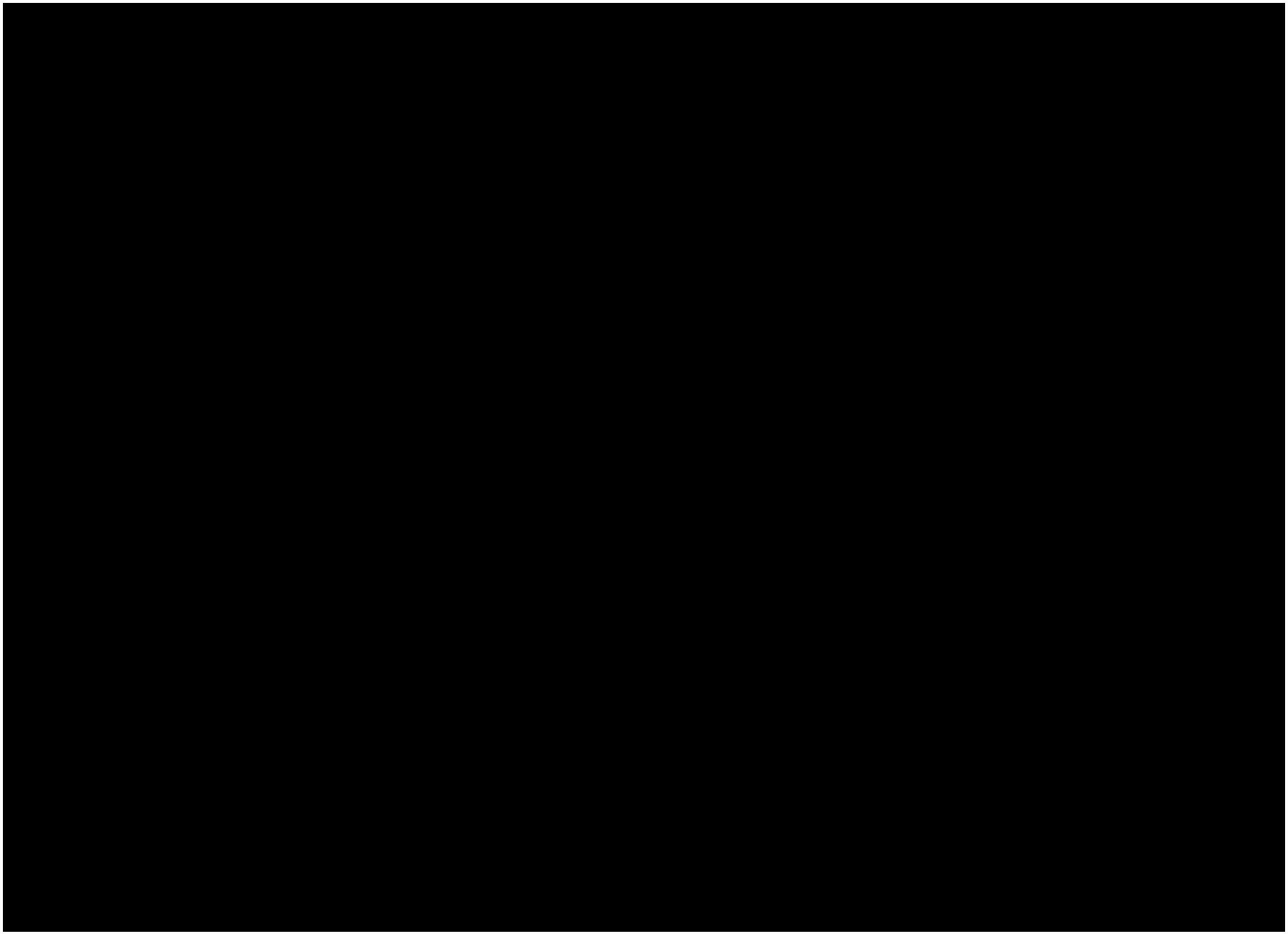

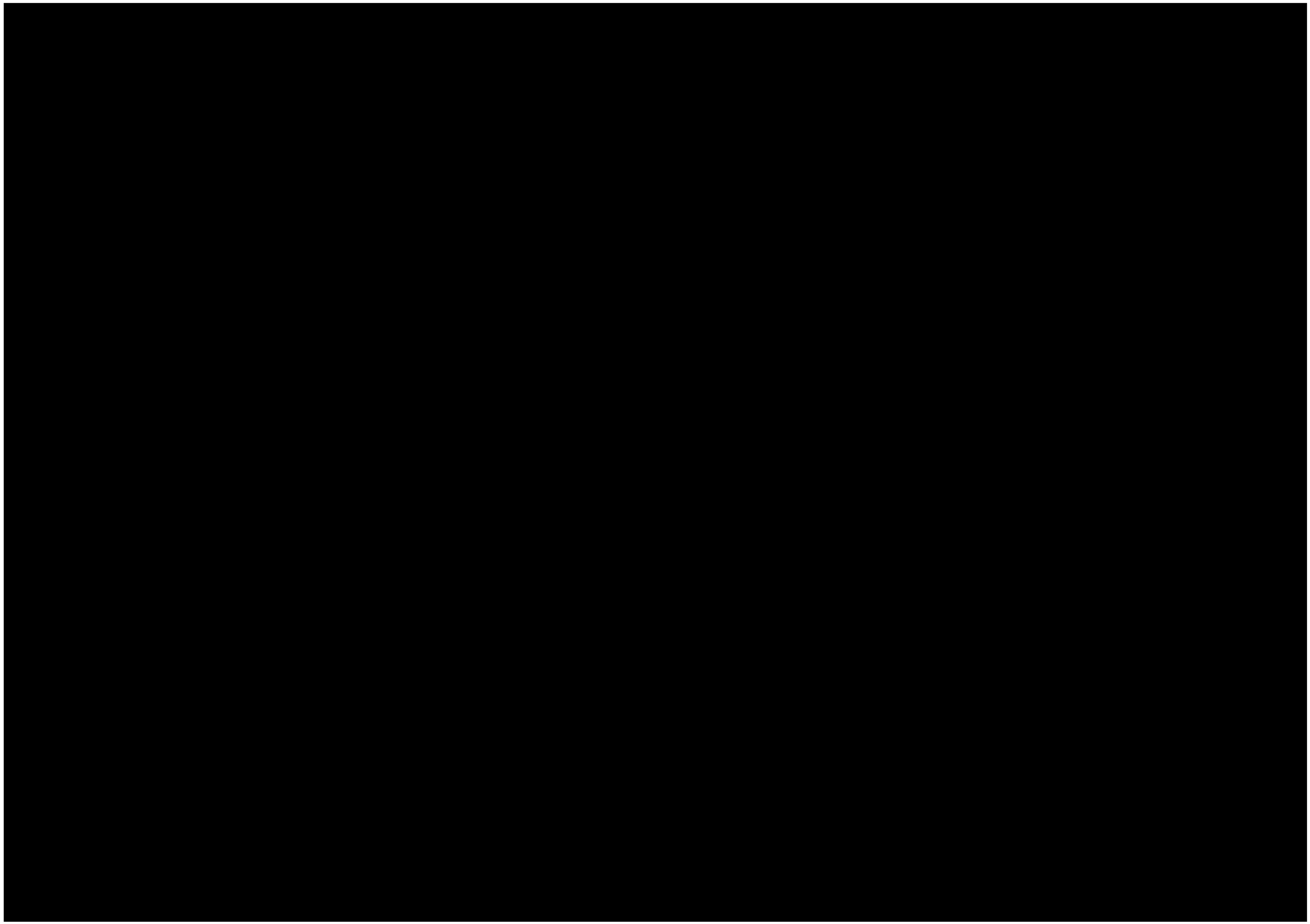

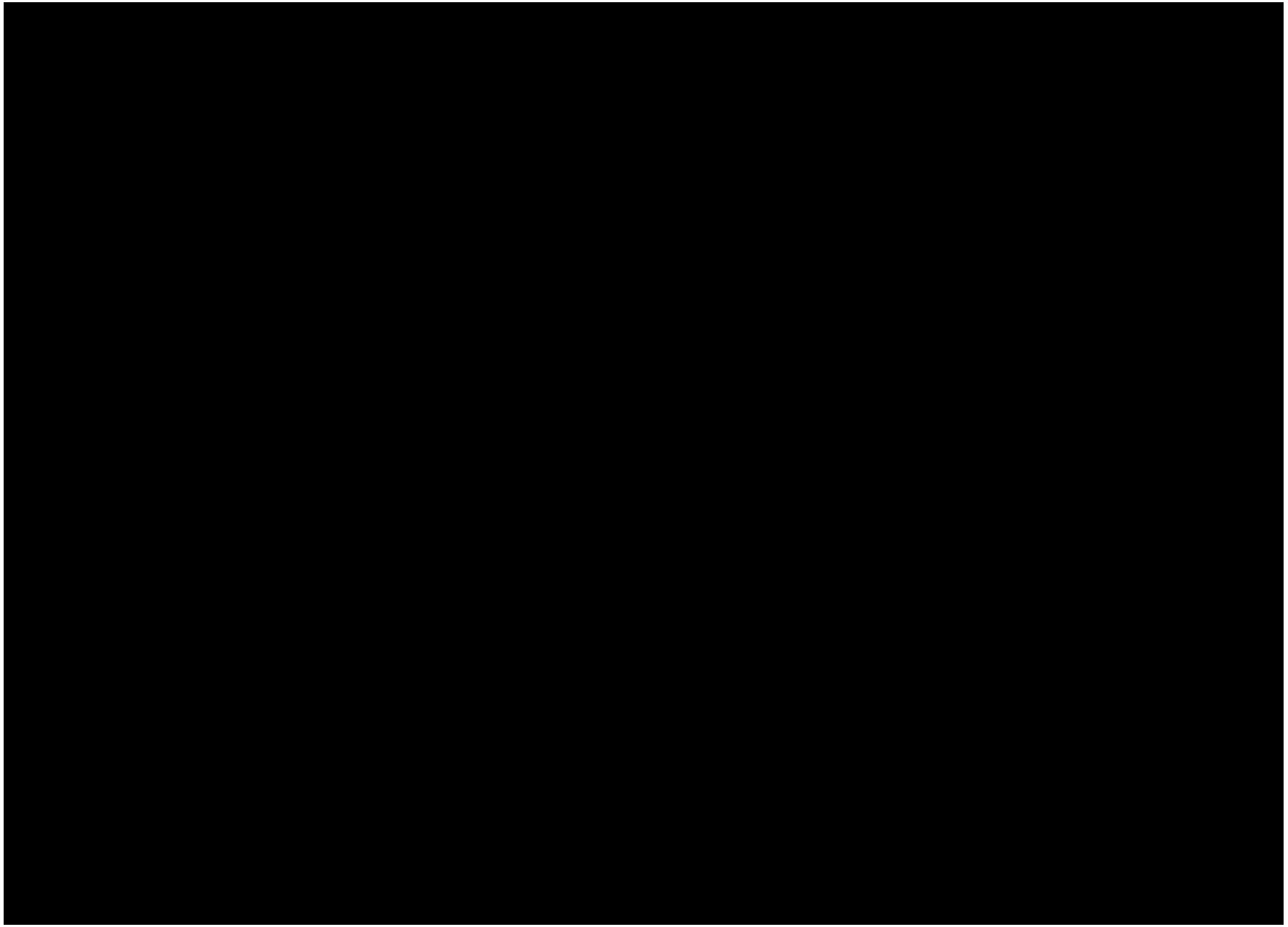

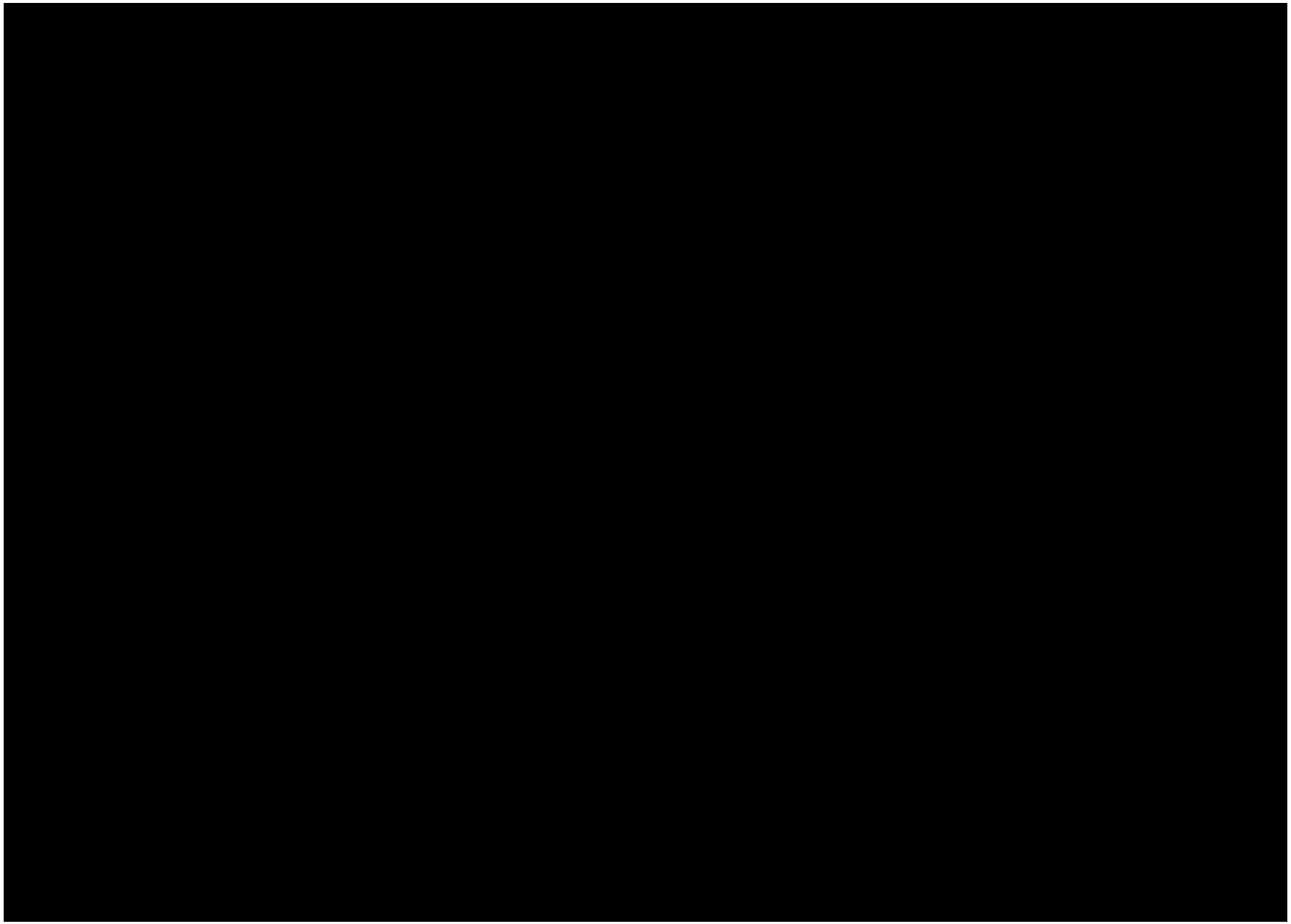

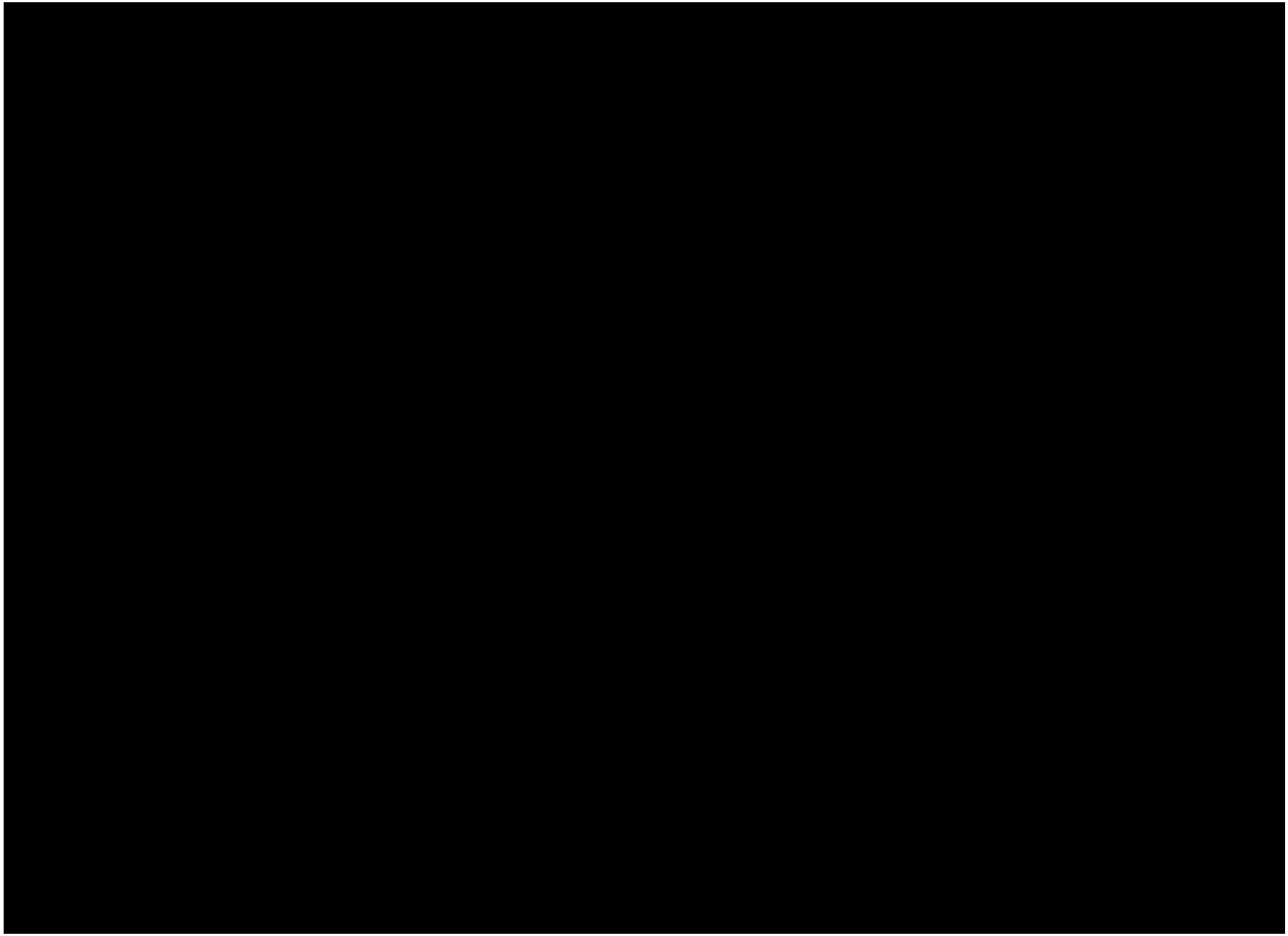

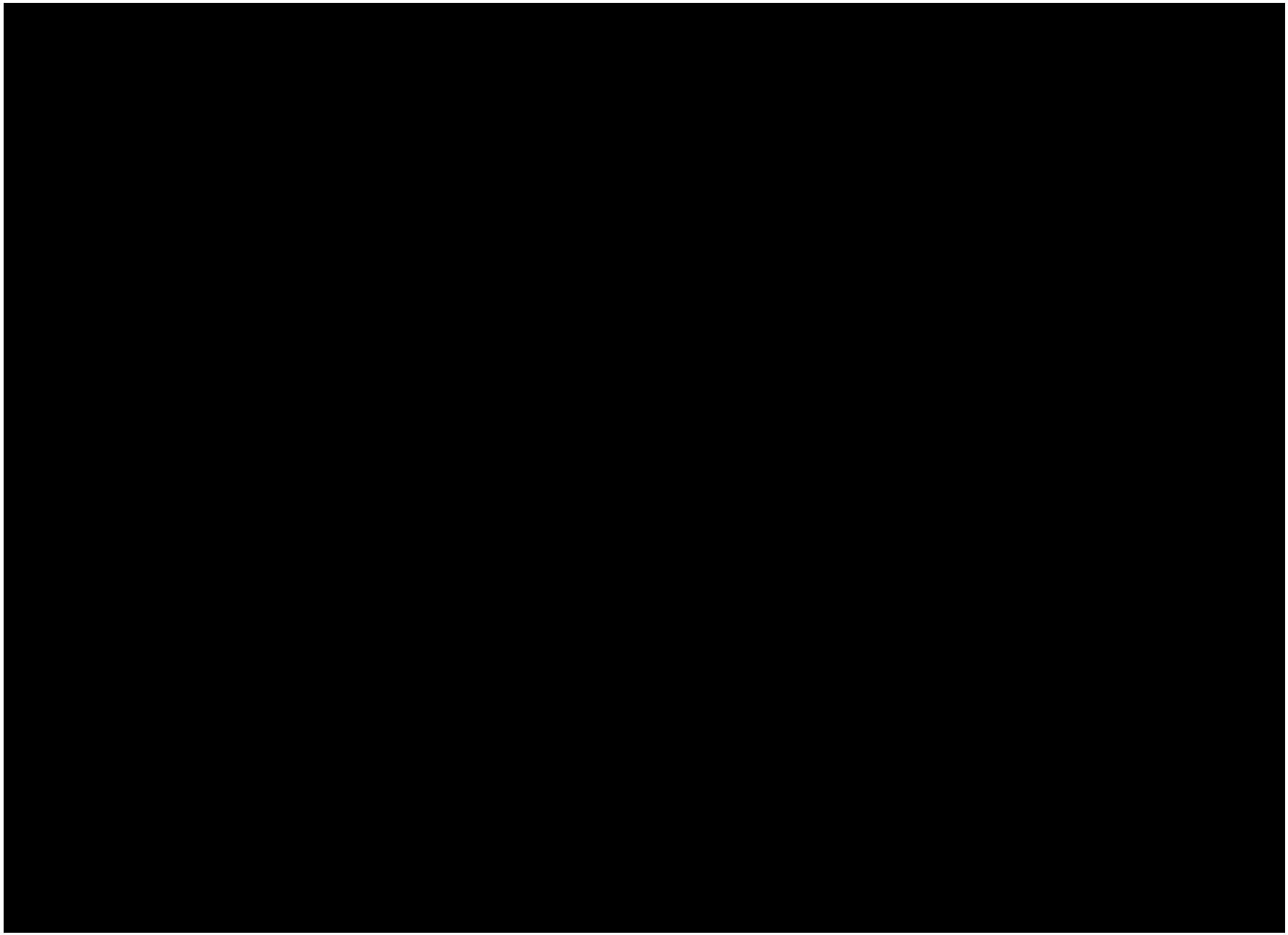

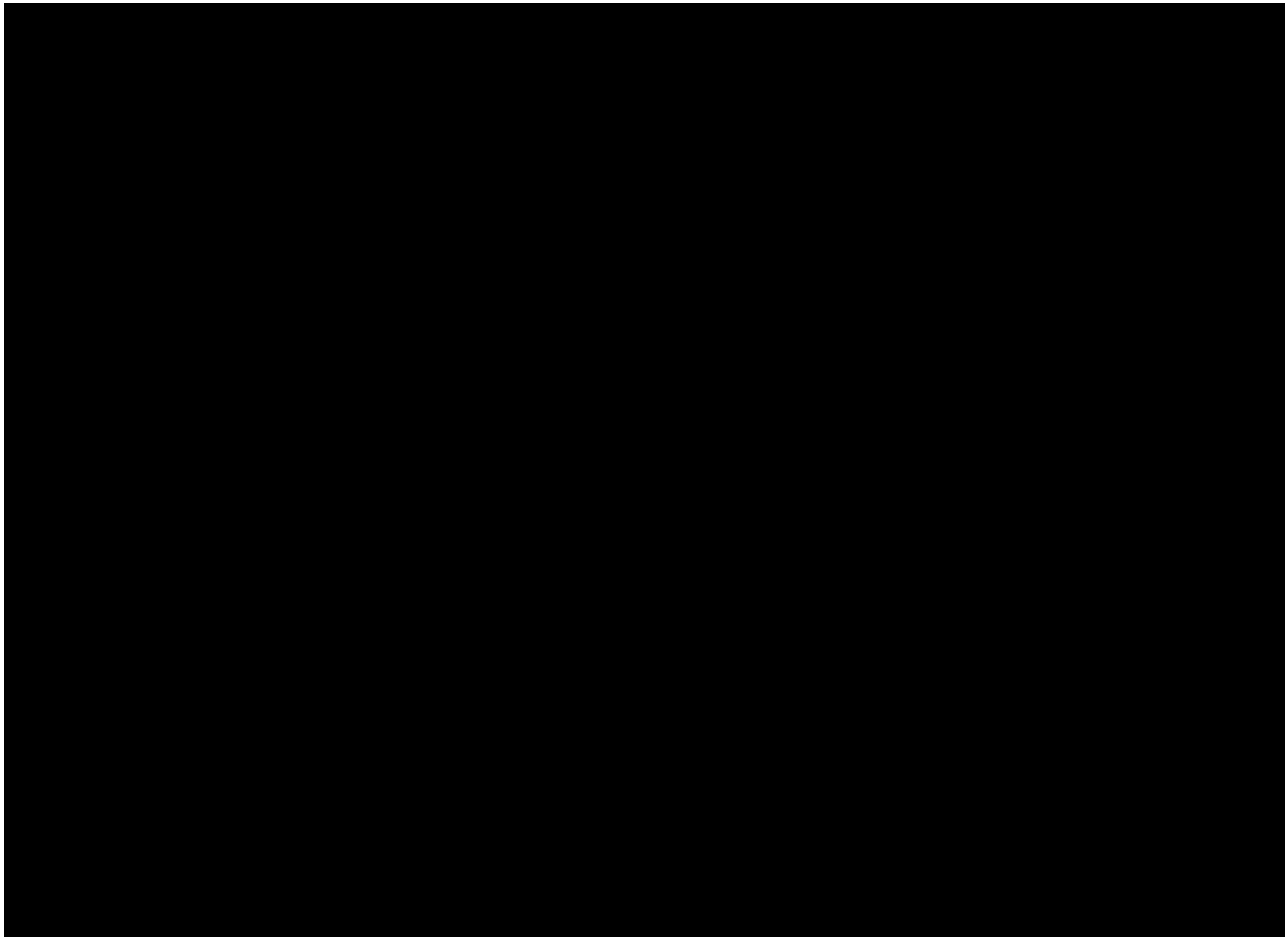

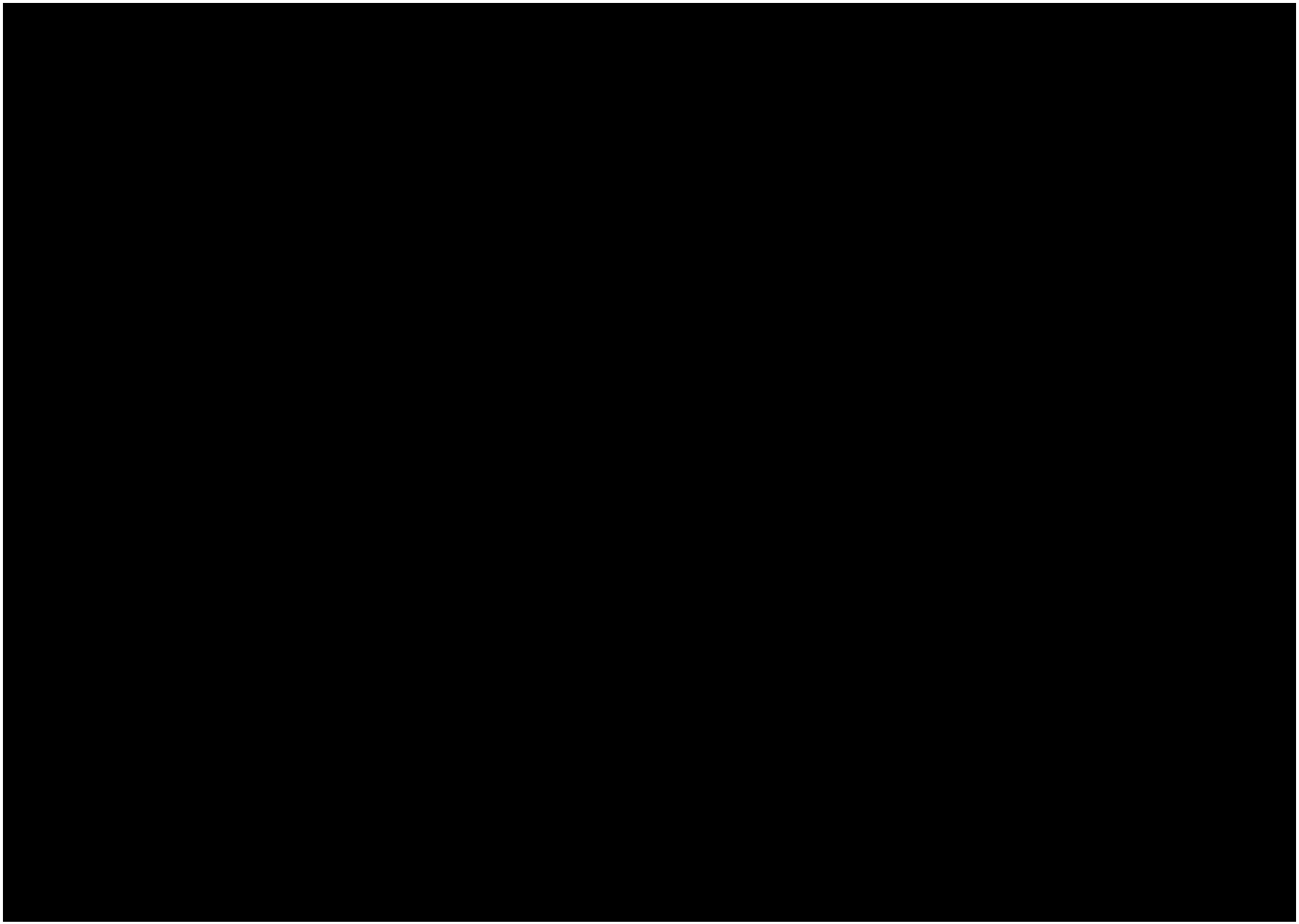

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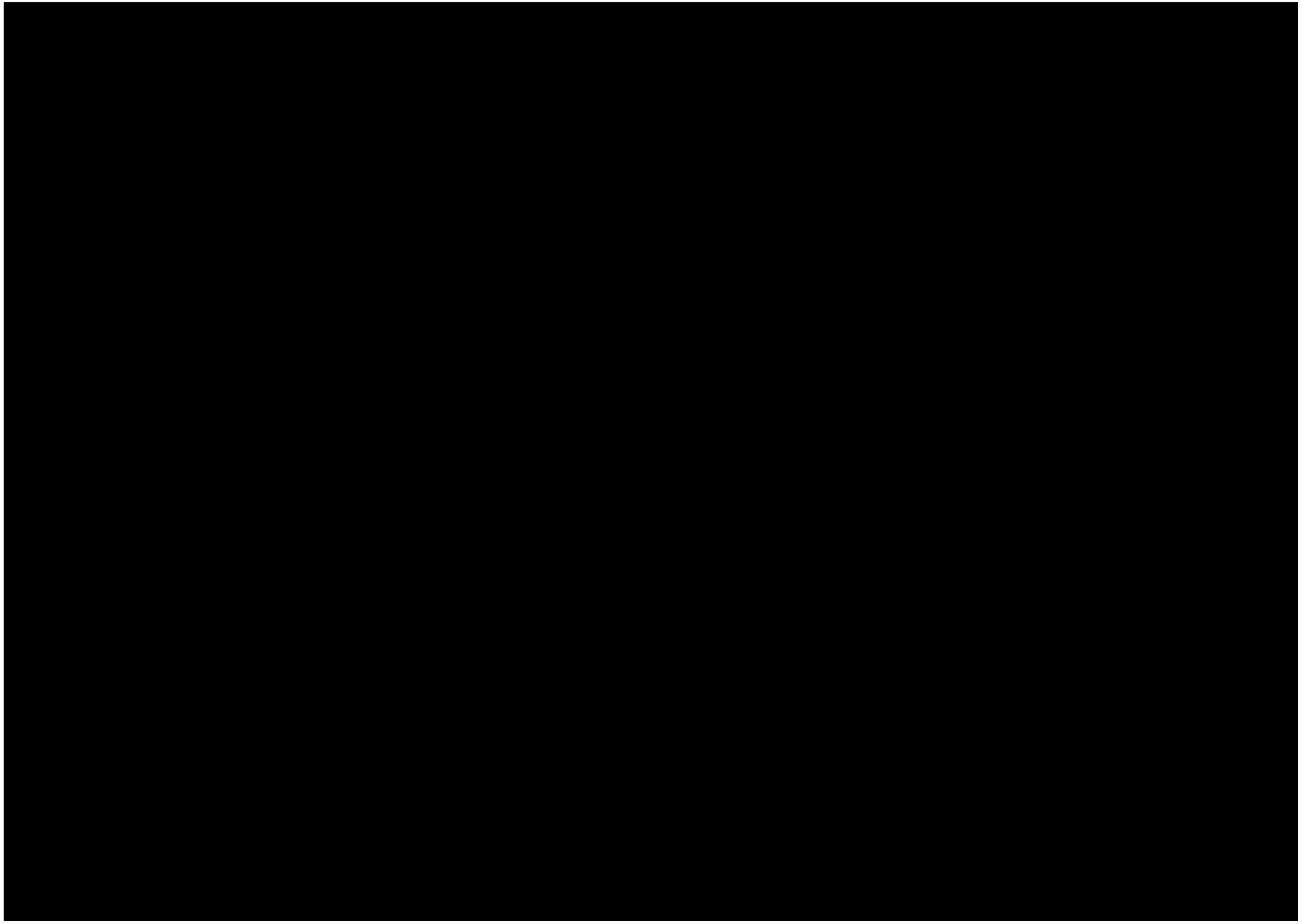

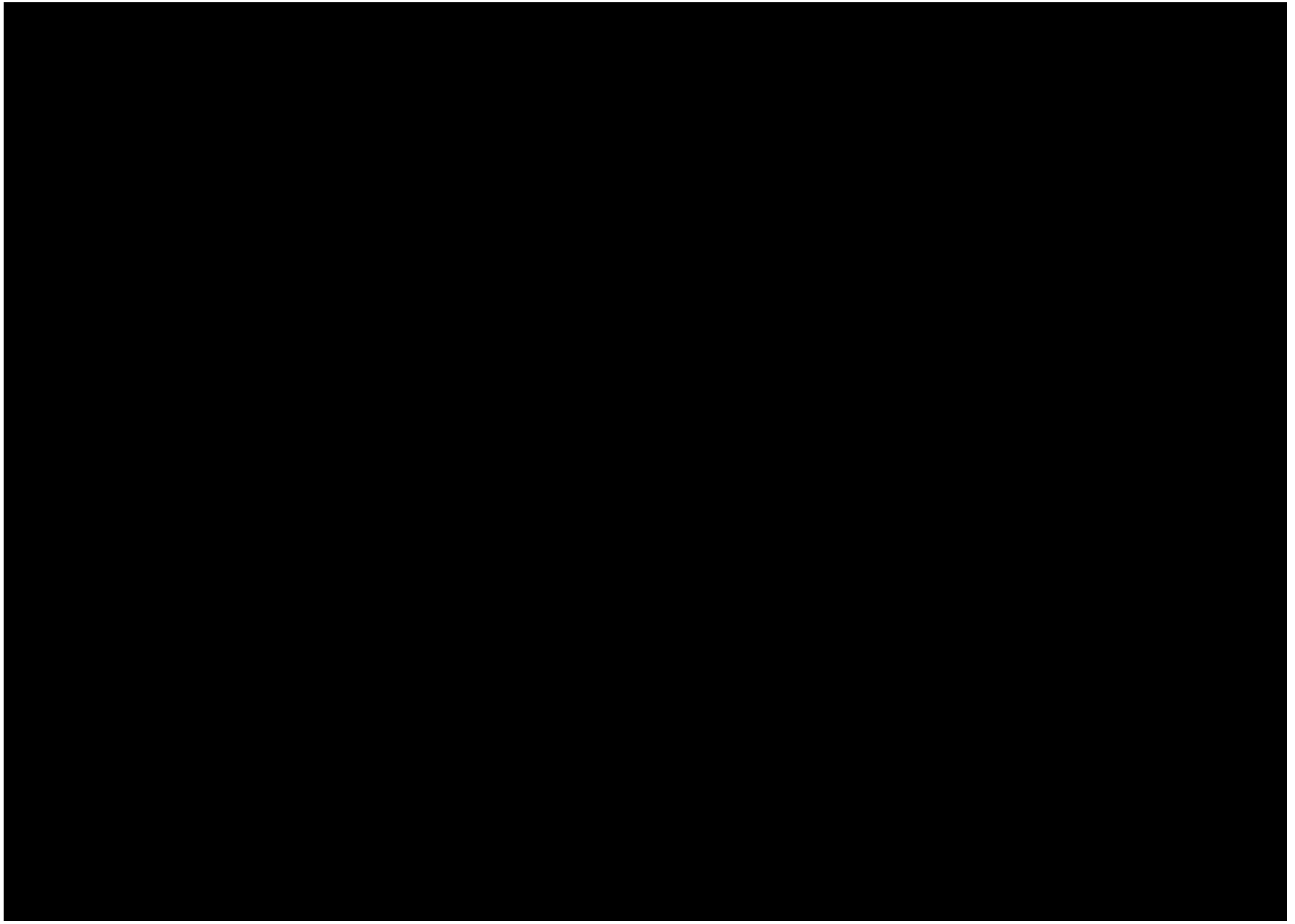

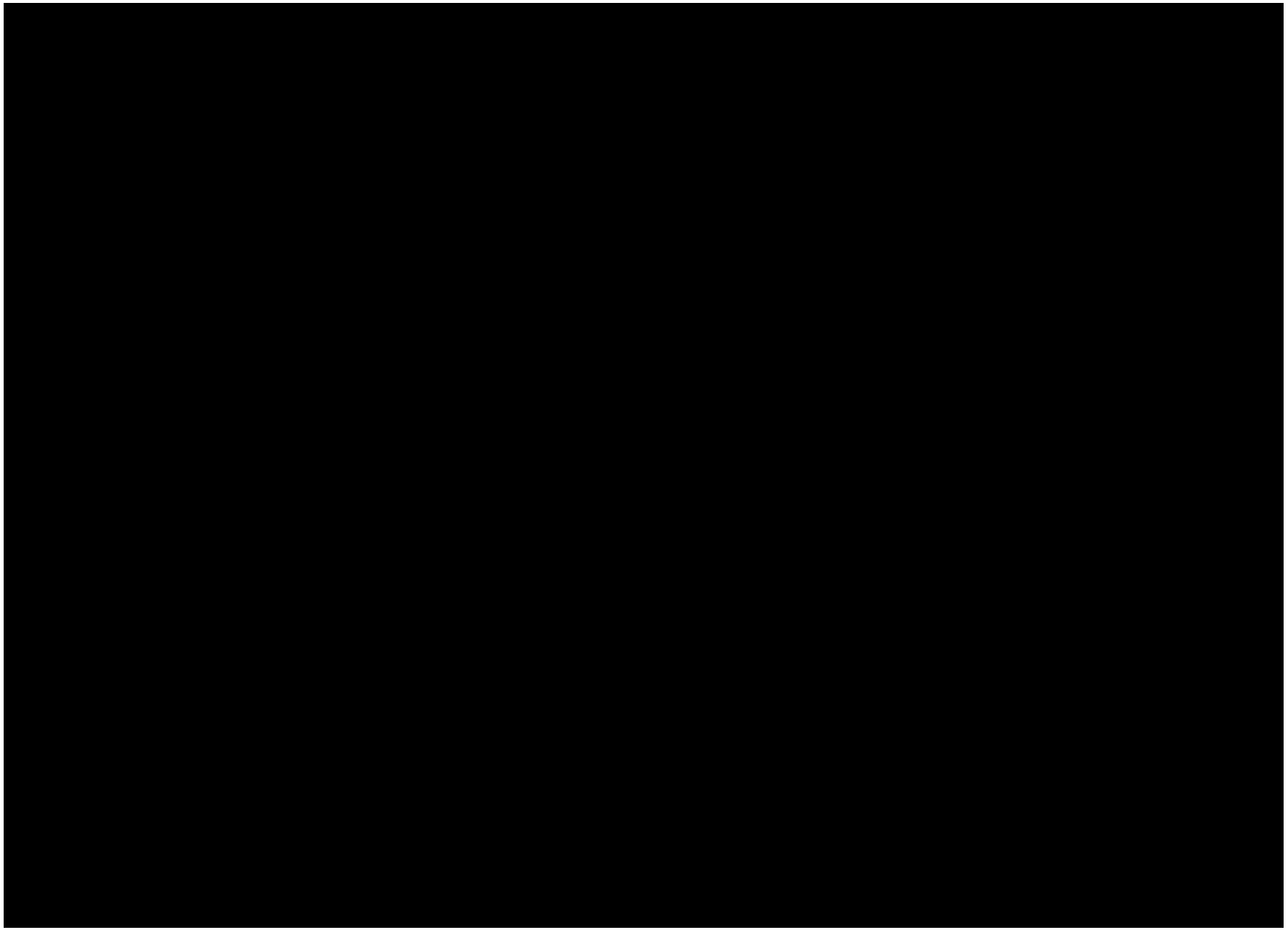

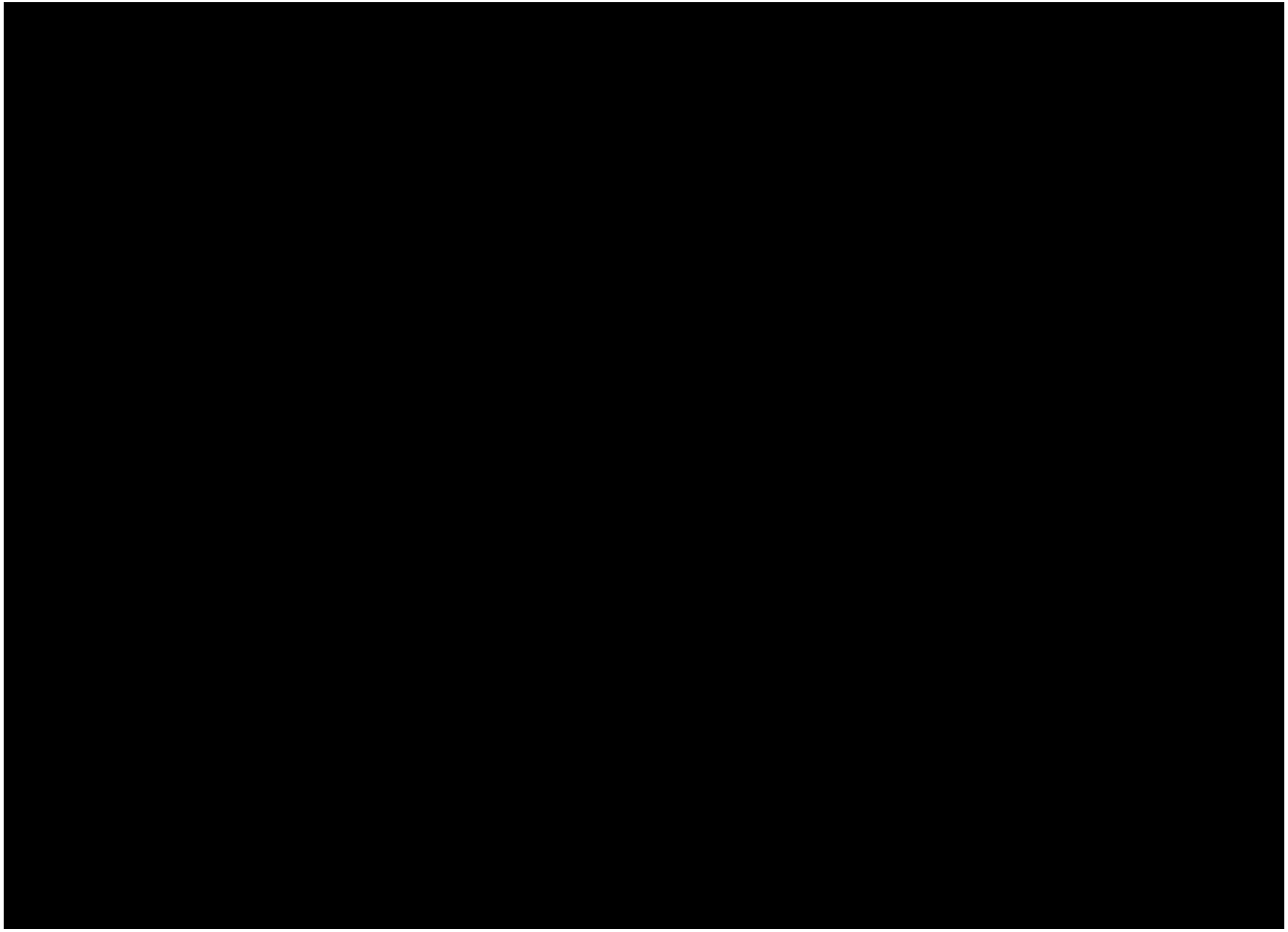

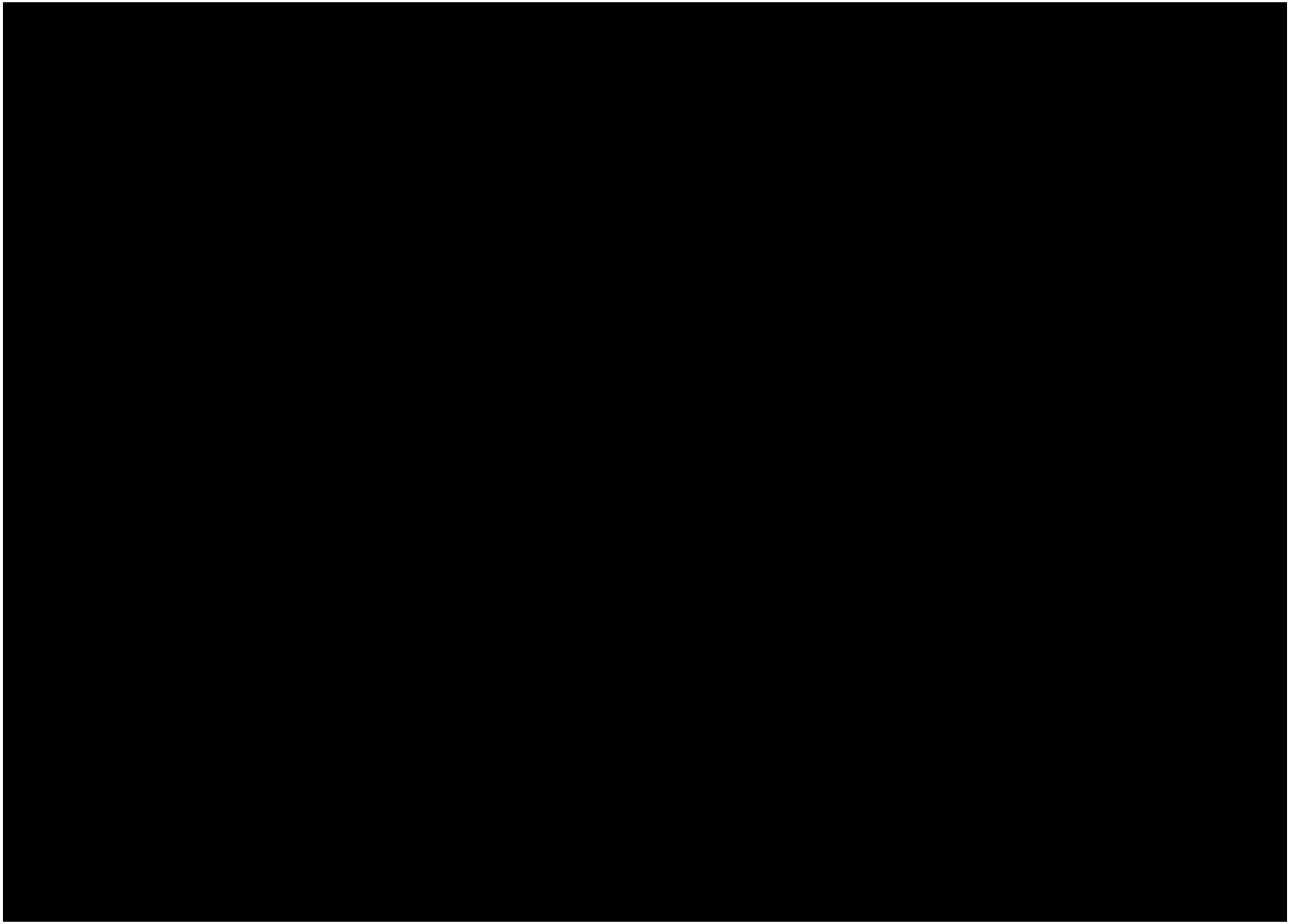

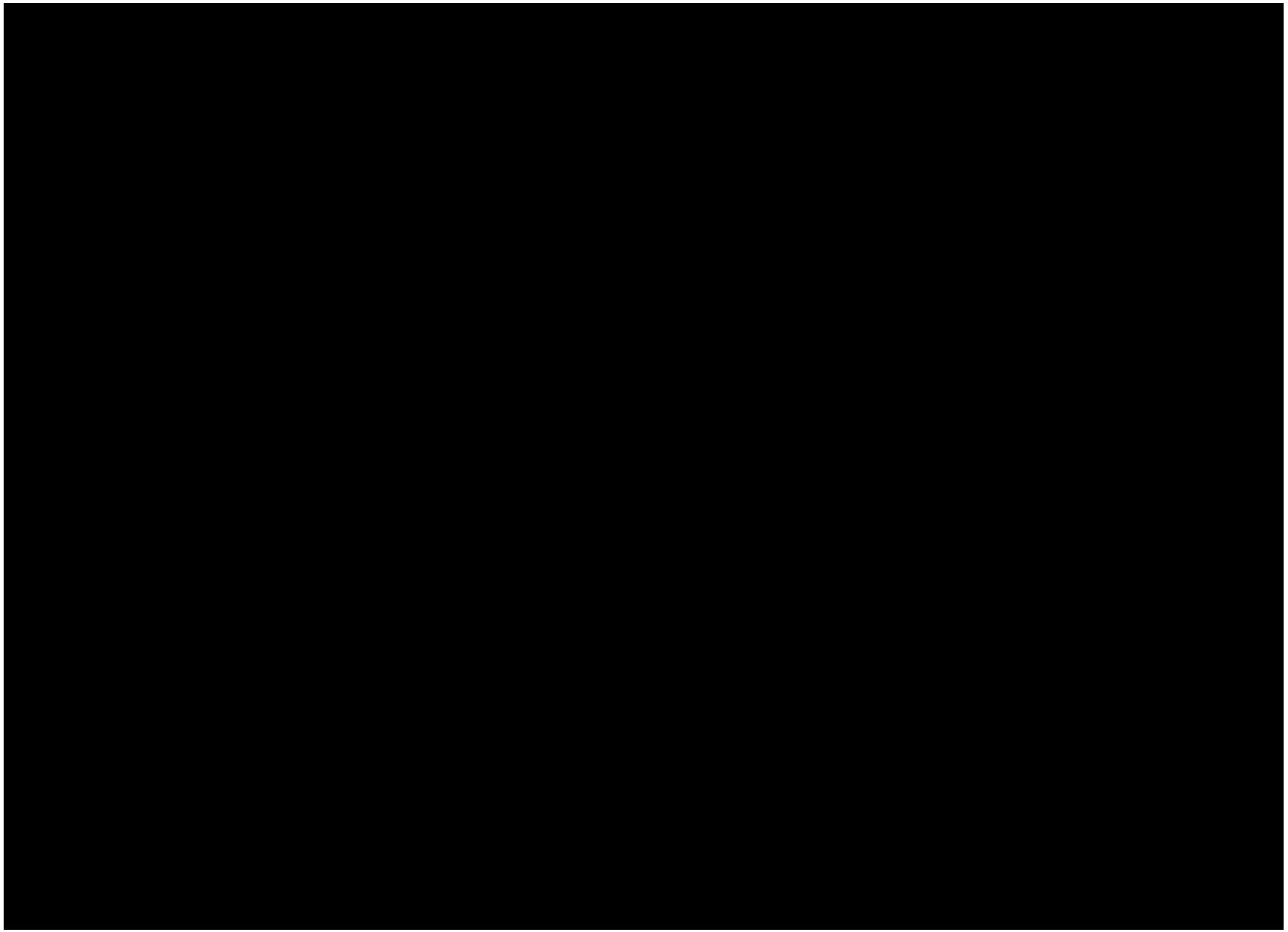

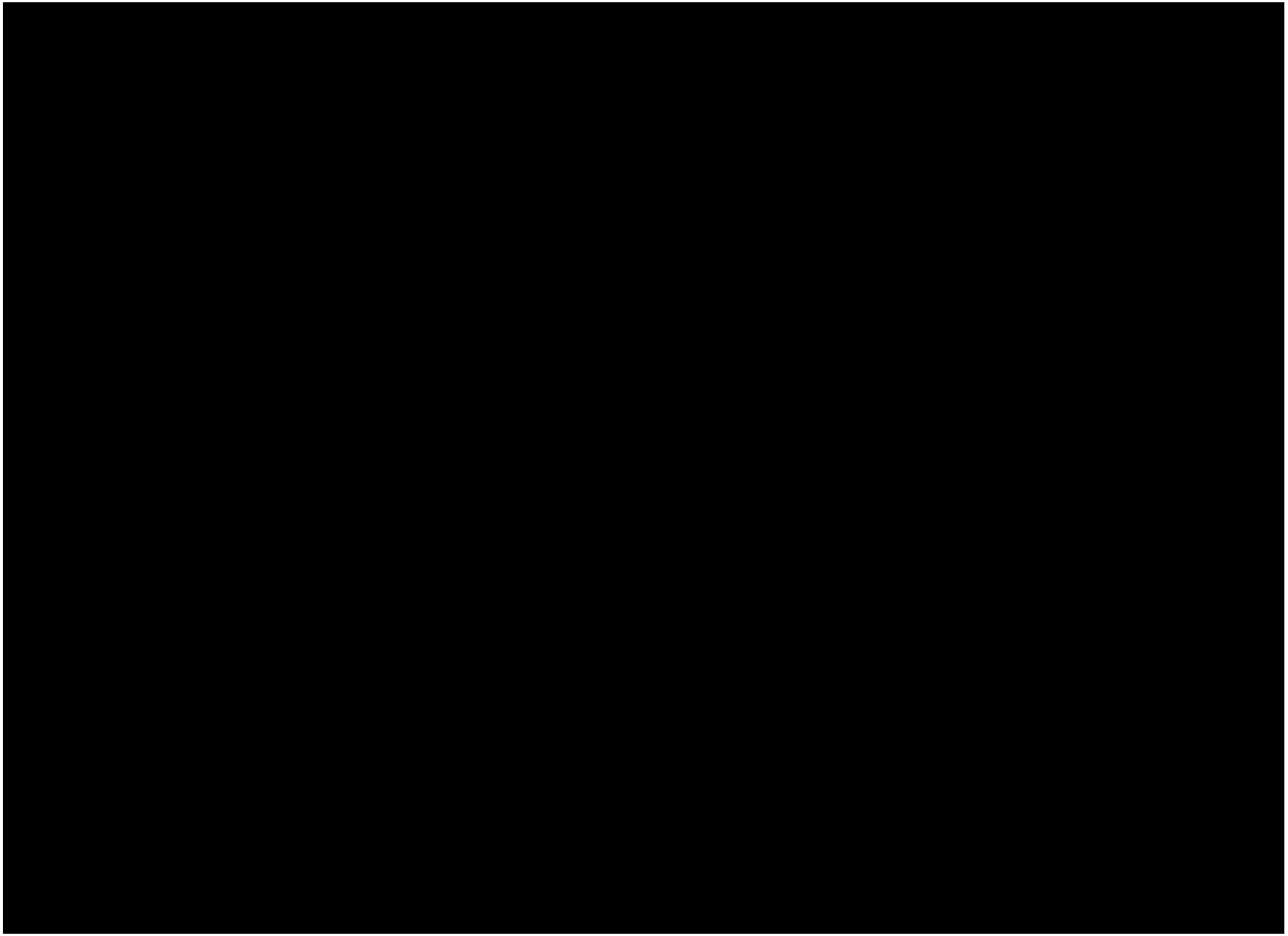

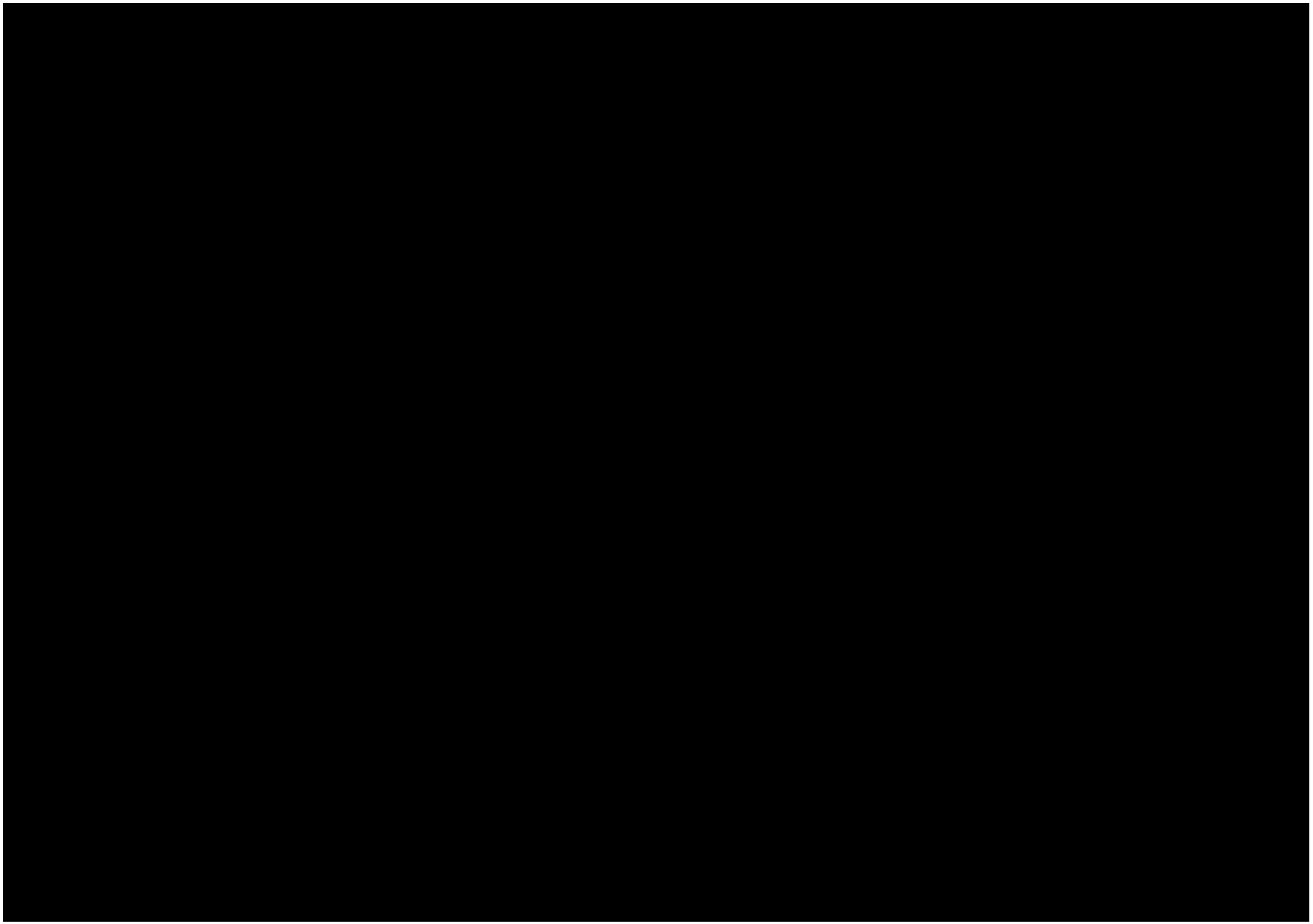

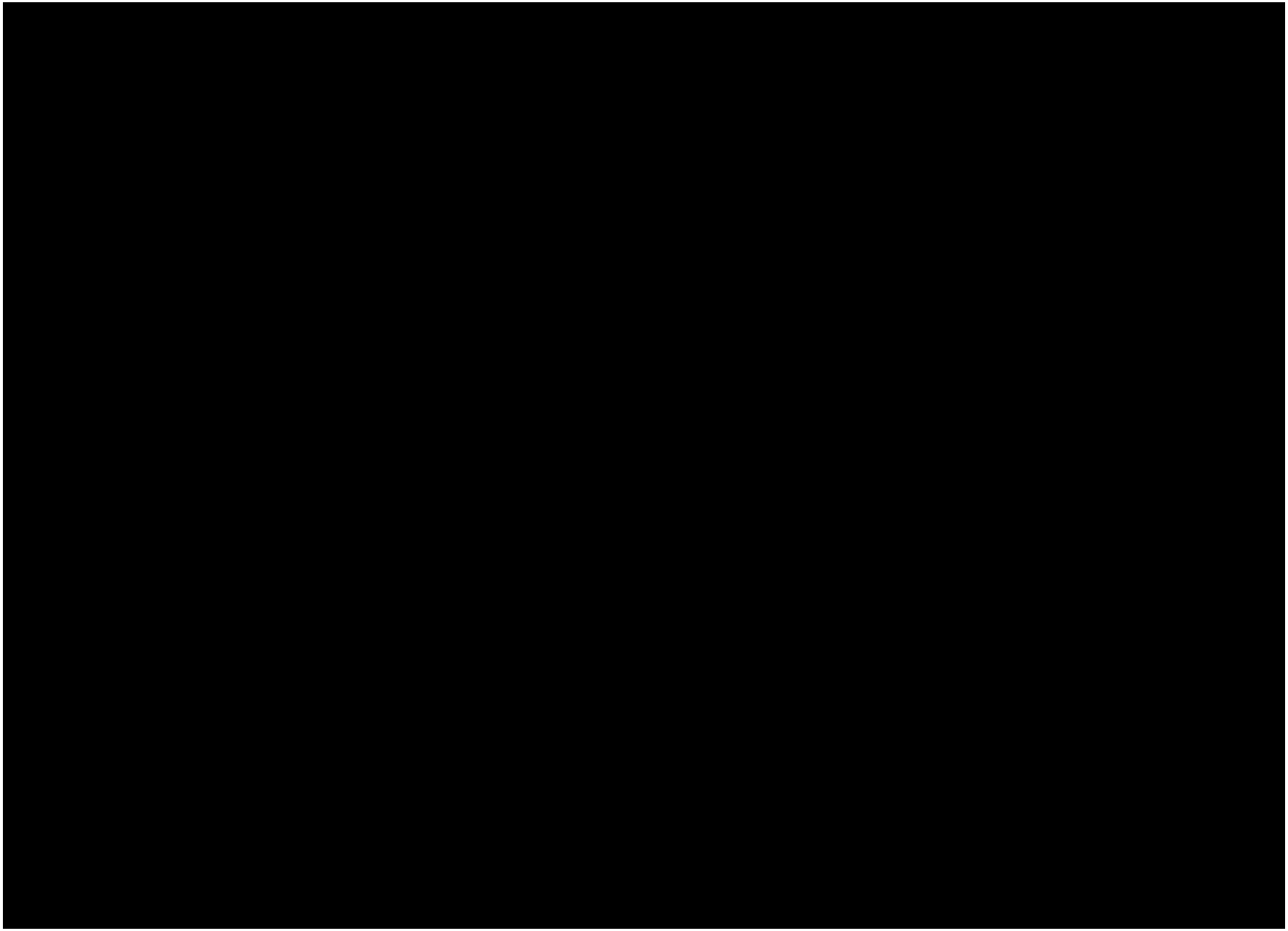

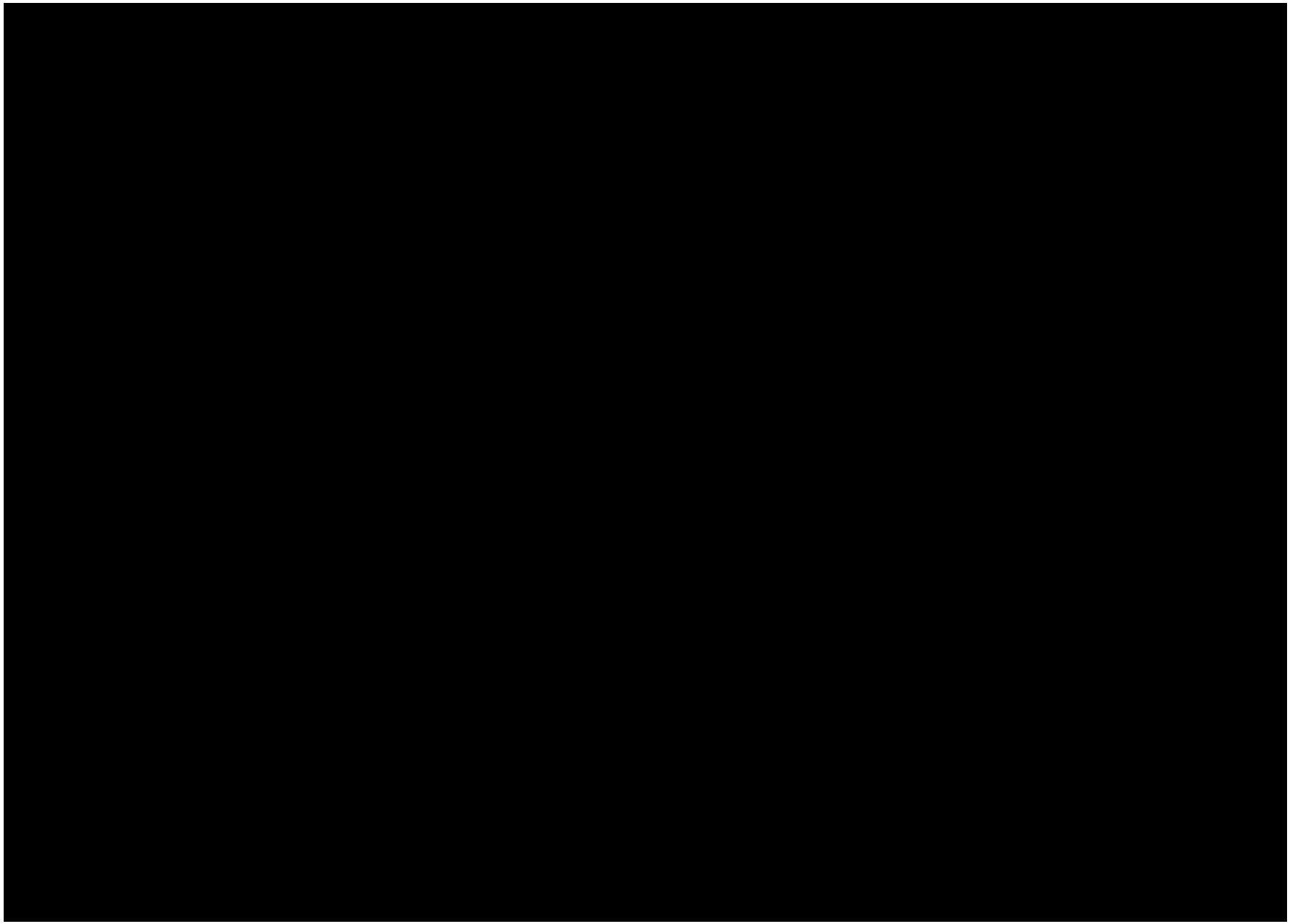

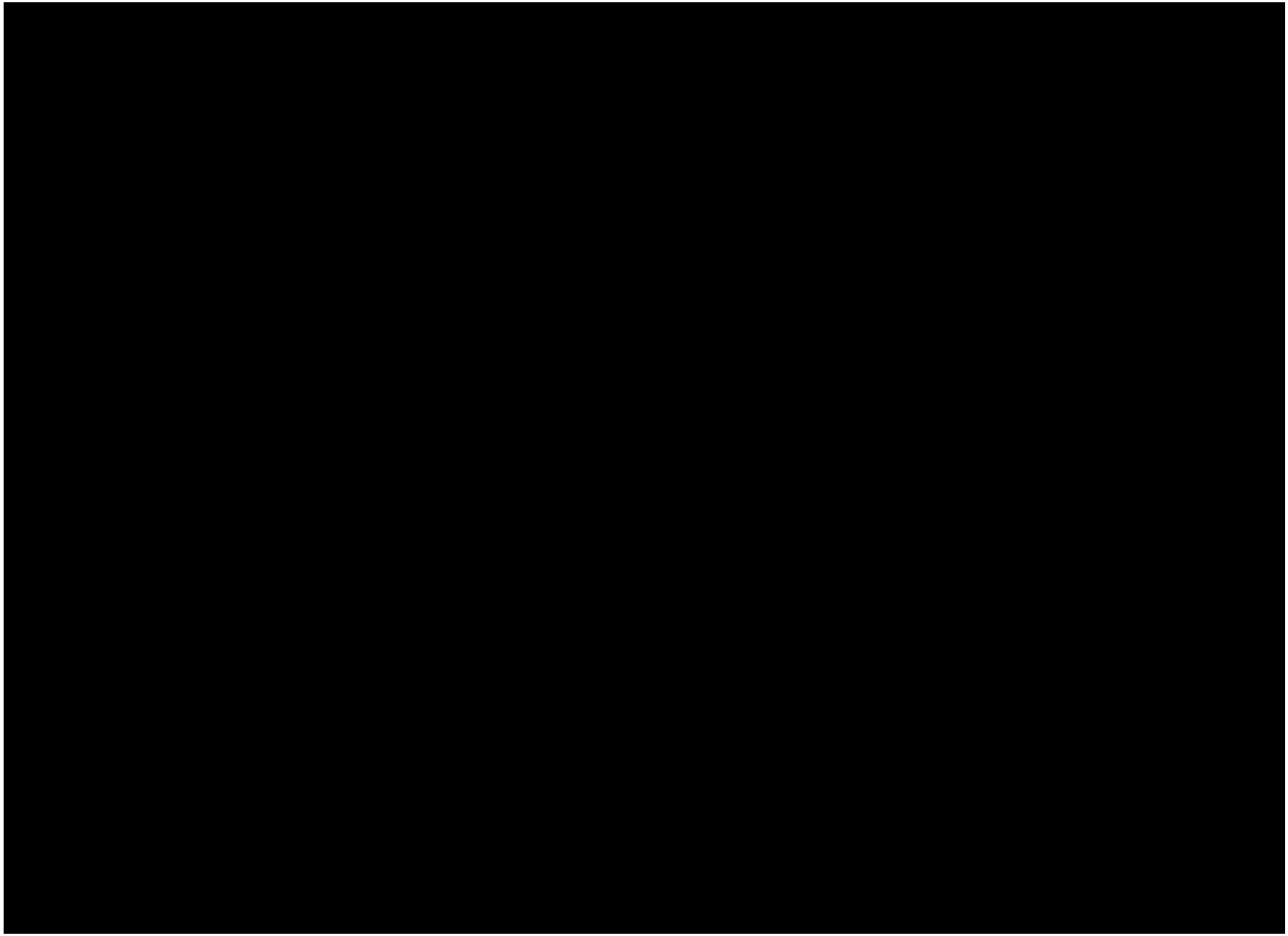

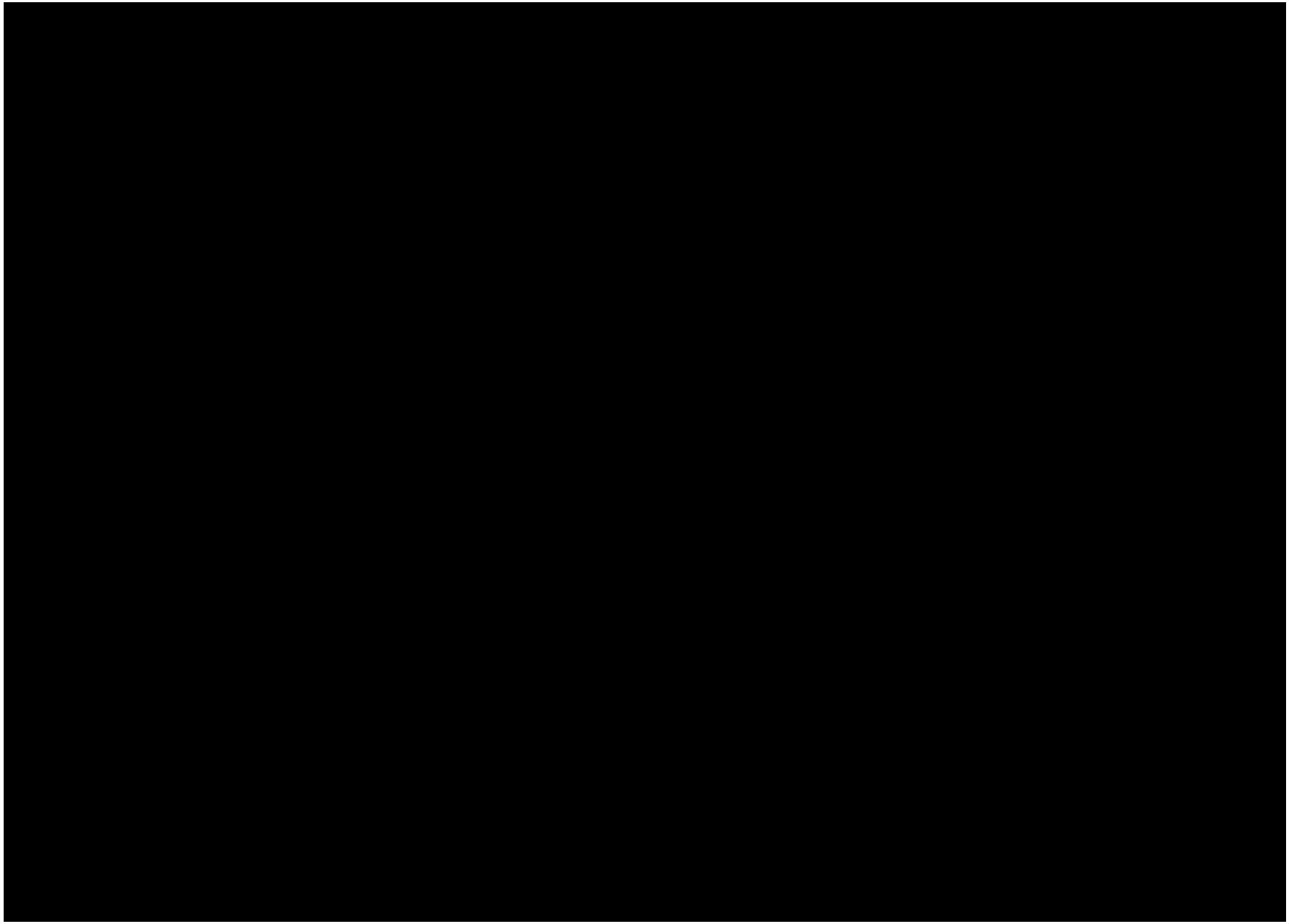

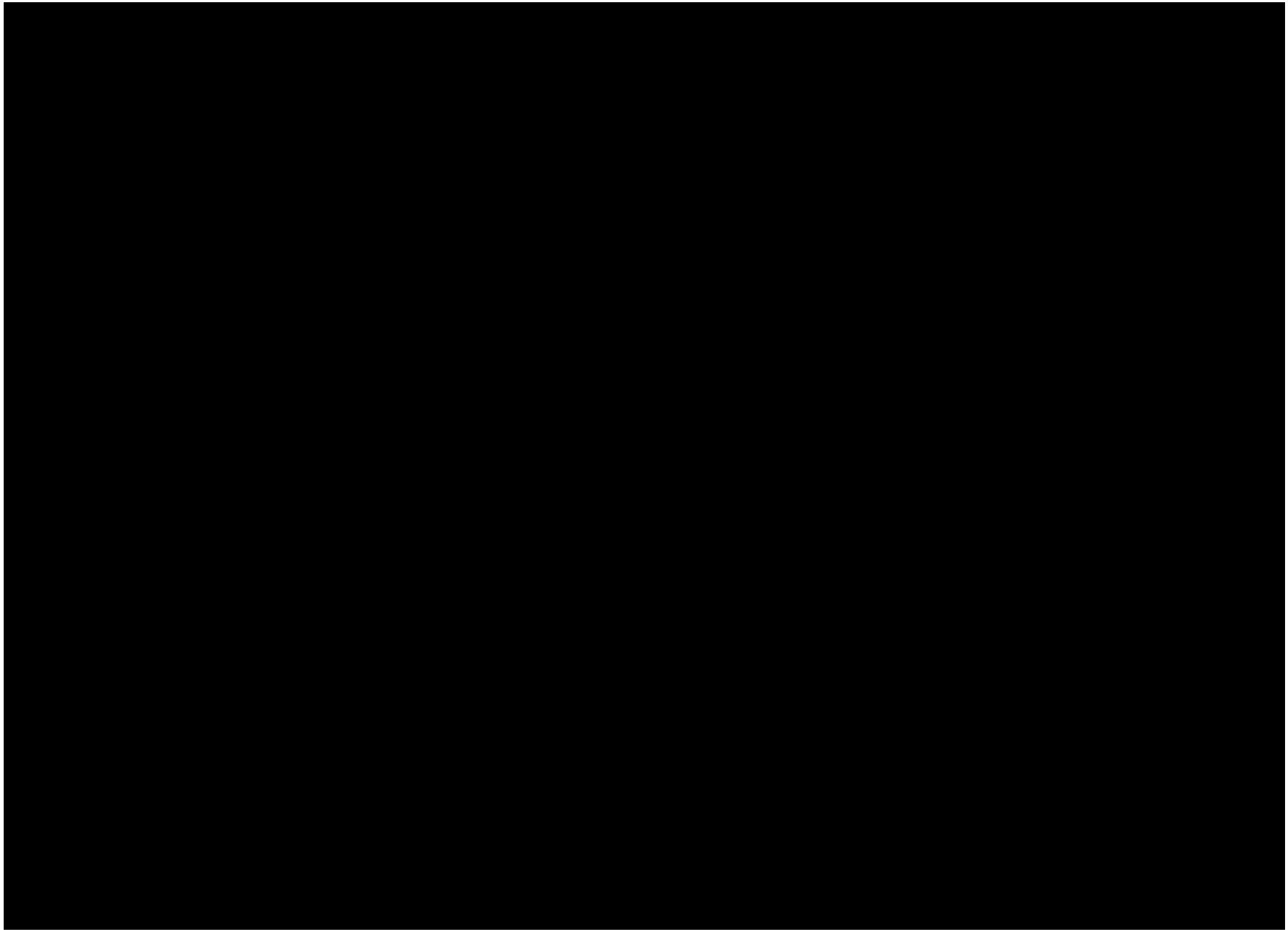

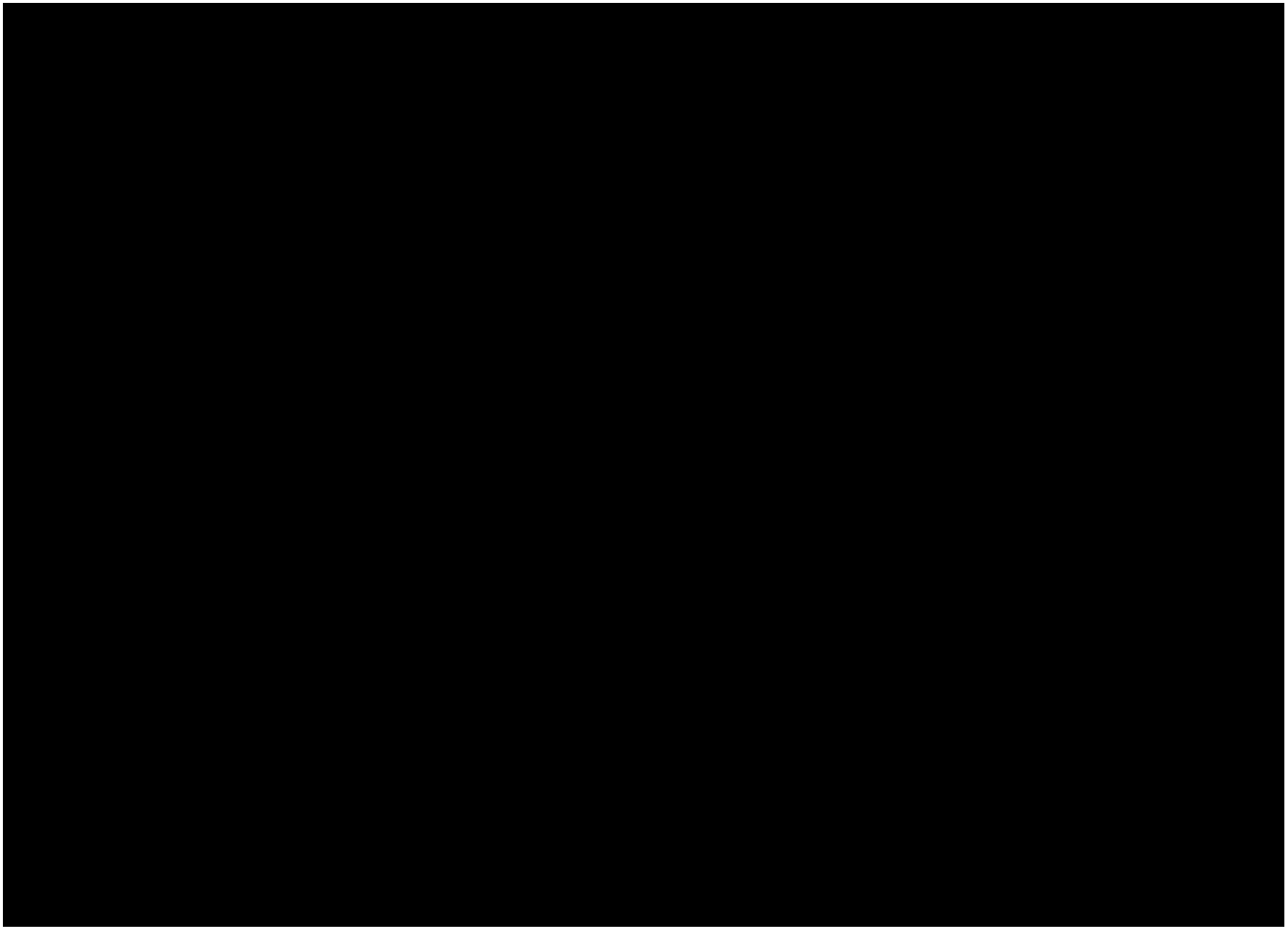

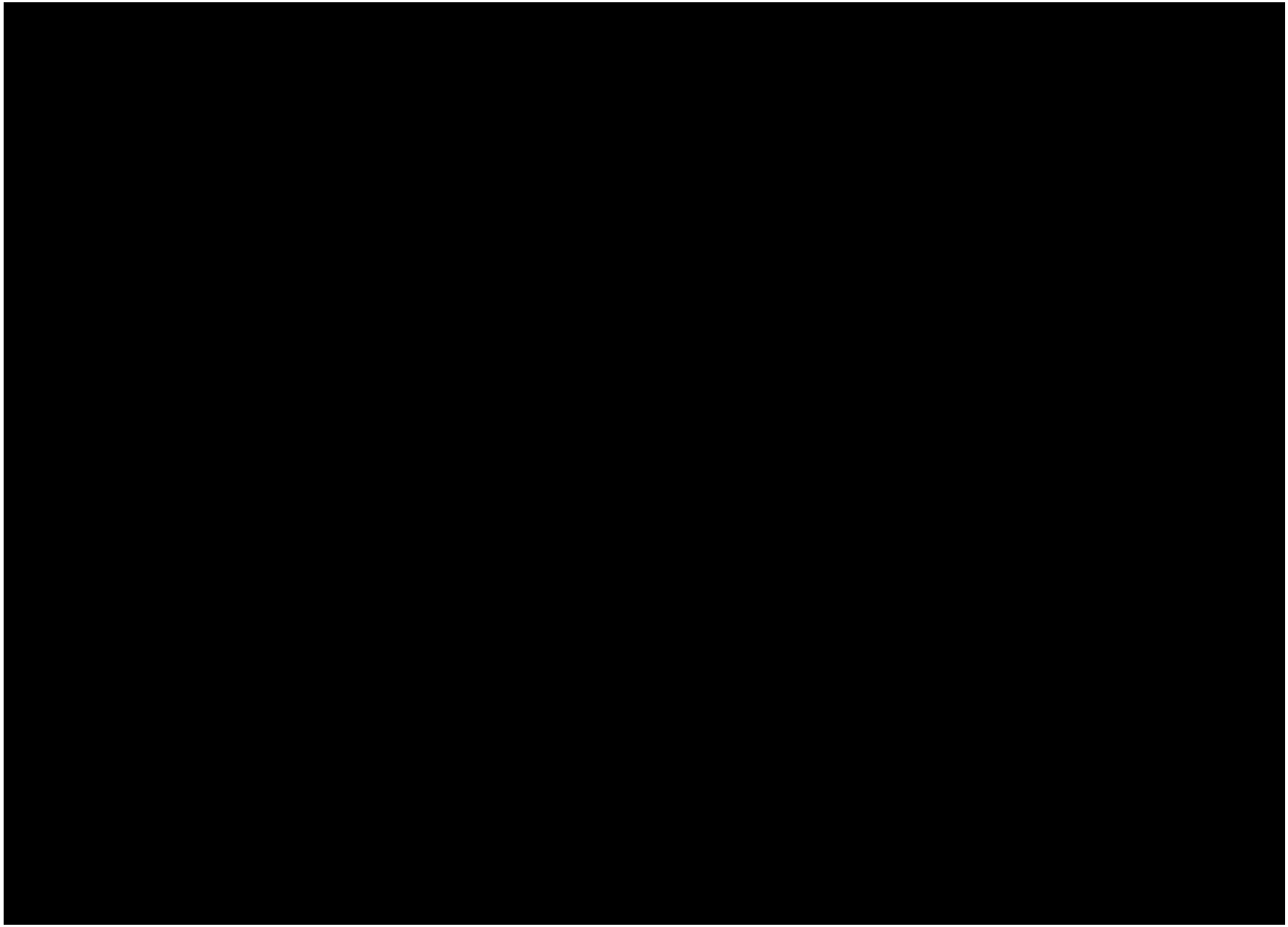

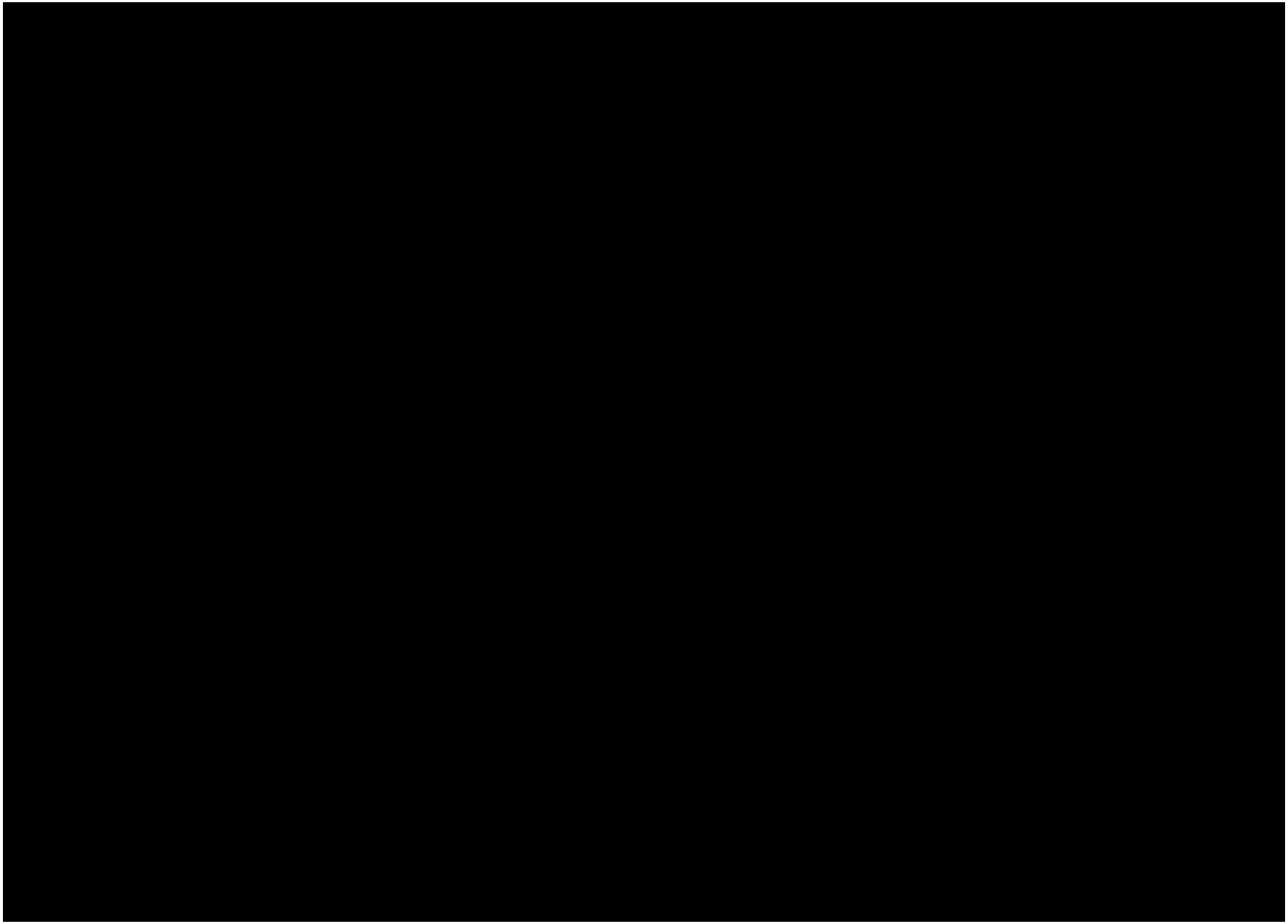

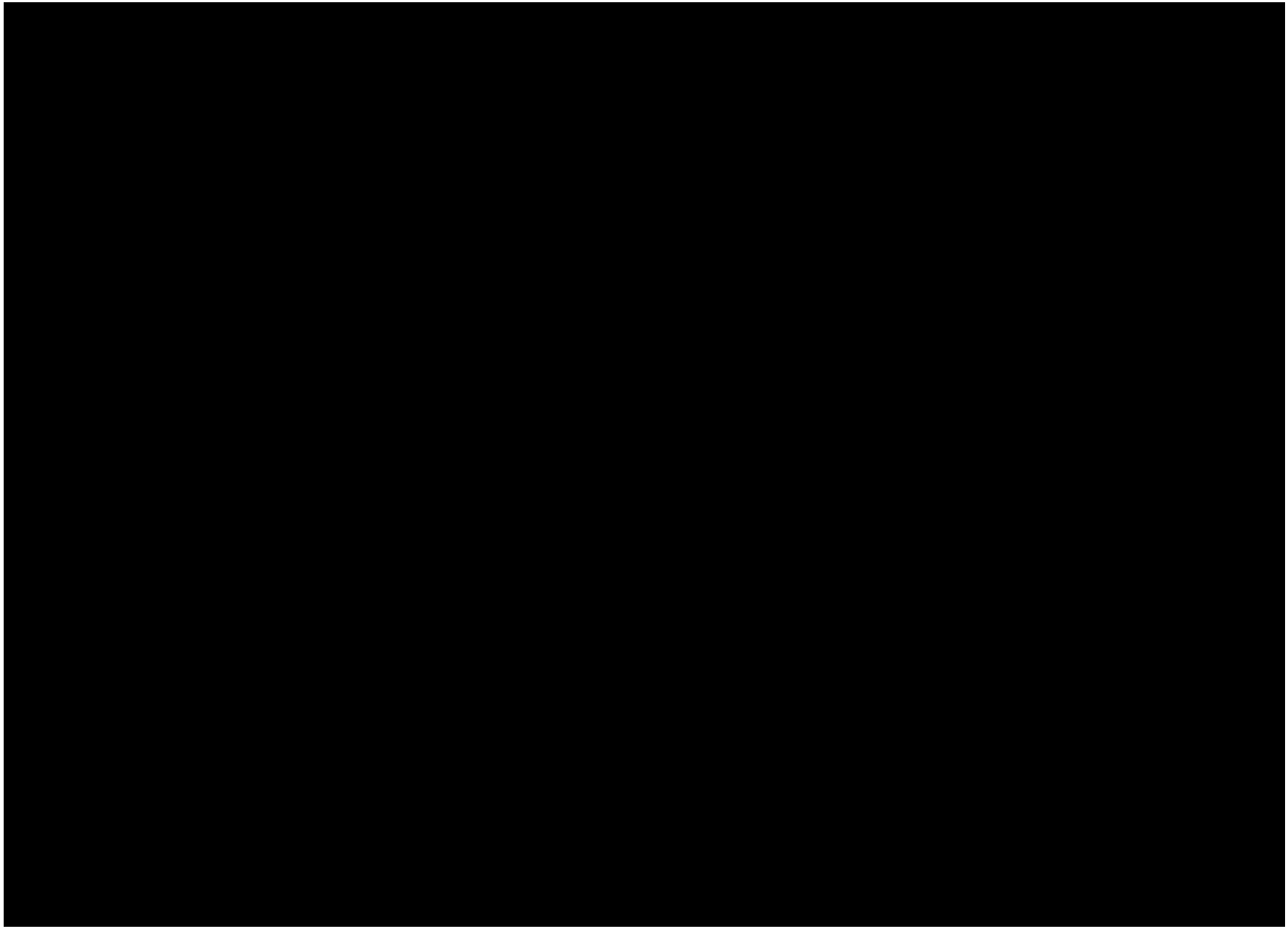

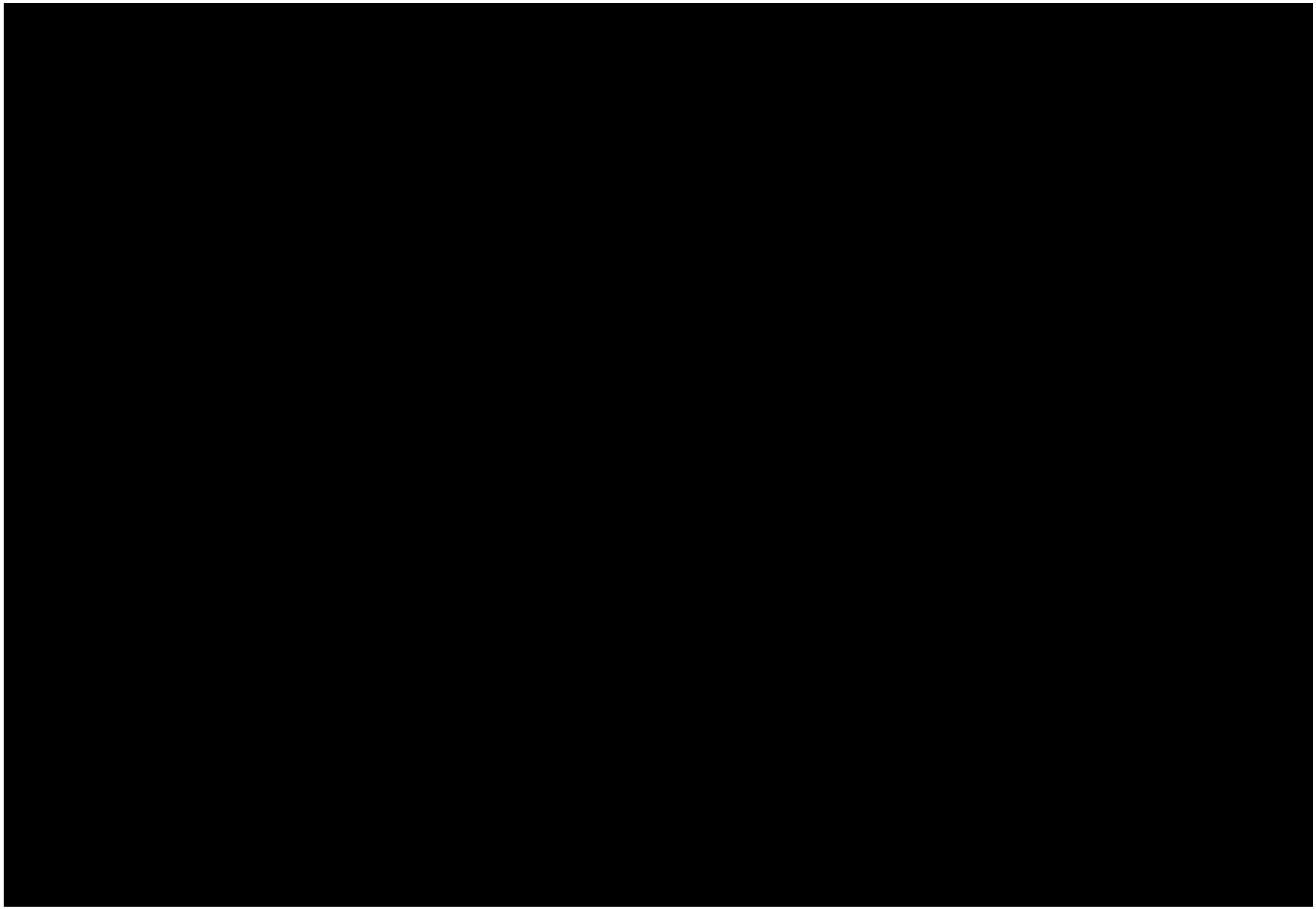

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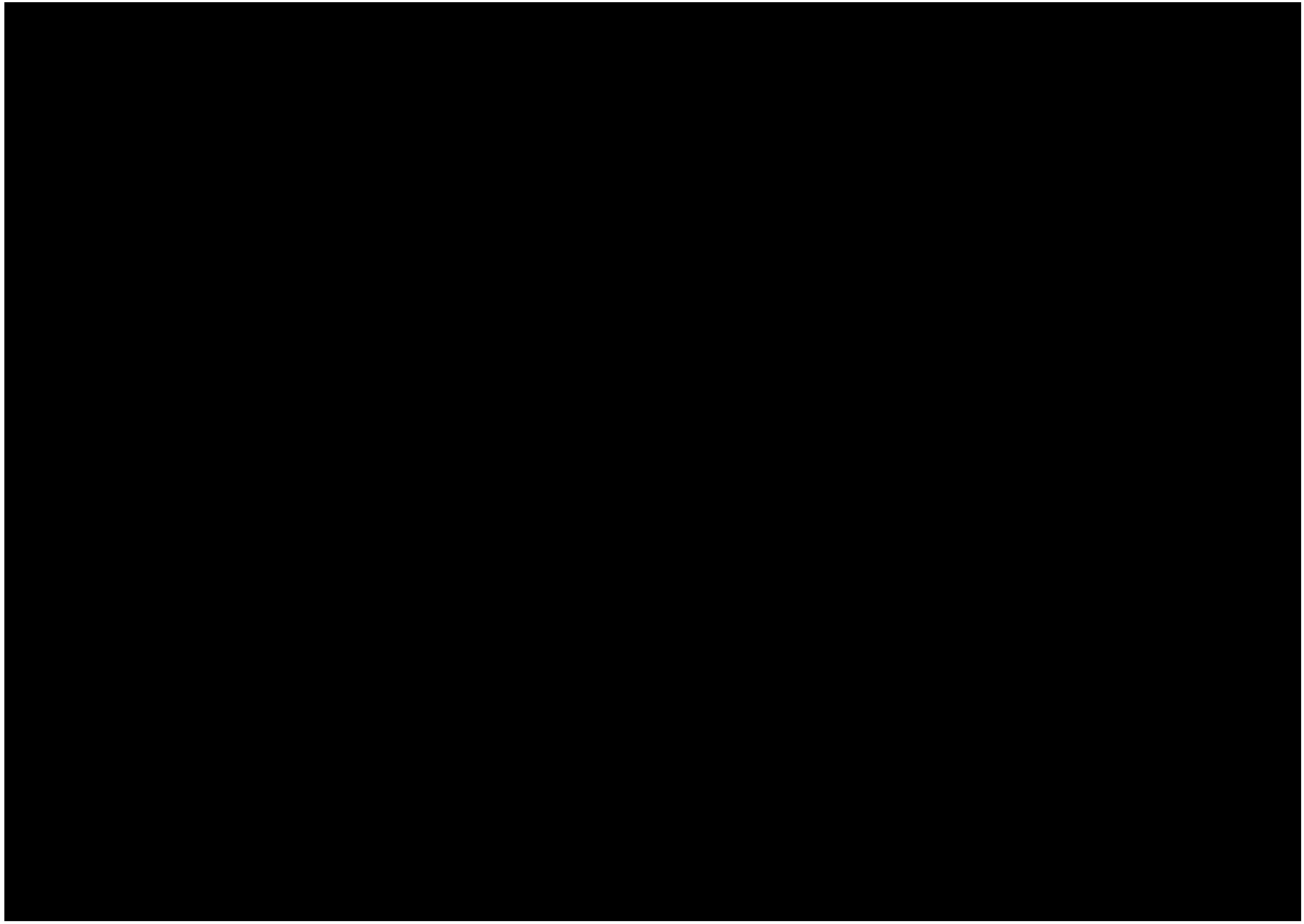

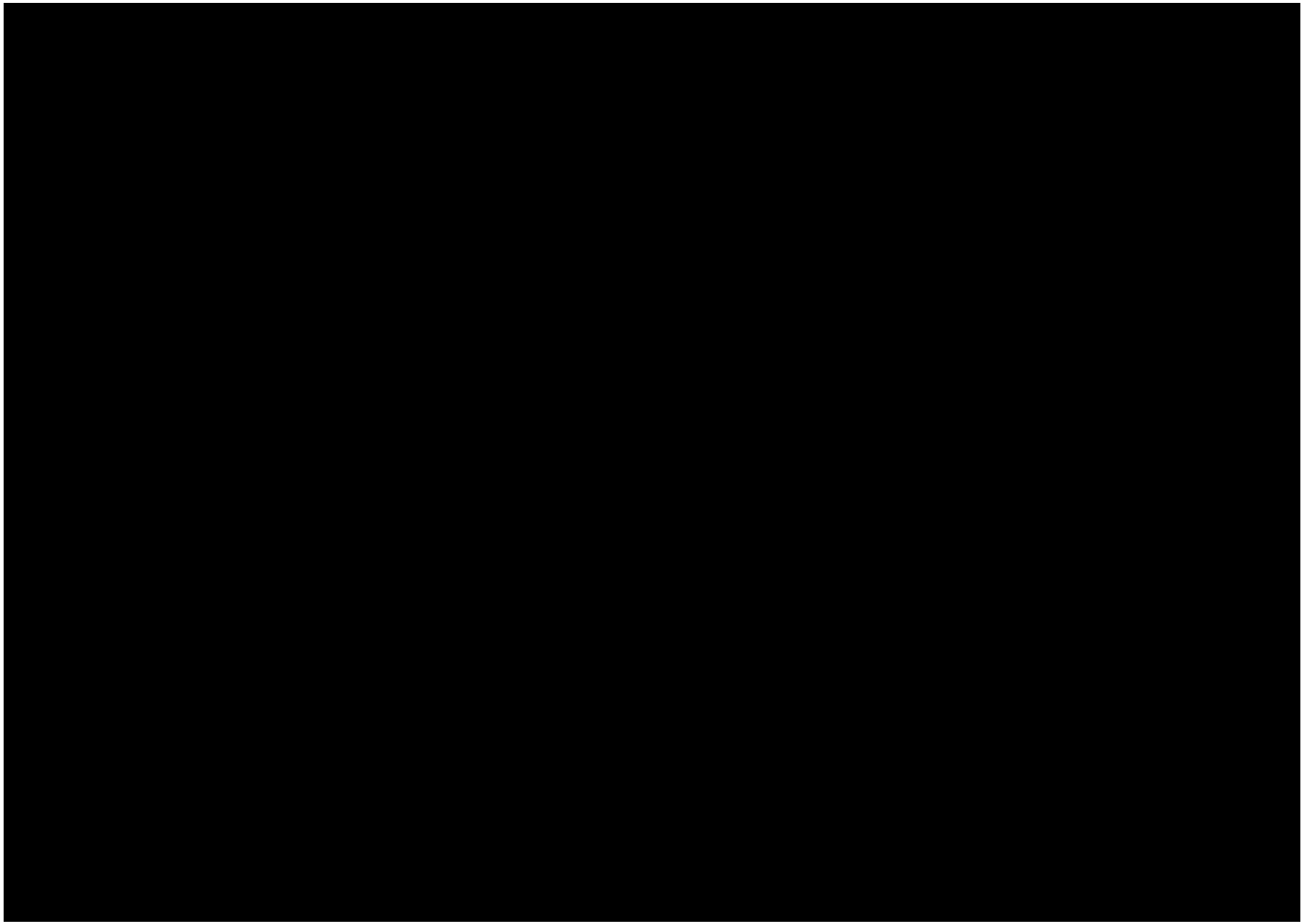

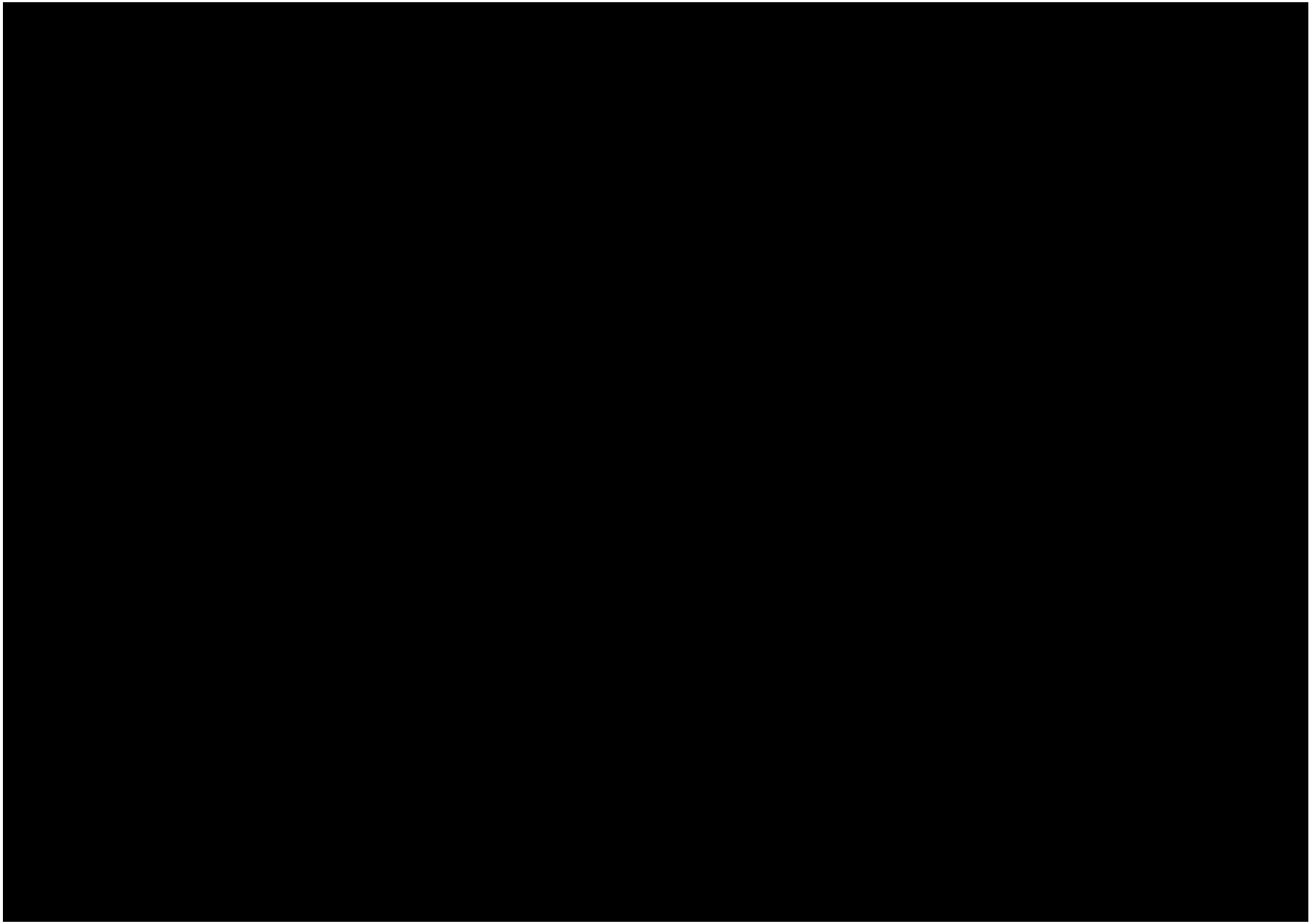

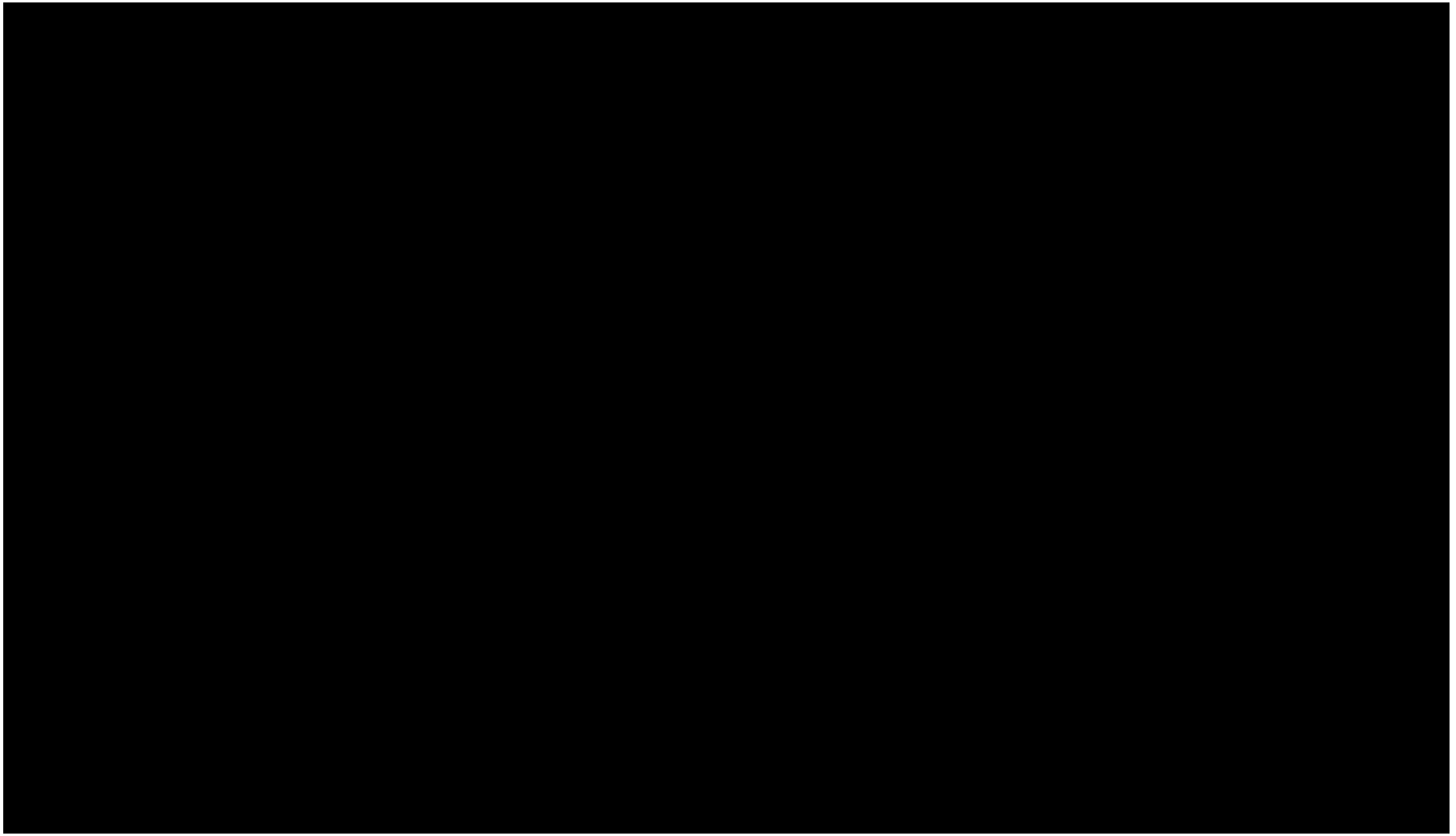

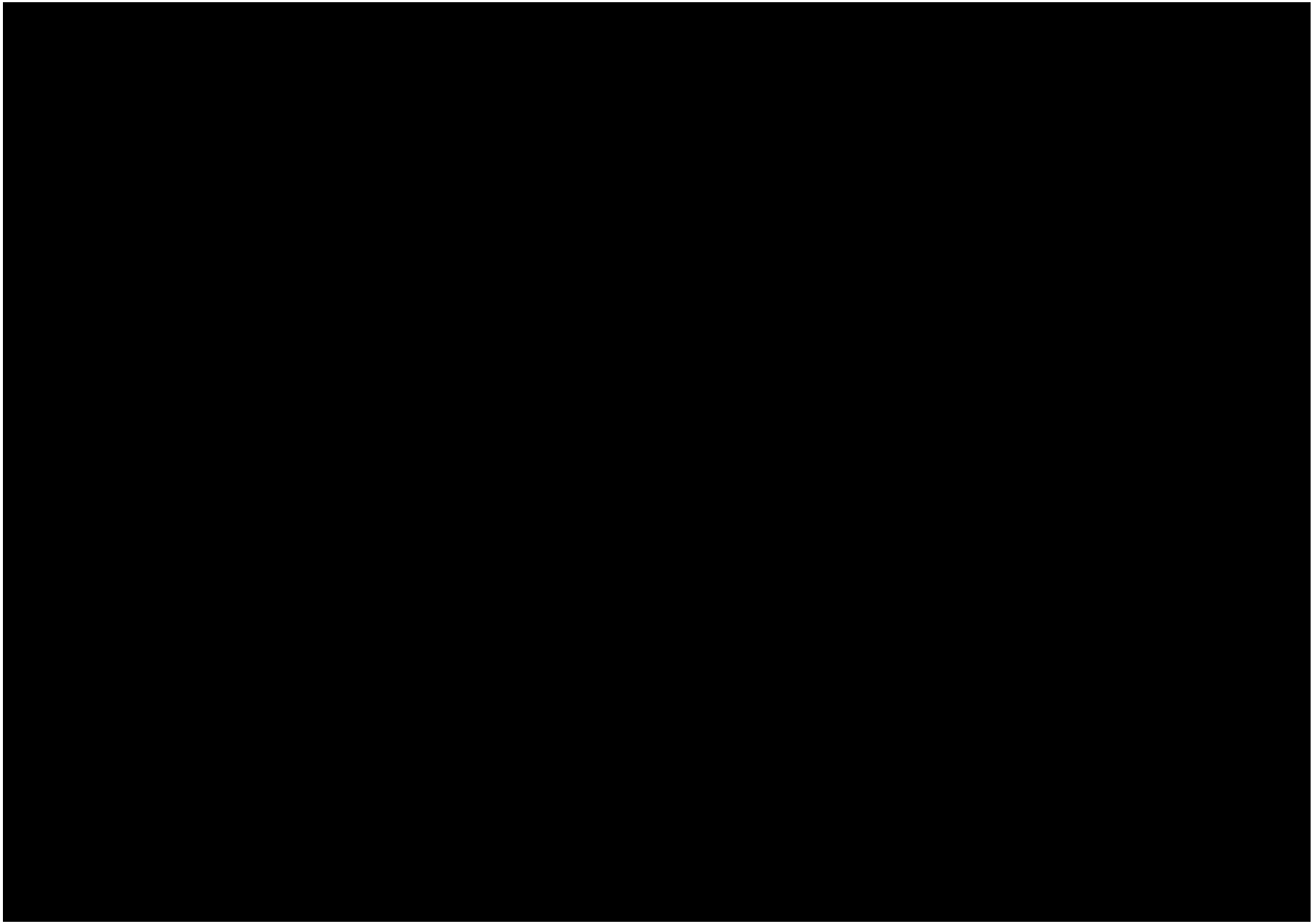

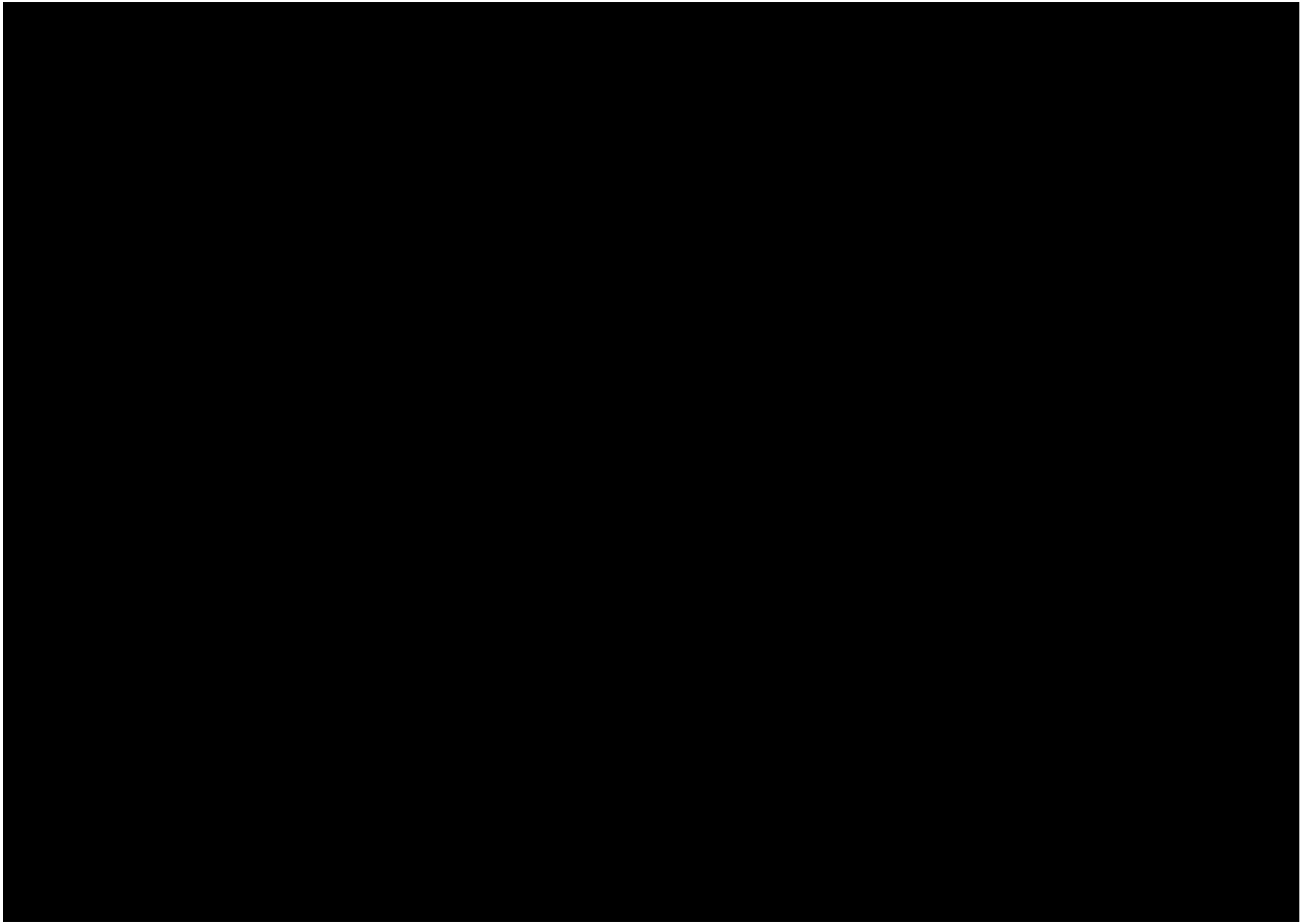

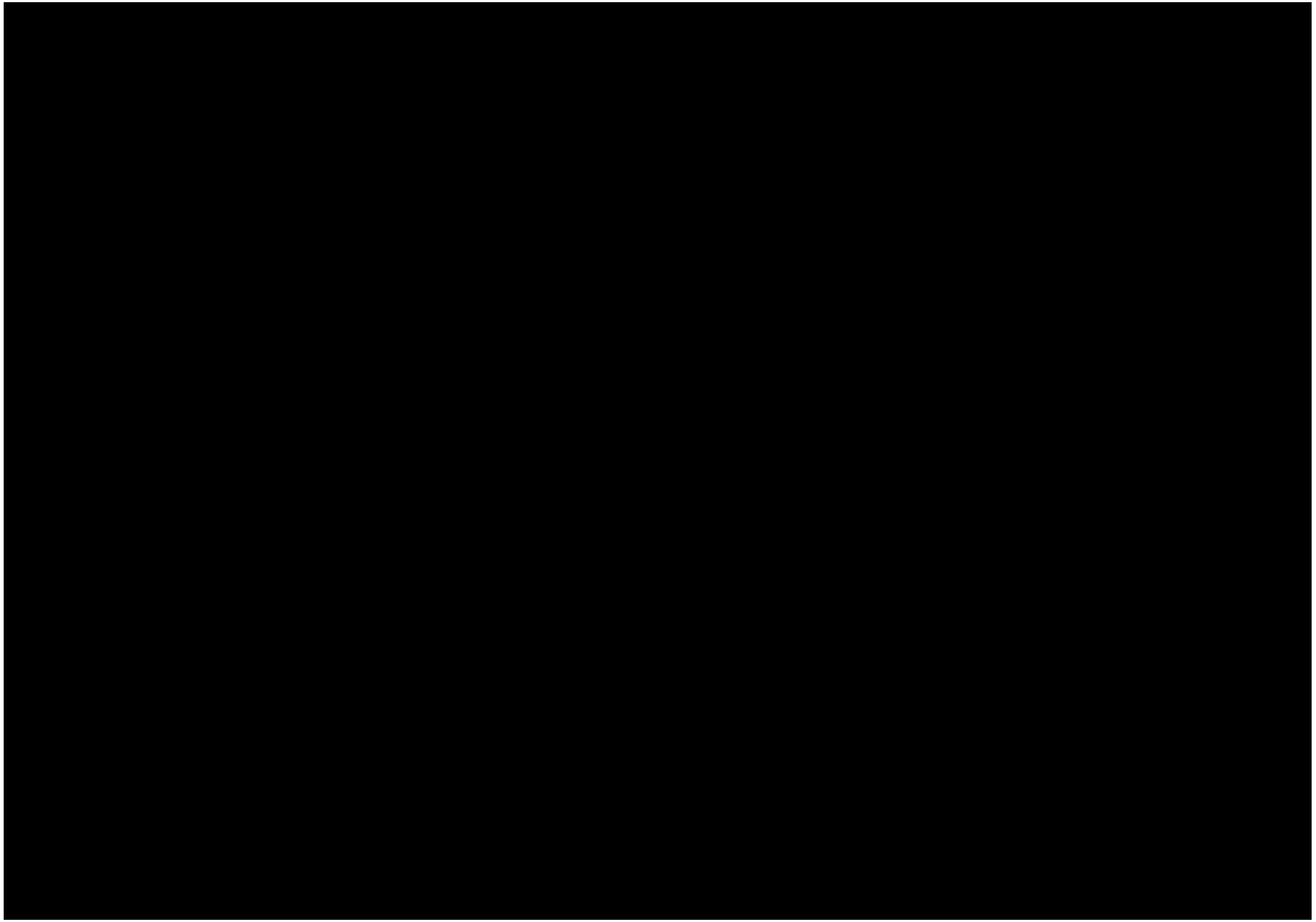

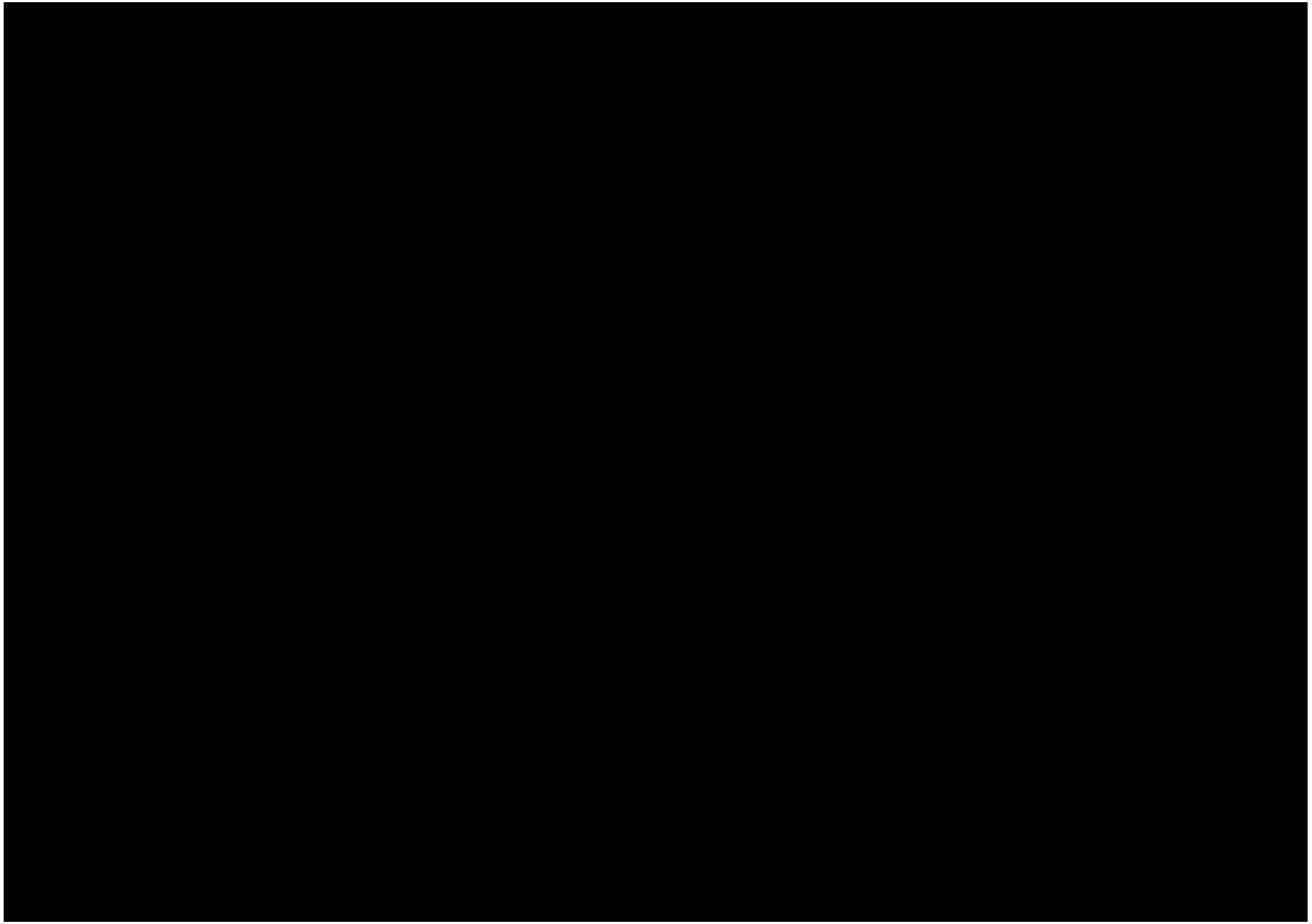

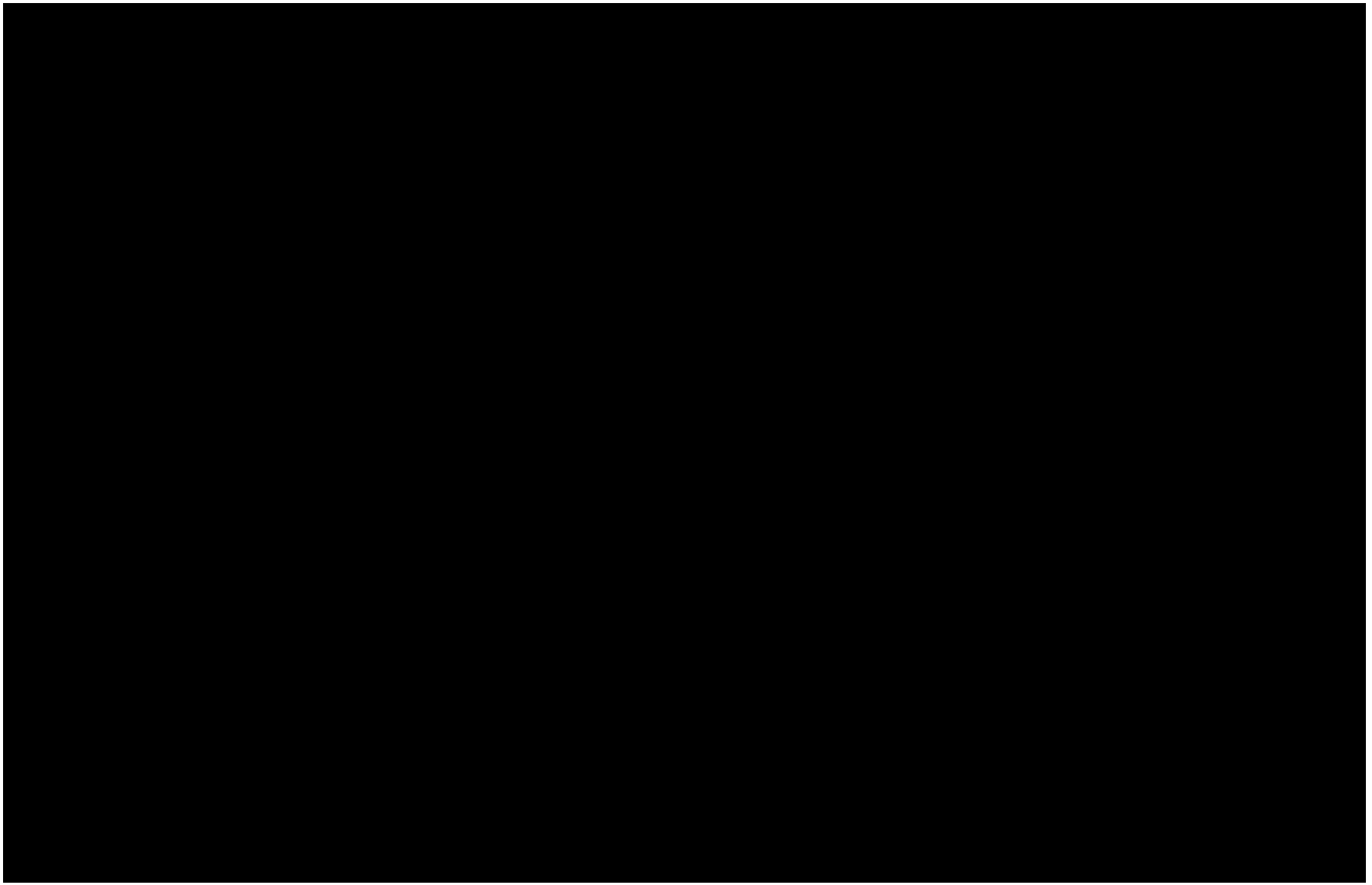

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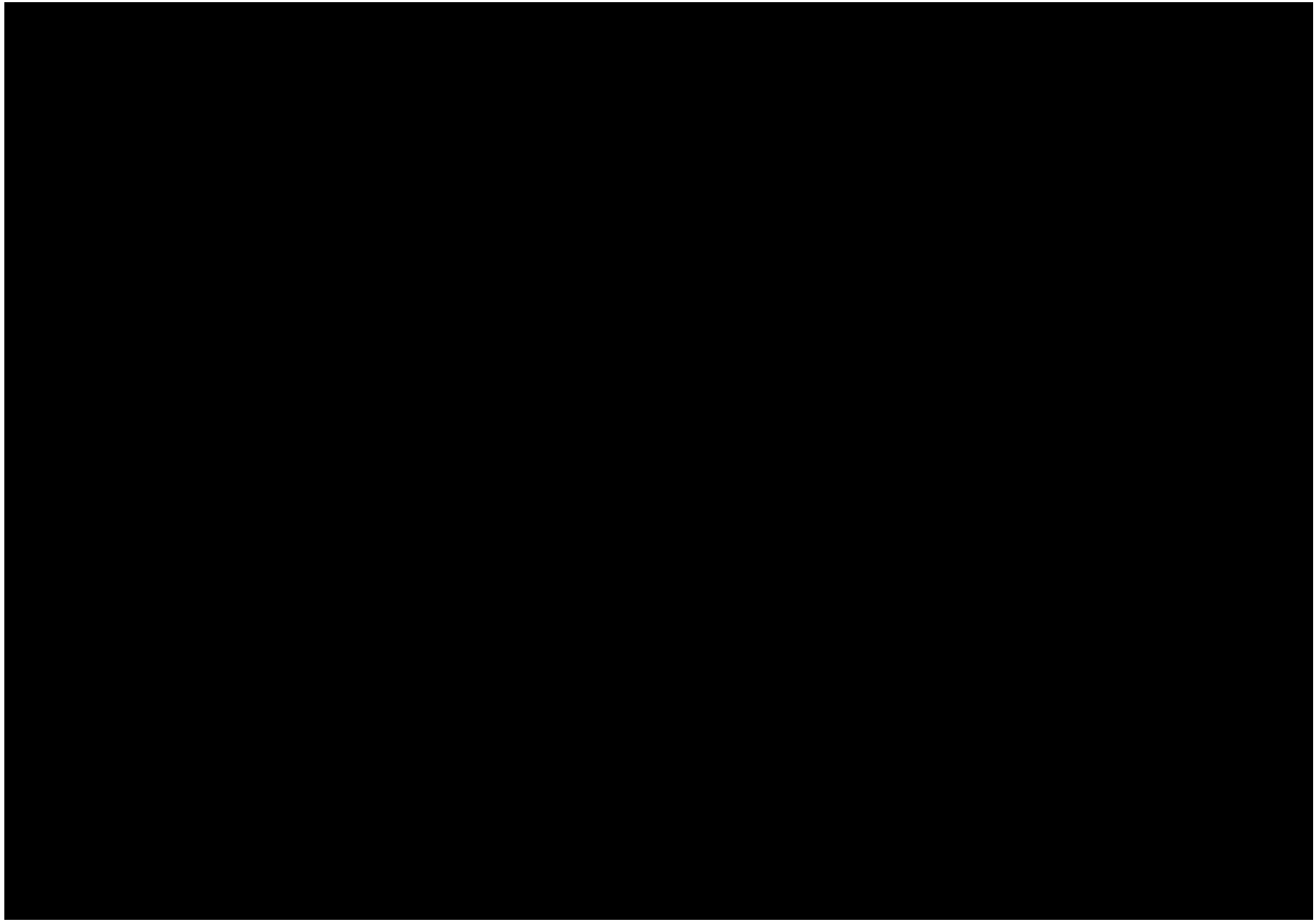

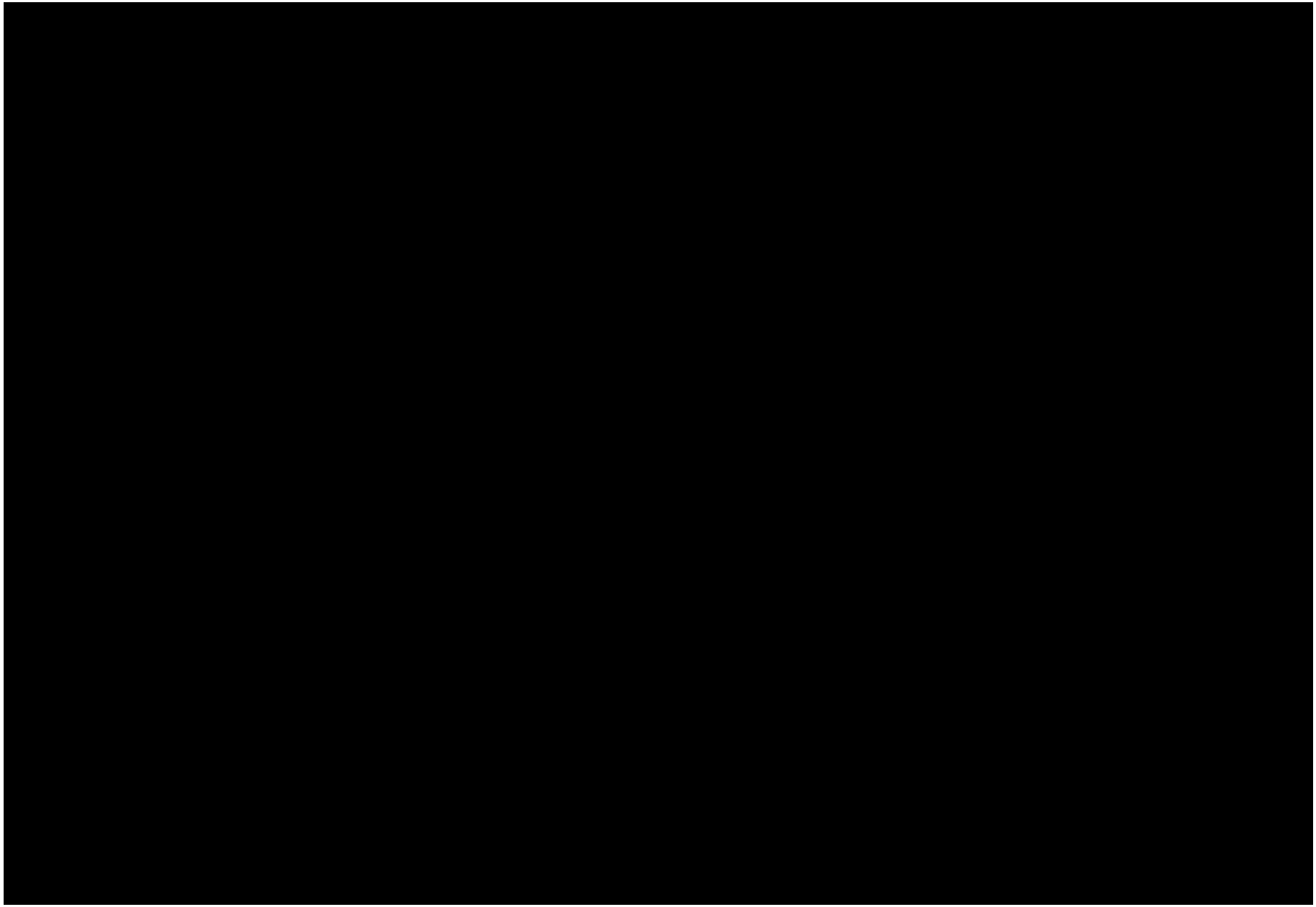

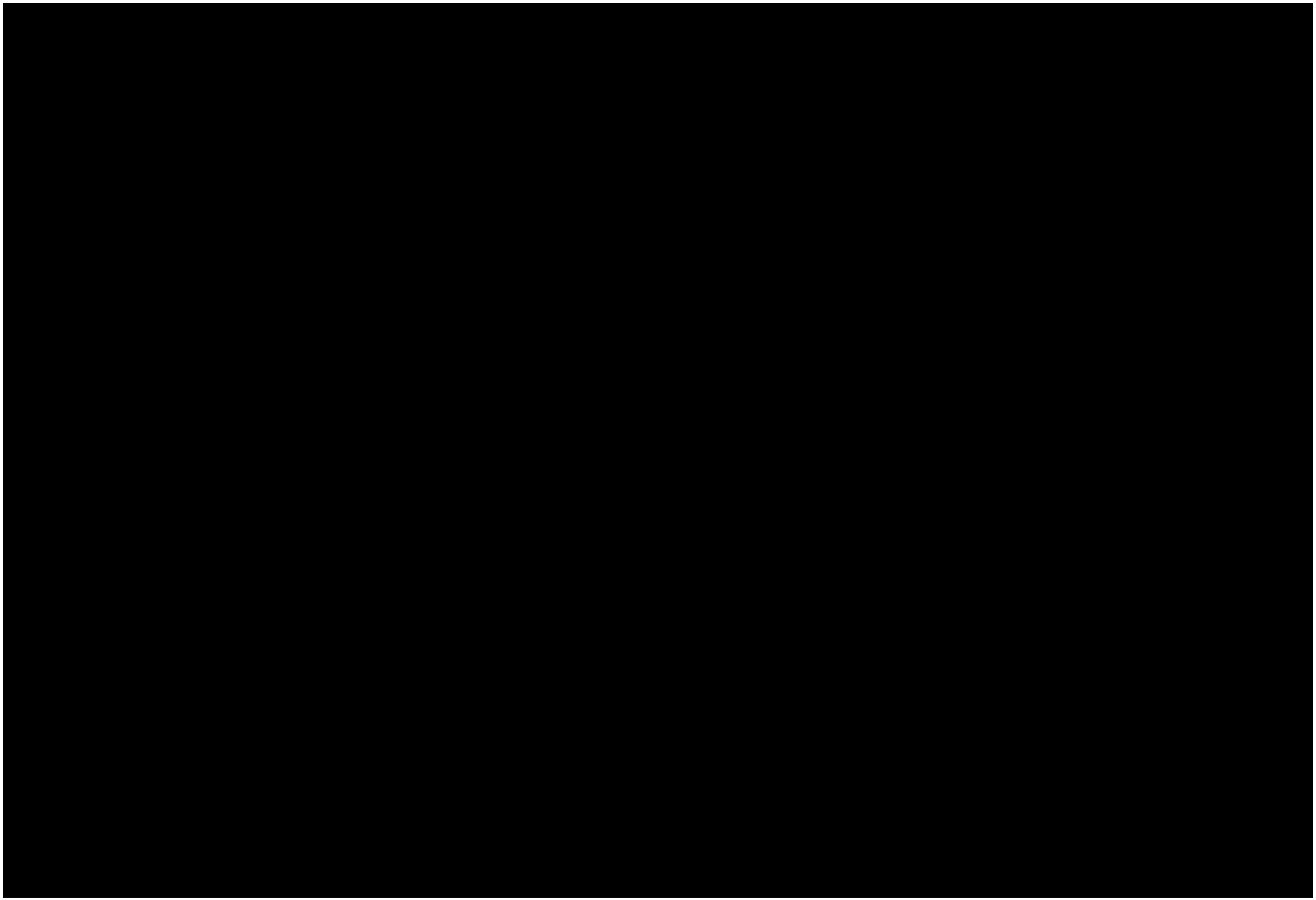

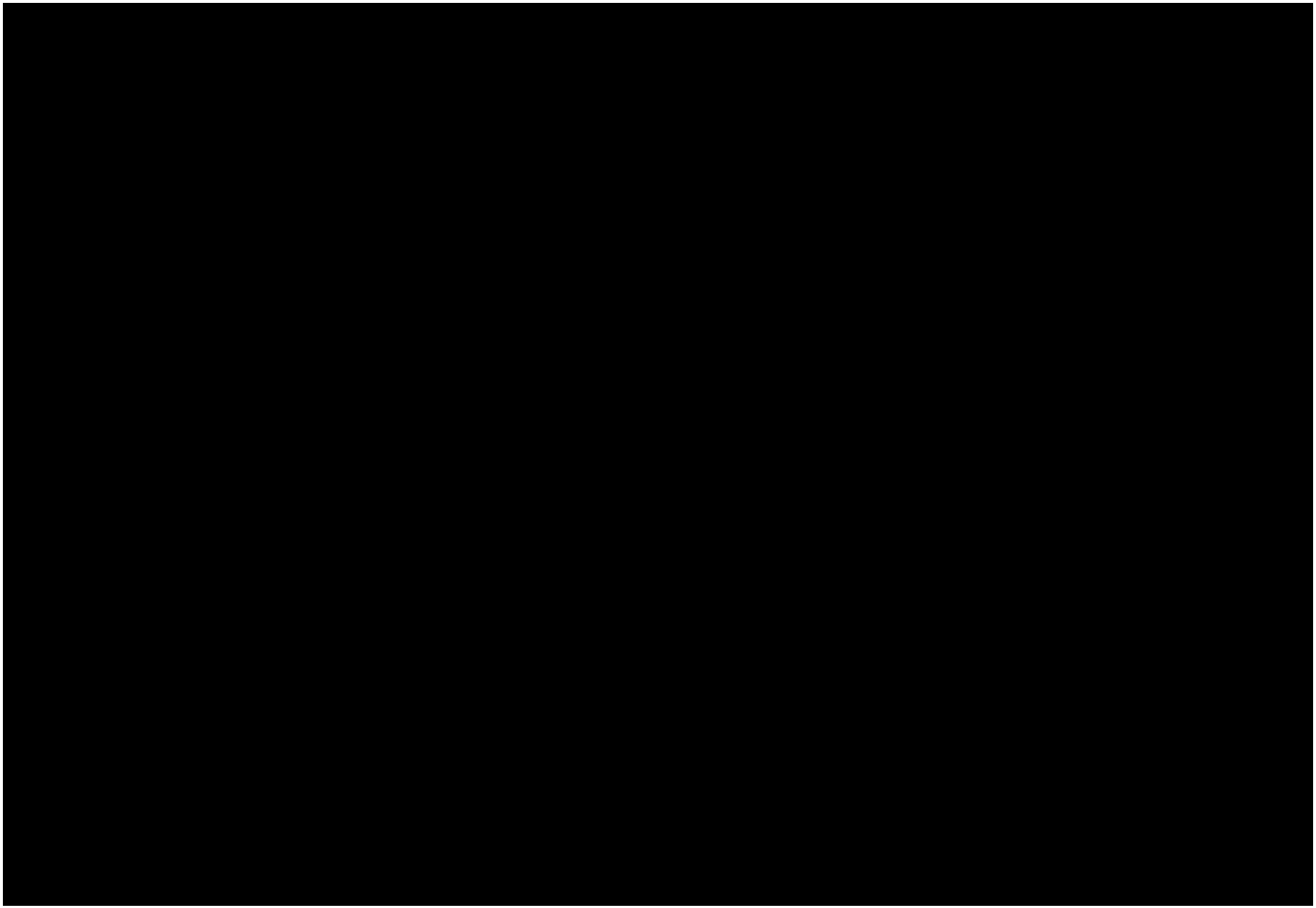

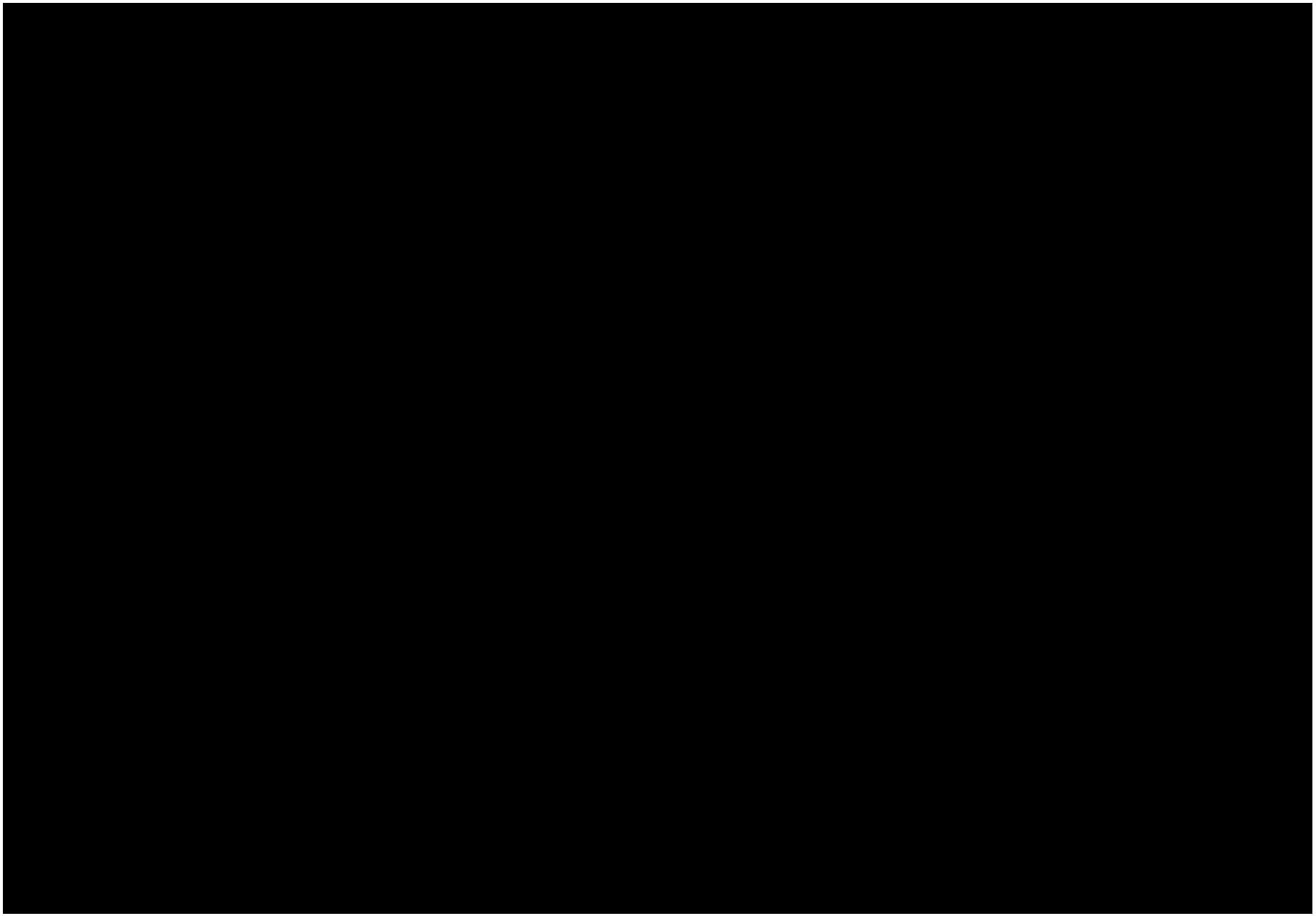

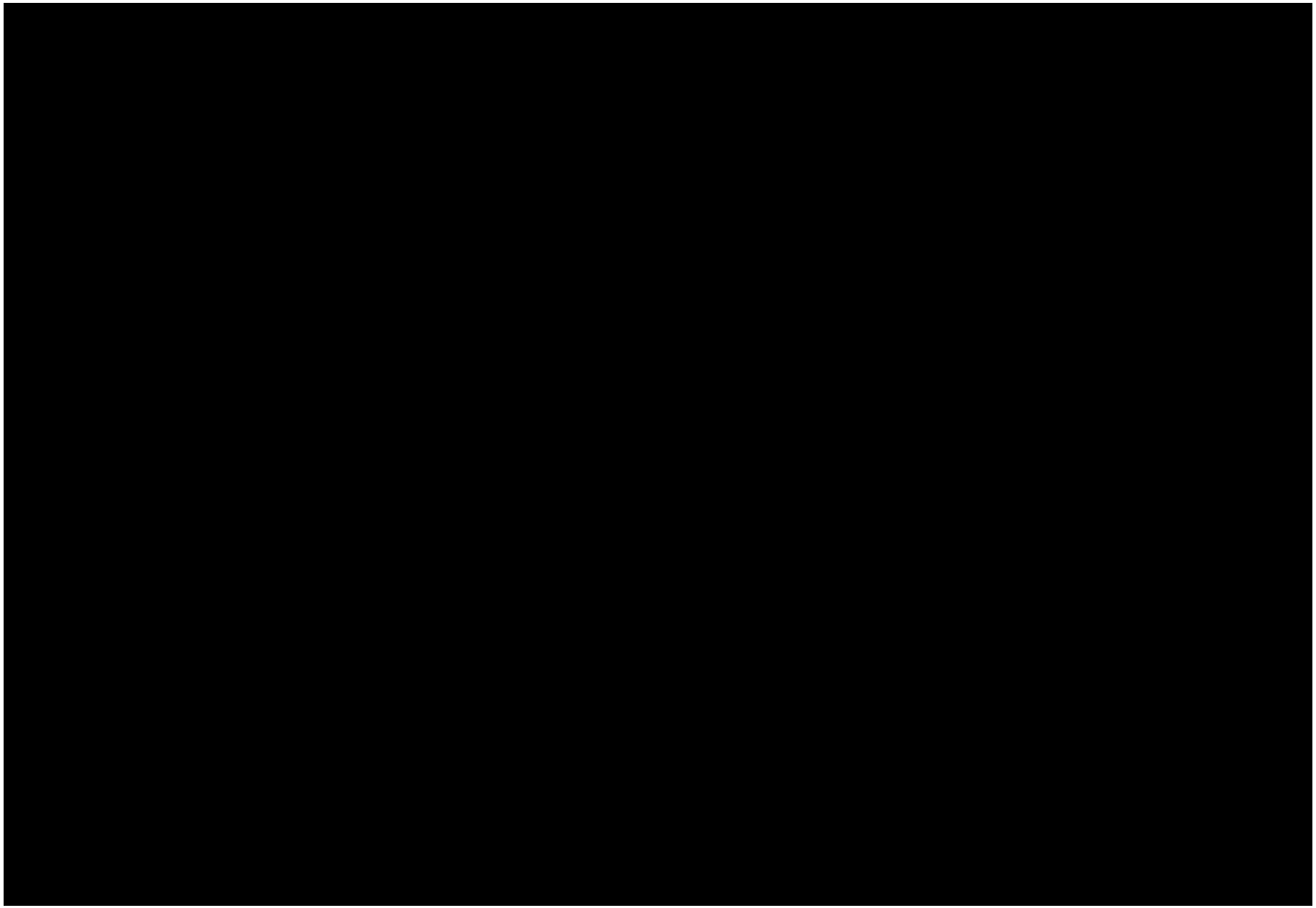

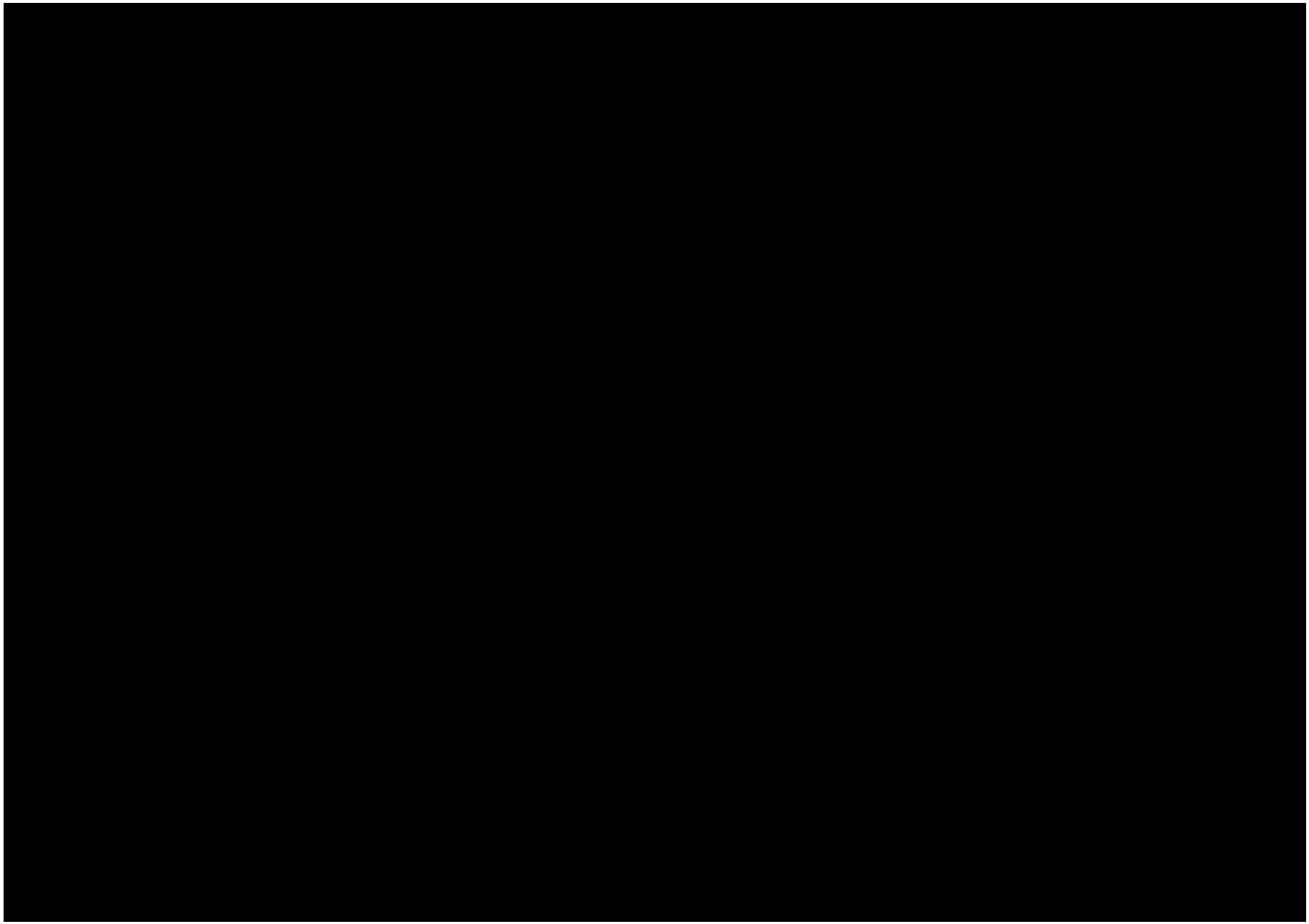

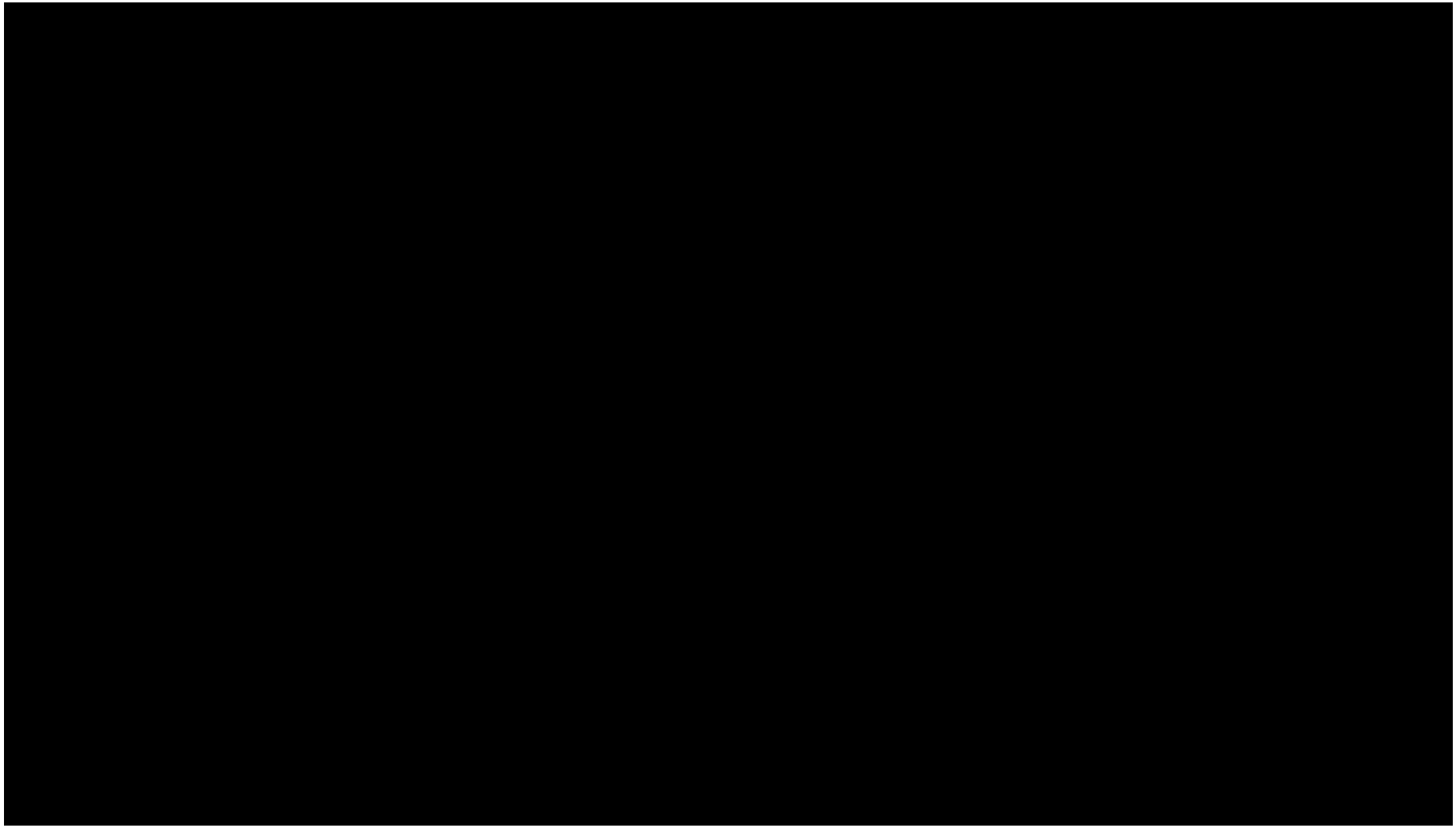

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